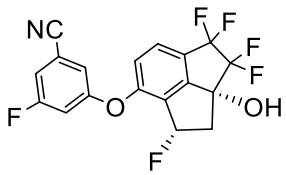
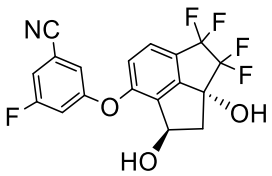
In an ~~first embodiment~~ example~~of a second aspect~~, provided is a process of preparing Compound (I):



(I)

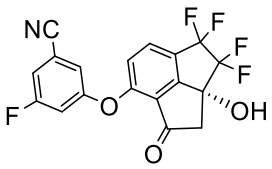
comprising:

(i) preparing compound (11):



(11)

comprising reducing the keto moiety of compound (10):



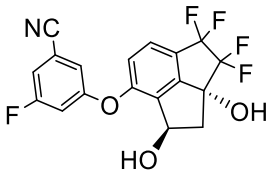
(10)

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

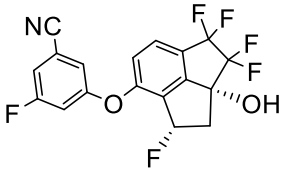
(b) lithium borohydride in a suitable organic solvent optionally containing acetic acid or trifluoroacetic acid; and

(ii) converting compound (11):



(11)

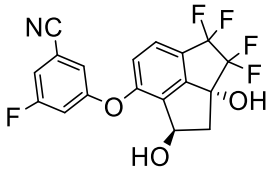
to Compound (I):



(I)

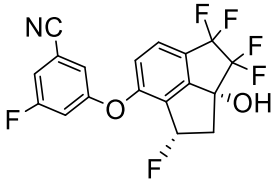
by reacting compound (11) with a deoxyfluorinating agent in the presence of an organic base in a suitable organic solvent.

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



(11)

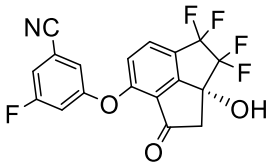
to Compound (I):



(I)

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

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



(10)

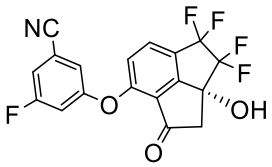
comprising reacting compound (9):



(9)

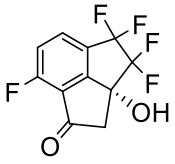
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

In another example ~~fourth aspect~~, the processes defined herein ~~of the first aspect and each embodiment of the second aspect,~~ further comprise preparing compound (10):



(10)

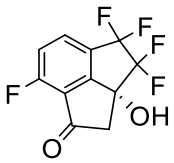
by reacting compound (9):



(9)

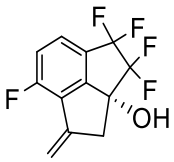
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent.

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



(9)

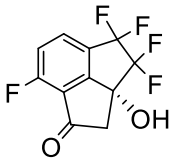
comprising carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

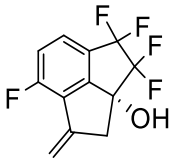
with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone® in the presence of ruthenium chloride in a suitable organic solvent, or (iii) Ozone® in a suitable organic solvent.

In another example ~~sixth aspect~~, the processes defined herein ~~of the third and fourth aspects,~~ further comprise preparing compound (9):



(9)

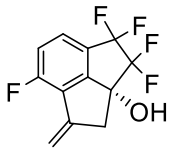
by carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

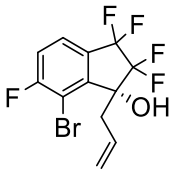
with a suitable oxidizing agent in a suitable organic or aqueous organic solvent.

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



(8)

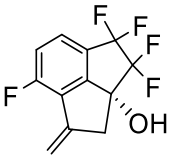
comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

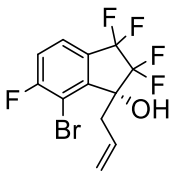
by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic solvent other than dimethylformamide.

In another example ~~eighth aspect~~, the processes defined herein ~~of the fifth and sixth aspects,~~ further comprise preparing compound (8):



(8)

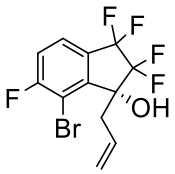
by performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

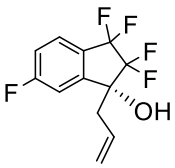
with a palladium catalyst in the presence of a base in a suitable organic solvent.

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



(7)

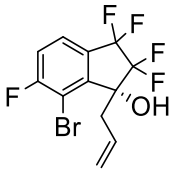
comprising brominating compound (6):



(6)

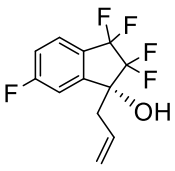
with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.

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



(7)

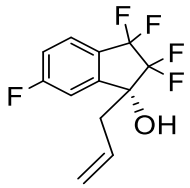
by treating compound (6):



(6)

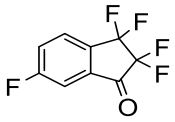
with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

In another example ~~eleventh aspect~~, the processes defined herein ~~of the ninth and tenth aspects,~~ further comprise preparing compound (6):



(6)

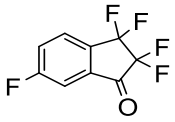
by treating compound (5):



(5)

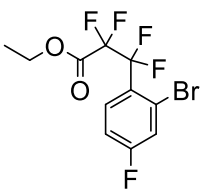
with 4,4,5,5-tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane in the presence of (S)-2-((3-(tert-butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethylbutanamide and a base in a suitable organic solvent.

In another example ~~a twelfth aspect~~, the process defined herein ~~of eleventh aspect,~~ further comprises preparing compound (5):



(5)

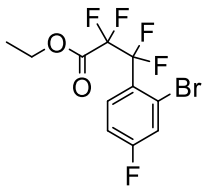
by treating compound (4):



(4)

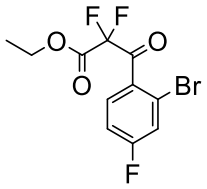
with an organolithium reagent in a suitable organic solvent.

In another example~~a thirteenth aspect~~, the process defined herein ~~of twelfth aspect,~~ further comprises preparing compound (4):



(4)

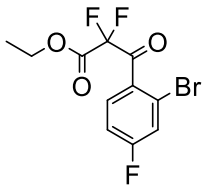
by treating compound (3):



(3)

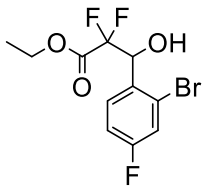
with a fluorinating agent in a suitable organic solvent.

In another example~~a fourteenth aspect~~, the process defined herein ~~of thirteenth aspect,~~ further comprises preparing compound (3):



(3)

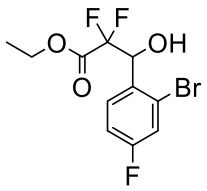
by treating compound (2):



(2)

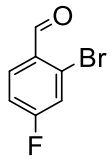
with an oxidizing agent in a suitable organic solvent.

In another example~~a fifteenth aspect~~, the process defined herein ~~of fourteenth aspect,~~ 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:

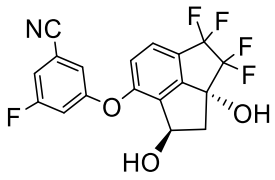
Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

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

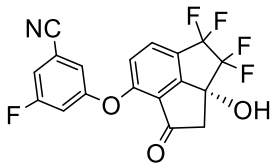
What is Claimed:

1. A process of preparing compound (11)



(11)

comprising reducing the keto moiety of compound (10):



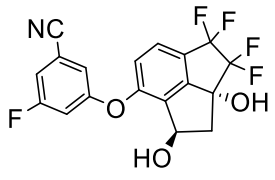
(10)

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

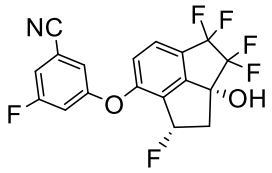
(b) lithium borohydride in a suitable organic solvent optionally containing acetic acid or trifluoroacetic acid.

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.

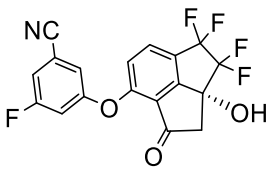
4. The process of claim 1 or 2, wherein the reduction of the keto ~~group~~ moiety of compound (10) is carried out with sodium borohydride in:

(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, ~~or~~ and methanol containing acetic acid or trifluoroacetic acid; or~~.~~

(ii)~~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.

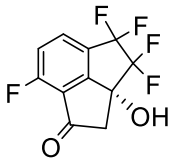
~~6~~5. The process of claim 3, wherein the molar ratio of 1,8-diazabicyclo[5.4.0]-undec-7-ene to compound (11) is at least about 2 to about 1 and the organic solvent is tetrahydrofuran.

~~7~~6. A process of preparing compound (10):



(10)

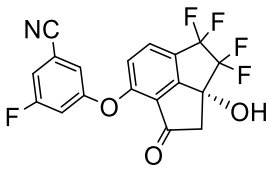
comprising reacting compound (9):



(9)

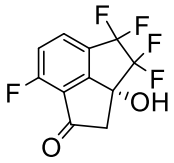
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

~~8~~7. The process of any one of claims 1 to ~~6~~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.

~~9~~8. The process of claim 6 or 7 ~~or 8~~, wherein the base is:

(i) ~~-~~an inorganic base or~~.~~

~~10. The process of claim 9, wherein the~~(ii) an inorganic base which is cesium carbonate or potassium carbonate.

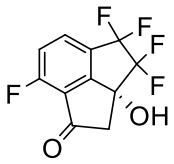
~~11~~9. The process of claim 6 to 8~~7 to 10~~, wherein the organic solvent is tetrahydrofuran.

~~12~~10. The process of any one of claims ~~7~~ 6 to ~~11~~9, further comprising crystallizing compound (10) from:

(i) ~~a~~a mixture of an ether and an alkane solvent; or~~.~~

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

~~14~~11. A process for preparing compound (9):



(9)

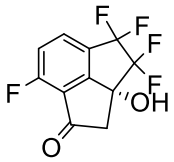
comprising carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

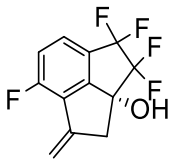
with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone® in the presence of ruthenium chloride in a suitable organic or aqueous organic solvent, or (iii) Ozone in a suitable organic or aqueous organic solvent.

~~15~~12. The process of any one of claims ~~7~~ 6 to ~~13~~10, further comprising preparing compound (9):



(9)

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

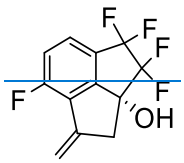


(8)

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

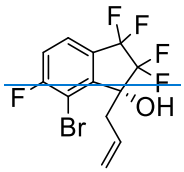
~~16~~13. The process of claim 11 or 12~~14 or 15~~, wherein the oxidative cleavage of the vinylidene is carried out with sodium periodate in the presence of catalytic amount of ruthenium chloride in aqueous acetonitrile.

~~17. A process for preparing compound (8):~~



~~(8)~~

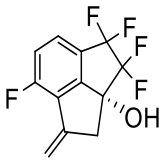
~~comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):~~



~~(7)~~

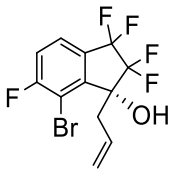
~~by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic solvent other than dimethylformamide.~~

~~18~~14. The process of any one of claims ~~14 to 16~~11 to 13, further comprising preparing compound (8):



(8)

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



(7)

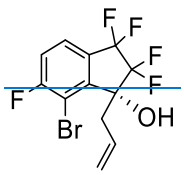
with a palladium catalyst in the presence of a base in a suitable organic solvent.

~~19~~15. The process of claim ~~17 or 18~~14, wherein:

(i) ~~the~~ 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~~.~~

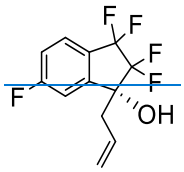
~~20. The process of claim 19, wherein~~(ii) the palladium catalyst is $Pd(PPh_3)_2Cl_2$, the base is potassium acetate, and the solvent is acetonitrile.

~~21. A process for preparing compound (7):~~



~~(7)~~

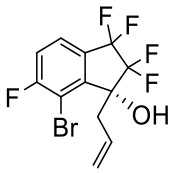
~~comprising brominating compound (6):~~



~~(6)~~

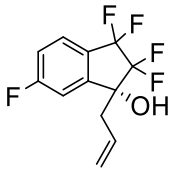
~~with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.~~

~~22~~16. The process of ~~any one of~~ claim~~s 17 to 20~~14 or 15, further comprising preparing compound (7):



(7)

by treating compound (6):



(6)

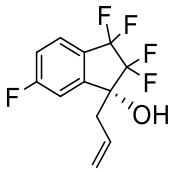
with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

~~23~~17. The process of claim ~~21 or 22~~16, wherein:

(i) ~~-~~the deprotonating ~~deprotenating~~ agent is lithium diisopropylamide; or~~.~~

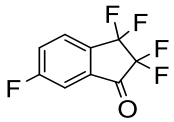
~~24. The process of claim 21 or 22, wherein~~(ii) ~~-~~the brominating agent is 1,2-dibromo-1,1,2,2-tetrafluoroethane, the deprotonating ~~deprotenating~~ agent is lithium diisopropylamide and the solvent is tetrahydrofuran.

~~25~~18. The process of ~~any one of~~ claim~~s 21 to 24~~ 16 or 17, further comprising preparing compound (6):



(6)

by treating compound (5):

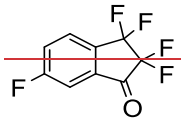


(5)

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.

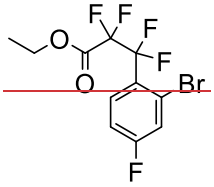
~~26~~19. The process of claim ~~25~~18, wherein the base is sodium tert-butoxide and the organic solvent is a mixture of methanol and toluene.

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



~~(5)~~

~~by treating compound (4):~~

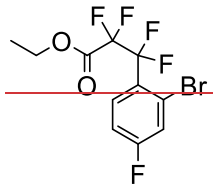


~~(4)~~

with an organolithium reagent in a suitable organic solvent.

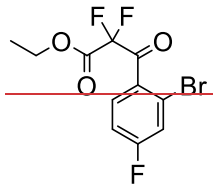
28. The process of claim 27, wherein the organolithium reagent is n-butyllithium and the organic solvent is tetrahydrofuran.

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



(4)

by treating compound (3):



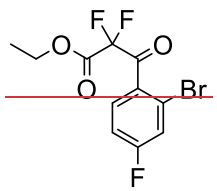
(3)

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.

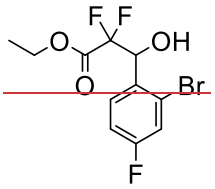
31. The process of claim 30, wherein the fluorinating agent is sulfur tetrafluoride and hydrofluoric acid and the solvent is dichloromethane.

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



(3)

by treating compound (2):



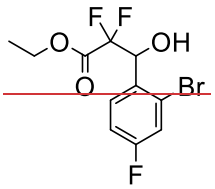
(2)

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.

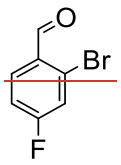
34. The process of claim 33, wherein the oxidizing agent is is TPAP/NMO and reaction is carried in dichloromethane.

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.