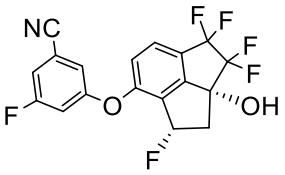
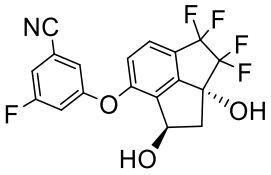
In an example, provided is a process of preparing Compound (I):



(I)

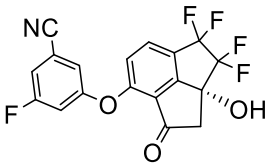
comprising:

(i) preparing compound (11):



(11)

comprising reducing the keto moiety of compound (10):



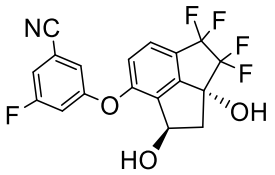
(10)

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

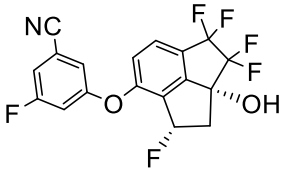
(b) lithium borohydride in a suitable organic solvent optionally containing acetic acid or trifluoroacetic acid; and

(ii) converting compound (11):



(11)

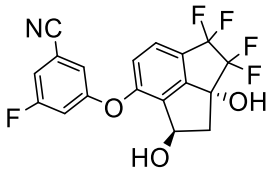
to Compound (I):



(I)

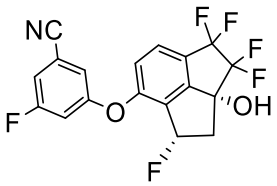
by reacting compound (11) with a deoxyfluorinating agent in the presence of an organic base in a suitable organic solvent.

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



(11)

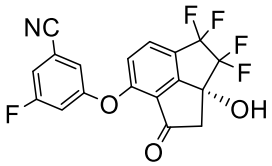
to Compound (I):



(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)

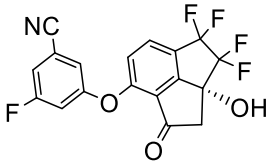
comprising reacting compound (9):



(9)

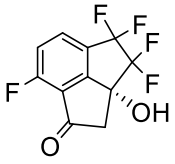
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

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



(10)

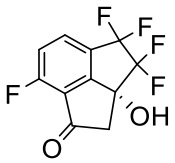
by reacting compound (9):



(9)

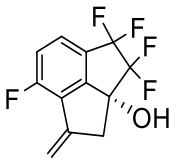
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent.

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



(9)

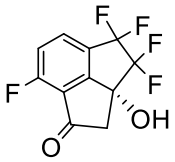
comprising carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(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 suitable organic solvent.

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



(9)

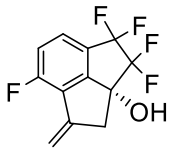
by carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

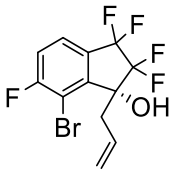
with a suitable oxidizing agent in a suitable organic or aqueous organic solvent.

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



(8)

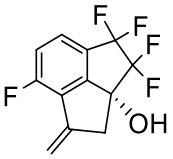
comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

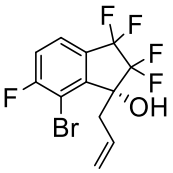
by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic solvent other than dimethylformamide.

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



(8)

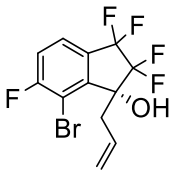
by performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

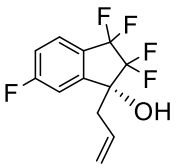
with a palladium catalyst in the presence of a base in a suitable organic solvent.

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



(7)

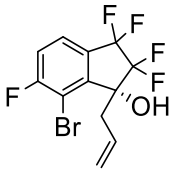
comprising brominating compound (6):



(6)

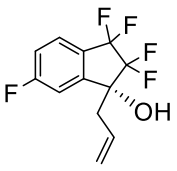
with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.

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



(7)

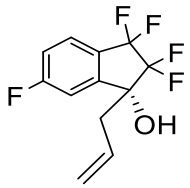
by treating compound (6):



(6)

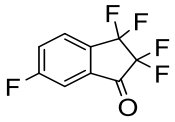
with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

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



(6)

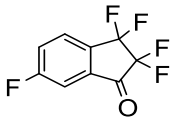
by treating compound (5):



(5)

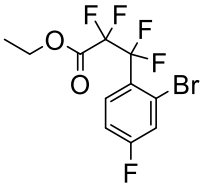
with 4,4,5,5-tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane in the presence of (S)-2-((3-(tert-butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethylbutanamide and a base in a suitable organic solvent.

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



(5)

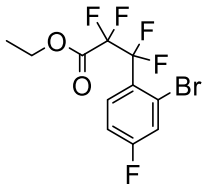
by treating compound (4):



(4)

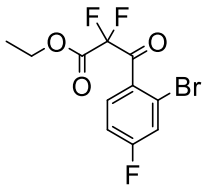
with an organolithium reagent in a suitable organic solvent.

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



(4)

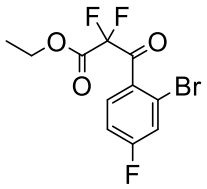
by treating compound (3):



(3)

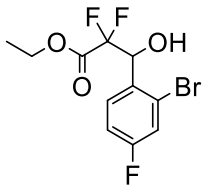
with a fluorinating agent in a suitable organic solvent.

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



(3)

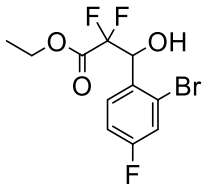
by treating compound (2):



(2)

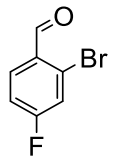
with an oxidizing agent in a suitable organic solvent.

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



(2)

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.

Detailed Description

Definitions:

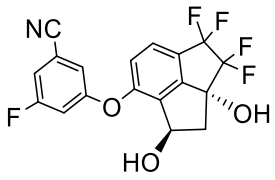
Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

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

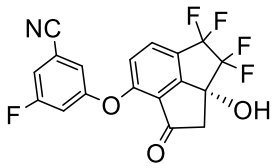
What is Claimed:

1. A process of preparing compound (11)



(11)

comprising reducing the keto moiety of compound (10):



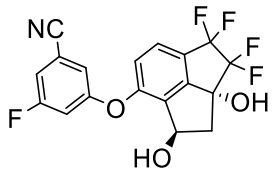
(10)

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

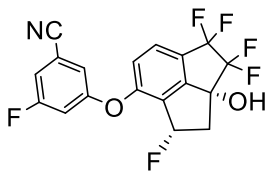
(b) lithium borohydride in a suitable organic solvent optionally containing acetic acid or trifluoroacetic acid.

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.

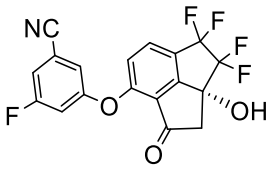
4. The process of claim 1 or 2, wherein the reduction of the keto moiety of compound (10) is carried out with sodium borohydride in:

(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.

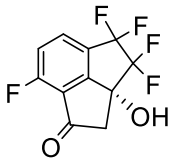
5. The process of claim 3, wherein the molar ratio of 1,8-diazabicyclo[5.4.0]-undec-7-ene to compound (11) is at least about 2 to about 1 and the organic solvent is tetrahydrofuran.

6. A process of preparing compound (10):



(10)

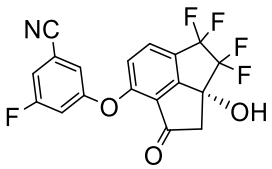
comprising reacting compound (9):



(9)

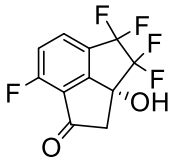
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

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.

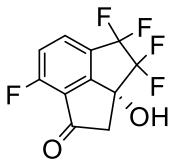
9. The process of claim 6 to 8, wherein the organic solvent is tetrahydrofuran.

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

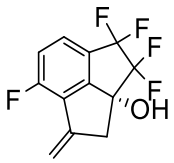
(ii) a mixture of methyl tert-butyl ether and n-heptane.

11. A process for preparing compound (9):



(9)

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



(8)

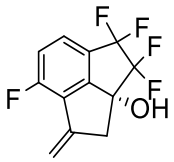
with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone® in the presence of ruthenium chloride in a suitable organic or aqueous organic solvent, or (iii) Ozone in a suitable organic or aqueous organic solvent.

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



(9)

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

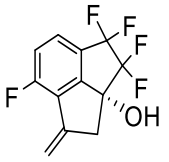


(8)

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

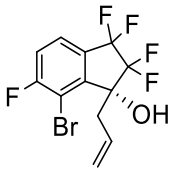
13. The process of claim 11 or 12, wherein the oxidative cleavage of the vinylidene is carried out with sodium periodate in the presence of catalytic amount of ruthenium chloride in aqueous acetonitrile.

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)

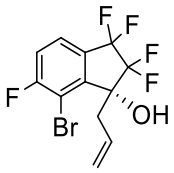
with a palladium catalyst in the presence of a base in a suitable organic solvent.

15. The process of claim 14, wherein:

(i) the palladium catalyst is $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_2(OAc)_2$, $Pd_2(dba)_3$/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; or

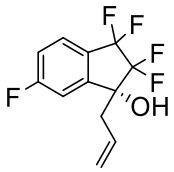
(ii) the palladium catalyst is $Pd(PPh_3)_2Cl_2$, the base is potassium acetate, and the solvent is acetonitrile.

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



(7)

by treating compound (6):



(6)

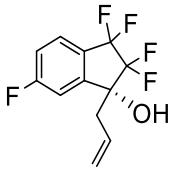
with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

17. The process of claim 16, wherein:

(i) the deprotonating agent is lithium diisopropylamide; or

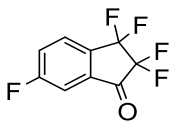
(ii) the brominating agent is 1,2-dibromo-1,1,2,2-tetrafluoroethane, the deprotonating agent is lithium diisopropylamide and the solvent is tetrahydrofuran.

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-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.