

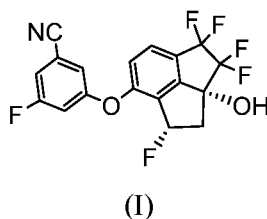
PROCESSES OF PREPARING 3-FLUORO-5-(((1S,2AR)-1,3,3,4,4-PENTAFLUORO-2A-HYDROXY-2,2A,3,4-TETRAHYDRO-1H-CYCLOPENTA[CD]INDEN-7-YL)OXY)-BENZONITRILE

Cross-Reference to Related Applications

This application is a PCT International Application claiming the benefit of PCT International Application No. PCT/CN2020/121745, filed on October 19, 2021, which is incorporated by reference herein in its entirety,

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:



or a pharmaceutically acceptable salt thereof.

Background

Compound (I) is a hypoxia inducible factor -2 α (HIF-2 α) inhibitor and is being developed for treating diseases mediated by aberrant activity of HIF-2 α 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.

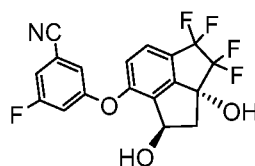
Synthesis of Compound (I) is disclosed in Example 5 of PCT Application Publication No. WO 2020/214853, filed on April 16, 2020. There is a need for alternative processes that allow for

large scale synthesis of Compound (I) in a cost-effective manner. The processes disclosed herein fulfill this and related needs.

Summary

5 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.

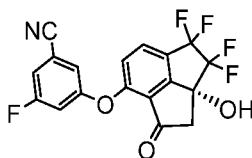
In one aspect, provided is a process of preparing compound (11)



10

(11)

comprising reducing the keto moiety of compound (10):

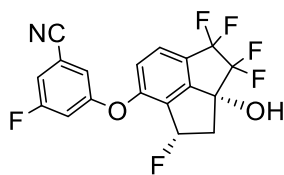


(10)

with:

- 15 (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
- 20 or trifluoroacetic acid.

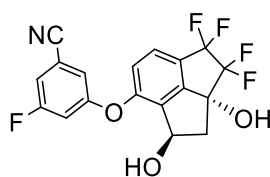
In an example, provided is a process of preparing Compound (I):



(I)

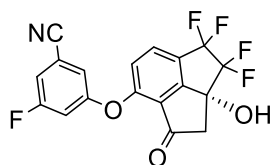
comprising:

- 5 (i) preparing compound (11):



(11)

comprising reducing the keto moiety of compound (10):

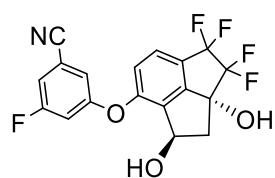


(10)

with:

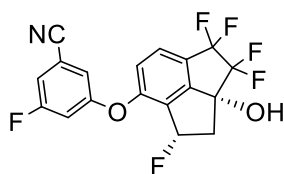
- 10 (a) sodium borohydride in an organic solvent selected from a group consisting of (i) an alcohol containing acetic acid or trifluoroacetic acid, (ii) a cyclic ether, and (iii) a mixture of a cyclic ether and an alcohol wherein the cyclic ether of (ii) and the mixture of a cyclic ether and an alcohol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

(ii) converting compound (11):



(11)

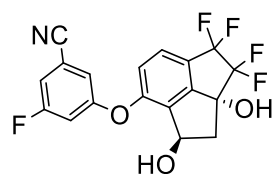
to Compound (I):



(I)

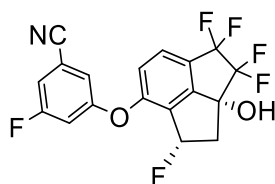
by reacting compound (11) with a deoxyfluorinating agent in the presence of an organic base in a suitable organic solvent.

In another example, the process further comprises converting compound (11):



(11)

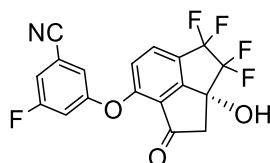
to Compound (I):



(I)

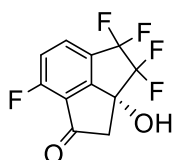
by reacting compound (11) with a deoxyfluorinating agent in the presence of an organic base in a suitable organic solvent.

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



(10)

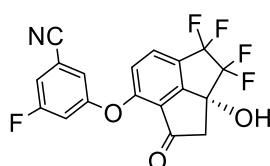
comprising reacting compound (9):



(9)

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

In another example, the processes defined herein further comprise preparing compound (10):



(10)

by reacting compound (9):



(9)

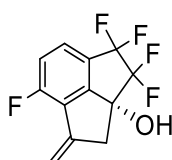
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent.

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



(9)

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



(8)

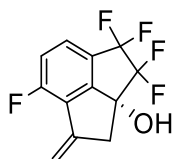
with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone[®] in the presence of ruthenium chloride in a suitable organic solvent, or (iii) Ozone[®] in a
10 suitable organic solvent.

In another example, the processes defined herein further comprise preparing compound (9):



(9)

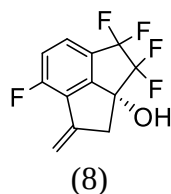
15 by carrying out oxidative cleavage of the vinylidene moiety of compound (8):



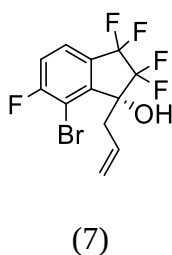
(8)

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

In another example, provided is a process for preparing compound (8):

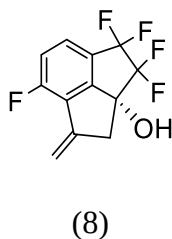


- 5 comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):

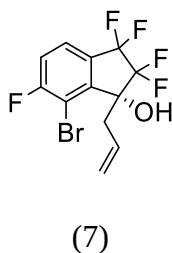


- by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic
10 solvent other than dimethylformamide.

In another example, the processes defined herein further comprise preparing compound (8):

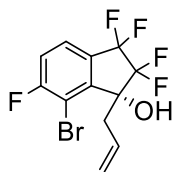


- 15 by performing intramolecular cyclization between the alkene and bromo groups in compound (7):



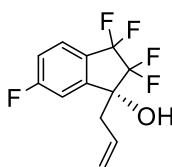
with a palladium catalyst in the presence of a base in a suitable organic solvent.

In another example, provided is a process for preparing compound (7):



(7)

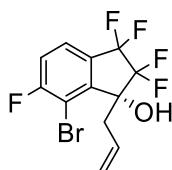
5 comprising brominating compound (6):



(6)

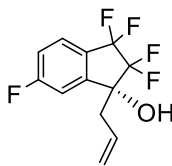
with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.

10 In another example, the processes defined herein further comprise preparing compound (7):



(7)

by treating compound (6):

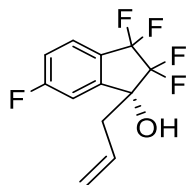


(6)

15

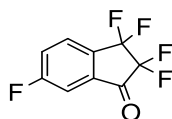
with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

In another example, the processes defined herein further comprise preparing compound (6):



(6)

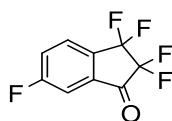
by treating compound (5):



(5)

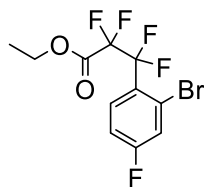
with 4,4,5,5-tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane in the presence of (S)-2-((3-(tert-butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethylbutanamide and a base in a suitable organic solvent.

In another example, the process defined herein further comprises preparing compound (5):



(5)

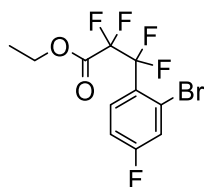
by treating compound (4):



(4)

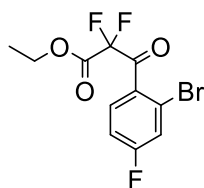
with an organolithium reagent in a suitable organic solvent.

In another example, the process defined herein further comprises preparing compound (4):



(4)

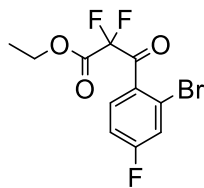
5 by treating compound (3):



(3)

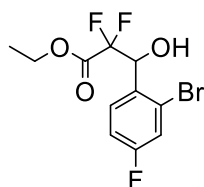
with a fluorinating agent in a suitable organic solvent.

In another example, the process defined herein further comprises preparing compound (3):



(3)

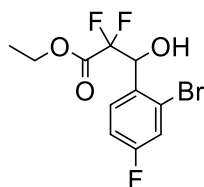
by treating compound (2):



(2)

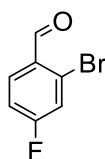
with an oxidizing agent in a suitable organic solvent.

In another example, the process defined herein further comprises preparing compound (2):



(2)

5 by treating compound (1):



(1)

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

10 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:

15 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.

20 “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, 1,3-dioxane, 1,4-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 (including, for example, alkane solvent) 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-methyl THF, or toluene solvent. In the preparation of compound (3), the reaction was also carried out in THF solvent. 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, or acetonitrile 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 K₂CO₃;

brominating reagents that were used in the preparation of compound (7) included CBr₄ and CF₂BrCF₂Br;

catalysts that were used in the preparation of compound (8) included Pd(dppf)Cl₂, Pd₂(dba)₃/XPhos, Pd(OAc)₂/PPh₃, and Pd(PPh₃)Cl₂;

fluorinating reagents that were used in the preparation of compound (4) included DAST, 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride, and HF/SF₄;

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), RuCl₃/NaBrO₃, TEMPO/NaClO, MnO₂, and TPAP/NMO.

oxidizing agents that were used in the oxidation of compound (8) to (9) included RuCl₃/NaIO₄, RuCl₃/Oxone[®] and O₃; and

reducing agents that were used in the reduction of compound (10) to (11) included LiBH₄ and NaBH₄.

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., ¹H or ¹³C), 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.

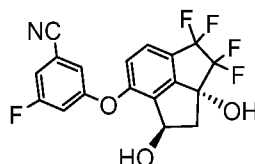
“Cyclic ether” refers to tetrahydrofuran, 2-methyltetrahydrofuran, or 1,4-dioxane.

5 “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.

10 “About” as used herein means $\pm 10\%$, preferably $\pm 5\%$ 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.

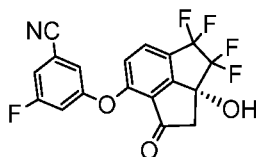
Embodiments:

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



(11)

15 comprising reducing the keto moiety of compound (10):



(10)

with:

20 (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.

25 2. In embodiment 2, provided is a process of preparing Compound (I) as described in the first and second embodiments of the second aspect of the Summary.

2a. In embodiment 2a, provided is a process of preparing Compound (I) as described in the first embodiment of the second aspect of the Summary.

2b. In embodiment 2b, provided is a process of preparing Compound (I) as described in the second embodiment of the second aspect of the Summary.

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

4. In embodiment 4, the process of embodiment 2, 2a (in step (ii)), 2b, 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, 2a, or 2b 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, 2a, 2b or 2b 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.

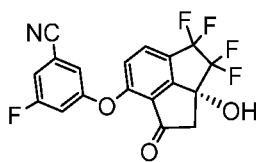
7. In embodiment 7, the process of embodiment 6 is wherein the organic solvent is a mixture of tetrahydrofuran and methanol and the reaction is carried out at about -5 °C to about 30°C.

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):

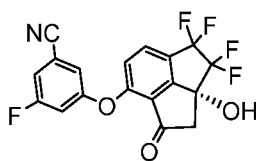


(9)

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

comprises 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.

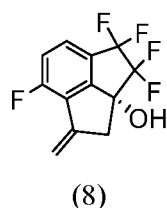
5 18. In embodiment 17, the process of any one of embodiments 11 to 17 further comprises crystallizing compound (10) from a mixture of an ether and an alkane solvent.

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):



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

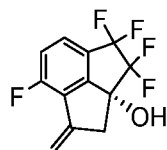


15 with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone® in the presence of ruthenium chloride in a suitable organic or aqueous organic solvent, or (iii) Ozone in a suitable organic or aqueous organic solvent.

21. In embodiment 21, the process of any one of embodiments 11 to 19 further comprises preparing compound (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.

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.

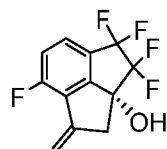
23. In embodiment 23, the process of embodiment 21, is wherein the solvent is a mixture of dichloromethane, acetonitrile and water or the solvent is aqueous acetonitrile.

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 comprises purification of compound (9) from a mixture of an ether and an alkane solvent.

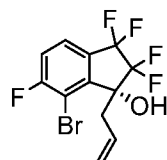
24b. In embodiment 24b, the process of embodiment 24a is wherein purification of compound (9) is from a mixture of methyl tert-butyl ether and n-heptane.

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



(8)

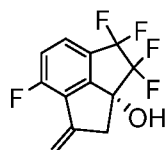
comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

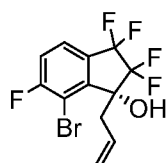
by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic solvent other than dimethylformamide.

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



(8)

5 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.

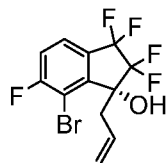
27. In embodiment 27, the process of embodiment 25 or 26 is wherein the palladium catalyst is Pd(PPh₃)₄, Pd(dppf)Cl₂, Pd(PPh₃)₂Cl₂, Pd(PPh₃)₂(OAc)₂, Pd₂(dba)₃/XPhos, or Pd(1,2-bis(diphenylphosphino)ethane)(OAc)₂, and the organic solvent is acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, 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.

15 29. In embodiment 29, the process of any one of embodiments 25, 26, or 28 is wherein the palladium catalyst is Pd(PPh₃)₂Cl₂, the base is potassium acetate, and the solvent is acetonitrile.

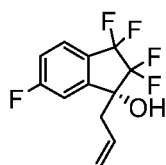
30. In embodiment 30, the process of embodiment 29 is wherein the reaction is carried out between about 60 °C to about 80 °C.

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



(7)

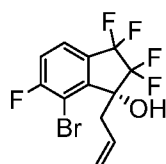
comprising brominating compound (6):



(6)

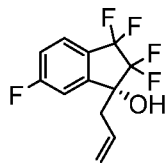
with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.

- 5 32. In embodiment 32, the process of any one of embodiments 25 to 30 further comprises 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.

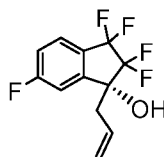
- 15 33. In embodiment 33, the process of embodiment 32 is wherein the brominating agent is carbon tetrabromide or 1,2-dibromo-1,1,2,2-tetrafluoroethane.

- 33a. In embodiment 33a, the process of embodiment 32 is wherein the brominating agent is bromotrichloromethane, 1,2-dibromo-1,1,2,2-tetrachloroethane, 1,2-dibromo-1,1,2,2-tetrafluoroethane, carbon tetrabromide, *N*-bromosuccinimide, *N*-bromophthalimide, *N*-bromosaccharin, *N*-bromoacetamide, 1,3-dibromo-5,5-dimethylhydantoin, dibromoisocyanuric acid, monosodium bromoisocyanurate, bromodimethylsulfonium bromide, 5,5-dibromomeldrum's acid, 2,4,4,6-tetrabromo-2,5-cyclohexadienone, bis(2,4,6-trimethylpyridine)-bromonium hexafluorophosphate; and bromine and its equivalents, such as bromine - 1,4-dioxane complex, tetrabutylammonium tribromide, trimethylphenylammonium tribromide, benzyltrimethylammonium tribromide, and 1-butyl-3-methylimidazolium tribromide.
- 20

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.

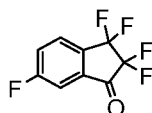
35. In embodiment 35, the process of embodiment 34 is wherein the reaction is carried out at about -100 °C to about -20 °C.

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



(6)

by treating compound (5):

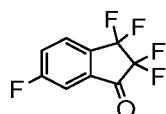


(5)

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.

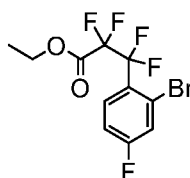
37. In embodiment 37, the process of embodiment 36 is wherein the base is sodium tert-butoxide and the organic solvent is a mixture of methanol and toluene.

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



(5)

by treating compound (4):



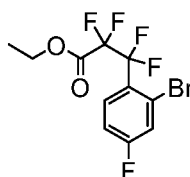
(4)

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 tert-butylether.

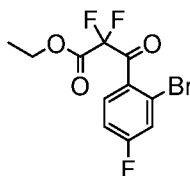
40. In embodiment 40, the process of embodiment 38 or 39 is wherein the solvent is tetrahydrofuran.

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



(4)

by treating compound (3):



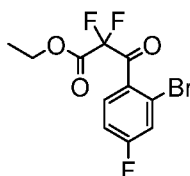
(3)

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.

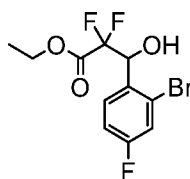
43. In embodiment 43, the process of embodiment 42 is wherein the fluorinating agent is sulfur tetrafluoride and hydrofluoric acid and the solvent is dichloromethane.

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



(3)

by treating compound (2):



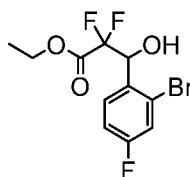
(2)

with an oxidizing agent in a suitable organic solvent.

5 45. In embodiment 45, the process of embodiment 44 is wherein the oxidizing agent is dimethyl sulfoxide/oxalyl chloride, 2-iodoxybenzoic acid, $\text{RuCl}_3/\text{NaBrO}_3$, MnO_2 , $\text{NaBrO}_3/\text{NaHSO}_3$, or TPAP/NMO.

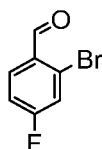
10 46. In embodiment 46, the process of embodiment 45 is wherein the oxidizing agent is TPAP/NMO and reaction is carried in dichloromethane, acetonitrile or tetrahydrofuran, preferably dichloromethane.

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



(2)

15 by treating compound (1):



(1)

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

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

EXAMPLES

Abbreviations:

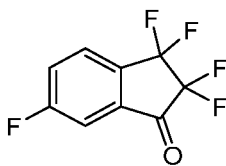
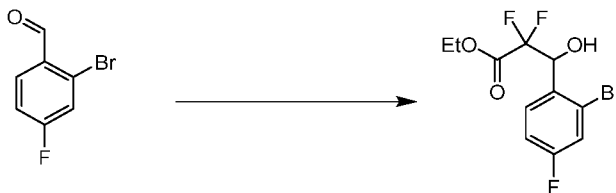
ACN: acetonitrile

25 AcOH or HOAc: acetic acid

- AlkylFluor: CAS Registry No. 2043361-32-4
Cs₂CO₃: cesium carbonate
DAST: diethylaminosulfur trifluoride
DCM: dichloromethane
- 5 HF: hydrofluoric acid
HCl: hydrochloric acid
KOAc: potassium acetate
LDA: Lithium diisopropylamide
MTBE: methyl tert-butyl ether
- 10 NMO: N-Methylmorpholine N-oxide
MeOH: methanol
NaBH₄: sodium borohydride
NaIO₄: sodium periodate
n-BuLi: n-butyllithium
- 15 Pd(PPh₃)₂(OAc)₂: bis(acetato)bis(triphenylphosphine)palladium(II)
Pd(PPh₃)₂Cl₂: bis(triphenylphosphine)palladium(II) dichloride
Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium(0)
PyFluor: 2-pyridinesulfonyl Fluoride
RuCl₃•3H₂O: ruthenium (III) chloride hydrate
- 20 SF₄: sulfur tetrafluoride
SulfoxFluor: [methyl(oxo){1-[6-(trifluoromethyl)-3-pyridyl]ethyl}-λ⁶-sulfanylidene]cyanamide
TEMPO: (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA: trifluoroacetic acid
THF: tetrahydrofuran
- 25 TPAP: tetrapropylammonium perruthenate
t-BuONa: sodium tert-butoxide
XPhos: 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

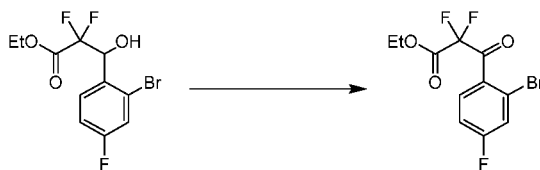
Example 1

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

5

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 Na₂SO₄, 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

20

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 N₂ 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 N₂ atmosphere, then was filtered through silica gel pad and

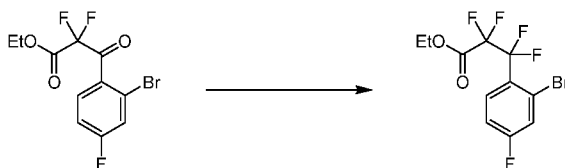
25

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 H₂O, 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.

Alternative Method:

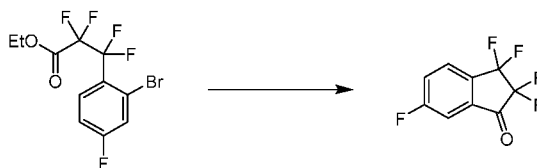
To a stirred mixture of ethyl 3-(2-bromo-4-fluorophenyl)-2,2-difluoro-3-hydroxypropanoate (285.9 g, after assay adjustment, 0.874 mol, 1.00 eq.) in acetonitrile (900 mL) and water (900 mL) were added NaH₂PO₄ (63.0 g, 0.525 mol, 0.60 eq.) and RuCl₃ (1.81 g, 8.726 mmol, 0.010 eq.) sequentially at 20-30 °C. NaBrO₃ (158.27 g, 1.049 mol, 1.20 eq.) was then added in portions at 20-30°C. After further stirring at 20-30°C for 2 h, the reaction mixture was diluted with EtOAc, followed by washing with water, aqueous Na₂SO₃, water and then brine. The organic layer was concentrated to obtain the title compound (272.8 g, 95.2% purity, 91.4% 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 SF₄ (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 Na₂CO₃ (2.5 L) and then extracted with petroleum ether. The combined organic layer was washed with 10% brine, dried over Na₂SO₄, 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.

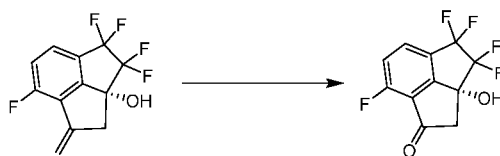
Step 4: 2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-one



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 NH₄Cl at -30 to -40 °C, followed by dilution with ethyl acetate and H₂O. After phase separation, the aqueous phase was extracted with ethyl acetate and the combined organic layer was washed with 10% brine, dried over Na₂SO₄, 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



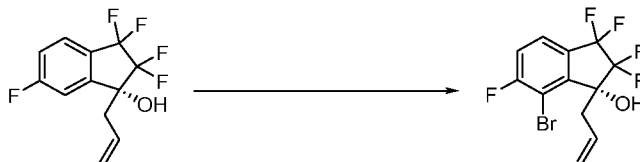
Step 1: (R)-1-allyl-2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-ol



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-trimethylbutanamide (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 and washed 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

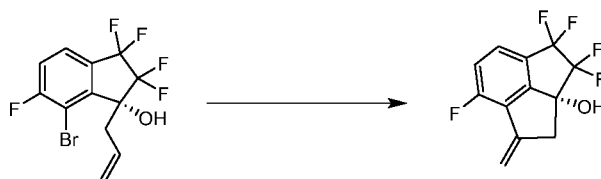


5

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 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 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(PPh₃)₂Cl₂ (10.30 g, 14.67 mmol, 0.050 eq.) under N₂ 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.).

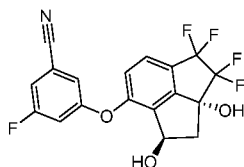
5 **Step 4:** (R)-3,3,4,4,7-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-1-one



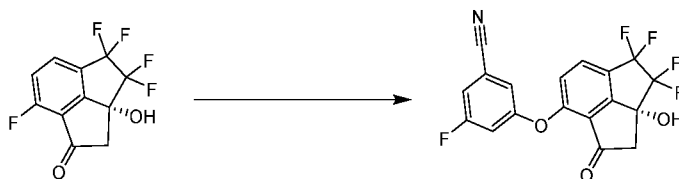
To a stirred mixture of (R)-3,3,4,4,7-pentafluoro-1-methylene-1,2,3,4-tetrahydro-2aH-cyclopenta[cd]inden-2a-ol (80.00 g, 305.13 mmol, 1.00 eq.) in ACN (1200 mL) and H₂O (3200 mL) was added RuCl₃•3H₂O (4.00 g, 15.30 mmol, 0.050 eq.), followed by NaIO₄ (456.87 g, 2.14 mol, 7.01 eq.) in portions while maintaining the reaction temperature at 10 to 20 °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 Na₂SO₃ and 10% aqueous Na₂SO₄. 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

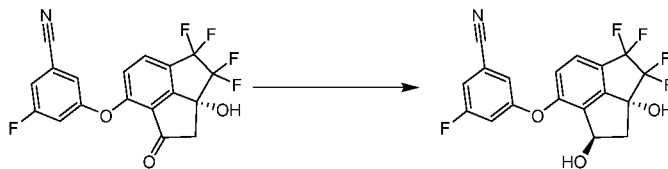


Step 1: (R)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-oxo-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile



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 Cs₂CO₃ (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 Na₂CO₃ 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

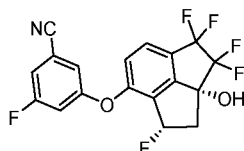


To a stirred solution of (R)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-oxo-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile (50.00 g, after assay adjustment, 131.14 mmol, 1.00 eq.) in MeOH (53.0 mL, 1.31 mol, 10.00 eq.) and THF (500 mL) was added NaBH₄ (1.84 g, 48.64 mmol, 0.37 eq.) 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.). ¹H NMR (400MHz, CDCl₃) 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

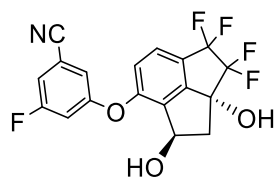
- 5 Synthesis of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile



- 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 was 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). The HPLC purity of the title compound was 95.4%. ¹H NMR (400MHz, CDCl₃) 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).

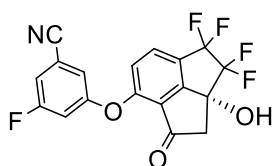
What is Claimed:

1. A process of preparing compound (11)



(11)

- 5 comprising reducing the keto moiety of compound (10):

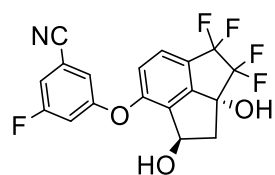


(10)

with:

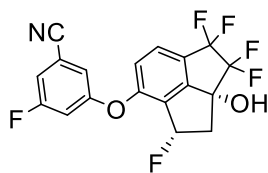
- 10 (a) sodium borohydride in an organic solvent selected from a group consisting of (i) an alcohol containing acetic acid or trifluoroacetic acid, (ii) a cyclic ether, and (iii) a mixture of a cyclic ether and an alcohol; wherein the cyclic ether of (ii) and the mixture of a cyclic ether and an alcohol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

- 15 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.

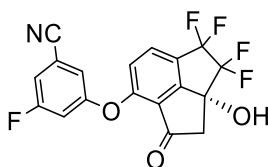
4. The process of claim 1 or 2, wherein the reduction of the keto moiety of compound (10) is carried out with sodium borohydride in:

(i) 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, and methanol containing acetic acid or trifluoroacetic acid; or

(ii) a mixture of tetrahydrofuran and methanol and the reaction is carried out at about -5 °C to about 30 °C.

5. 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.

6. A process of preparing compound (10):



(10)

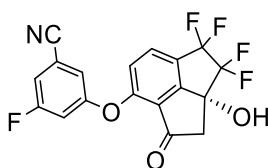
comprising reacting compound (9):



(9)

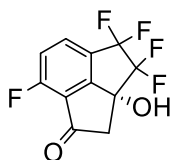
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

- 5 7. The process of any one of claims 1 to 5, 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.

8. The process of claim 6 or 7, wherein the base is:

(i) an inorganic base or

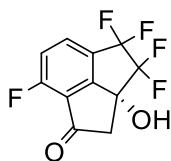
(ii) an inorganic base which is cesium carbonate or potassium carbonate.

9. The process of claim 6 to 8, wherein the organic solvent is tetrahydrofuran.

10. The process of any one of claims 6 to 9, further comprising crystallizing compound (10) from:

- (i) a mixture of an ether and an alkane solvent; or
- (ii) a mixture of methyl tert-butyl ether and n-heptane.

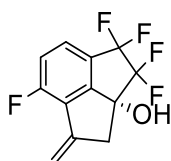
11. A process for preparing compound (9):



5

(9)

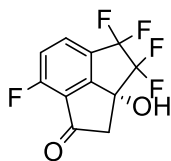
comprising carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

- with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii)
- 10 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.

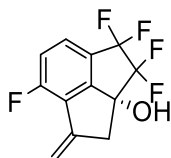
12. The process of any one of claims 6 to 10, further comprising preparing compound (9):



15

(9)

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

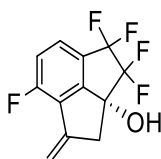


(8)

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

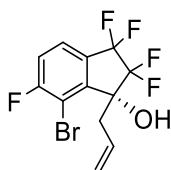
13. The process of claim 11 or 12, wherein the oxidative cleavage of the vinylidene is
5 carried out with sodium periodate in the presence of catalytic amount of ruthenium chloride in aqueous acetonitrile.

14. The process of any one of claims 11 to 13, further comprising preparing compound
(8):



(8)

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



(7)

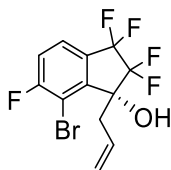
with a palladium catalyst in the presence of a base in a suitable organic solvent.

15. The process of claim 14, wherein:

(i) the palladium catalyst is $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{dppf})\text{Cl}_2$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, $\text{Pd}(\text{PPh}_3)_2(\text{OAc})_2$, $\text{Pd}_2(\text{dba})_3/\text{Xphos}$, or $\text{Pd}(1,2\text{-bis}(\text{diphenylphosphino})\text{-ethane})(\text{OAc})_2$, and the organic solvent is acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, 1,4-dioxane, or dimethylformamide; or

(ii) the palladium catalyst is $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, the base is potassium acetate, and the solvent is acetonitrile.

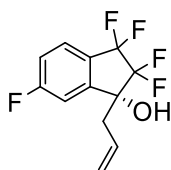
16. The process of claim 14 or 15, further comprising preparing compound (7):



5

(7)

by treating compound (6):



(6)

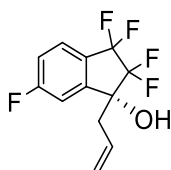
10 with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

17. The process of claim 16, wherein:

(i) the deprotonating agent is lithium diisopropylamide; or

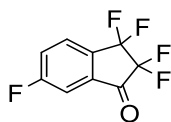
(ii) the brominating agent is 1,2-dibromo-1,1,2,2-tetrafluoroethane, the deprotonating agent is lithium diisopropylamide and the solvent is tetrahydrofuran.

15 18. The process of claim 16 or 17, 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-
5 butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethylbutanamide and a base in a suitable organic solvent.

19. The process of claim 18, wherein the base is sodium tert-butoxide and the organic solvent is a mixture of methanol and toluene.