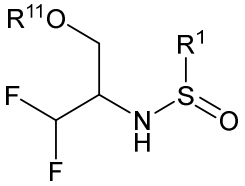
Inavolisib, also known as GDC-0077 or by the IUPAC name: (*S*)-2-((2-((*S*)-4-(difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[*f*]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)propanamide, has potent PI3K activity (WO 2017/001645, US 2017/0015678, Edgar K. et al, #156, "Preclinical characterization of GDC-0077, a specific PI3K alpha inhibitor in early clinical development", and Staben. S. #DDT02-0 "Discovery of GDC-0077, a highly isoform selective inhibitor of PI3K alpha that promotes selective loss of mutant-p110alpha", American Assoc. for Cancer Res. (AACR) annual meeting, April 2, 2017, Washington DC), and is being studied in patients with locally advanced or metastatic solid tumors. There remains a need for new processes for making benzoxazepin oxazolidinone compounds such as inavolisib.

SUMMARY

The disclosure relates to methods of making benzoxazepin oxazolidinone compounds and intermediates thereof.

In one aspect, provided is a compound of Formula (8A):



(8A), or a salt thereof, wherein:

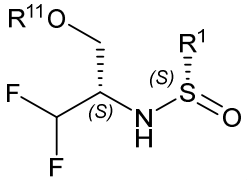
R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and

R^{11} is hydrogen or a hydroxyl protecting group.

In some examples, R^1 is the optionally substituted C_{1-12} alkyl. In some examples, R^1 is an optionally substituted tertiary C_{4-12} alkyl. In some examples, R^1 is selected from the group consisting of *tert*-butyl, *tert*-pentyl, 3-ethylpentan-3-yl, 1-methylcyclohexyl, 1-adamantyl, phenyl, and naphthyl.

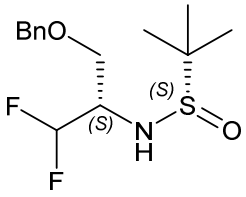
In some examples, R^{11} is hydrogen. In some examples, R^{11} is benzyl.

In some examples, the compound of the Formula (8A) is of Formula (8B):

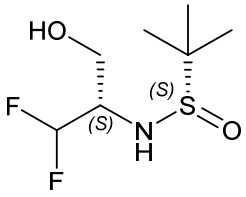


, or a salt thereof, wherein R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and R^{11} is hydrogen or a hydroxyl protecting group.

In some examples, the compound of the Formula (8A) is of Formula (8-1):

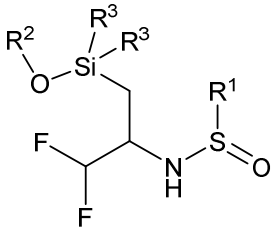


(8-1), or a salt thereof; or Formula (8-2):



(8-2), or a salt thereof.

In another aspect, provided is a compound of Formula (7A):



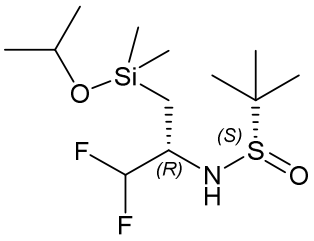
(7A), or a salt thereof, wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl;

R^2 is an optionally substituted C_{1-12} alkyl or an optionally substituted C_{6-14} aryl; and

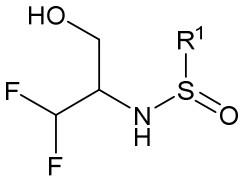
each R^3 is independently an optionally substituted C_{1-12} alkyl, an optionally substituted C_{6-14} aryl, or OR^2.

In some examples, the compound of the Formula (7A) is of the formula (7):



(7), or a salt thereof.

In yet another example, provided is a process for the preparation of a compound of Formula (8C):

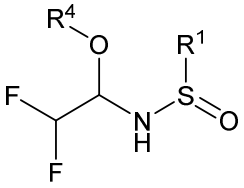


(8C), or a salt thereof, wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl;

the process comprising the steps of:

(iii) reacting a compound of Formula (4A):

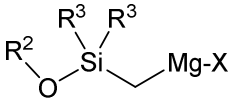


(4A), or a salt thereof, wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and

R^4 is an optionally substituted C_{1-6} alkyl or hydrogen;

with a Grignard reagent of formula (5A):



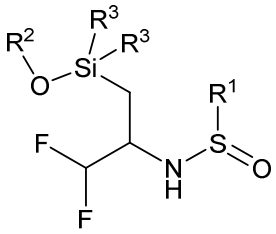
(5A), wherein:

R^2 is an optionally substituted C_{1-12} alkyl or an optionally substituted C_{6-14} aryl;

each R^3 is independently an optionally substituted C_{1-12} alkyl, an optionally substituted C_{6-14} aryl, or OR^2; and

X is a halide;

to thereby form a compound of Formula (7A):

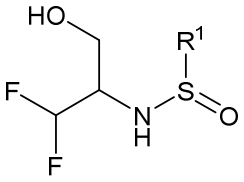


(7A), or a salt thereof,

and

(iv) reacting the compound of Formula (7A) with a fluoride salt, a base, and an oxidant to form the compound of Formula (8C).

In one aspect, provided is a process of preparing a compound of Formula (8C):



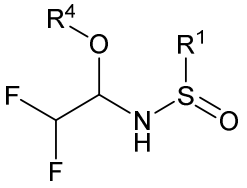
(8C), or a salt thereof,

wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl;

the process comprising the steps of:

(iii) reacting a compound of Formula (4A):



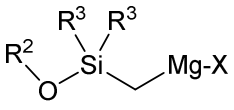
(4A), or a salt thereof,

wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and

R^4 is an optionally substituted C_{1-6} alkyl or hydrogen;

with a Grignard reagent of formula (5A):



(5A),

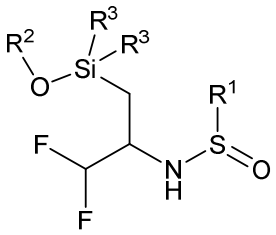
wherein:

R^2 is an optionally substituted C_{1-12} alkyl or an optionally substituted C_{6-14} aryl;

each R^3 is independently an optionally substituted C_{1-12} alkyl, an optionally substituted C_{6-14} aryl, or OR^2; and

X is a halide;

to thereby form a compound of Formula (7A):



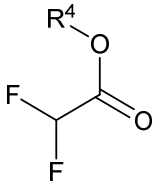
(7A), or a salt thereof,

and

(iv) reacting the compound of Formula (7A) with a fluoride salt, a base, and an oxidant to form the compound of Formula (8C).

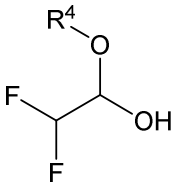
In some examples, the process further comprises the steps of:

(i) partially reducing a compound of Formula (1A):



(1A), or a salt thereof,

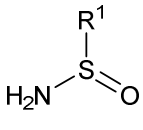
wherein R^4 is an optionally substituted C_{1-6} alkyl or hydrogen, to form a compound of Formula (2A):



(2A), or a salt thereof,

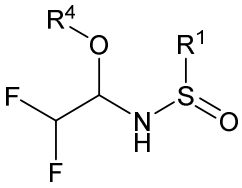
and

(ii) reacting the compound of Formula (2A) with a sulfonamide compound of Formula (3A):



(3A),

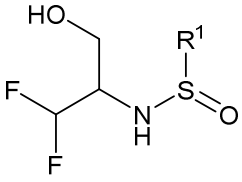
wherein R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl, in the presence of a dehydrating reagent to form the compound of Formula (4A):



(4A), or a salt thereof.

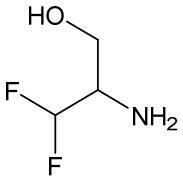
In some of these examples, the process further comprises the step of:

(v) reacting the compound of Formula (8C):



(8C), or a salt thereof,

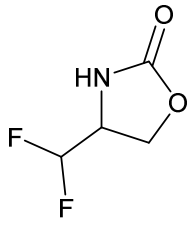
wherein R^1 is as defined in claim 11, with an acid to thereby yield an amine compound of Formula (9-1):



(9-1), or an acid addition salt thereof.

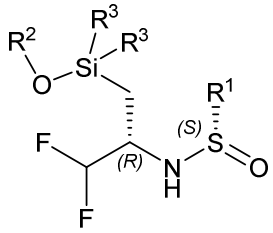
In some of these examples, the process further comprises the step of:

(vi) reacting the compound of Formula (9-1), or the acid addition salt thereof, with an acylating reagent to form a compound of Formula (10-1):

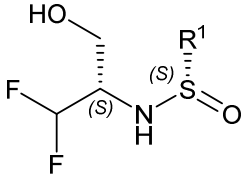


(10-1), or a salt thereof.

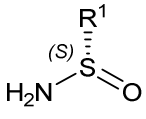
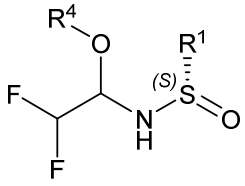
In some examples, the compound of Formula (7A) is of Formula (7B):

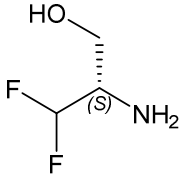


, or a salt thereof, and the compound of Formula (8C) is of Formula (8D):



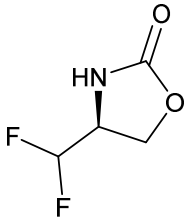
, or a salt thereof, wherein R^1, R^2, and R^3 are as defined above.

In some examples, the compound of Formula (3A) is of Formula (3B): , and the compound of Formula (4A) is of Formula (4B): , or a salt thereof, wherein R^1 and R^4 are as defined above.



In some examples, the compound of Formula (9-1) is of Formula (9-3): .

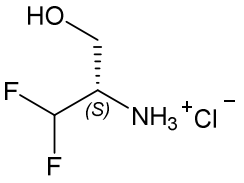
In some of these examples, the compound of Formula (10-1) is of Formula (10-2):



.

In some of these examples, R^1 is *tert*-butyl. In some of these examples, R^2 is 2-propyl, each R^3 is methyl, and X is chloride. In some of these examples, R^4 is ethyl.

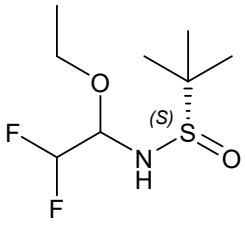
In some of these examples, the acid for step (v) is HCl, and the acid addition salt of the compound of Formula (9-1) is a hydrochloride salt having the structure (9-2):



.

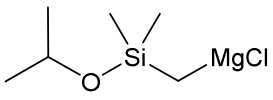
In one example, the process of preparing a compound of Formula (8C) is a process comprising the steps of:

(iii) reacting a compound of formula (4):



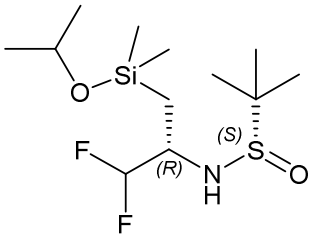
(4), or a salt thereof,

with a compound of formula (5):



(5);

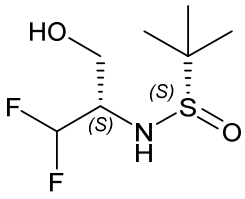
in a solvent (e.g., THF) to form a compound of formula (7):



(7), or a salt thereof;

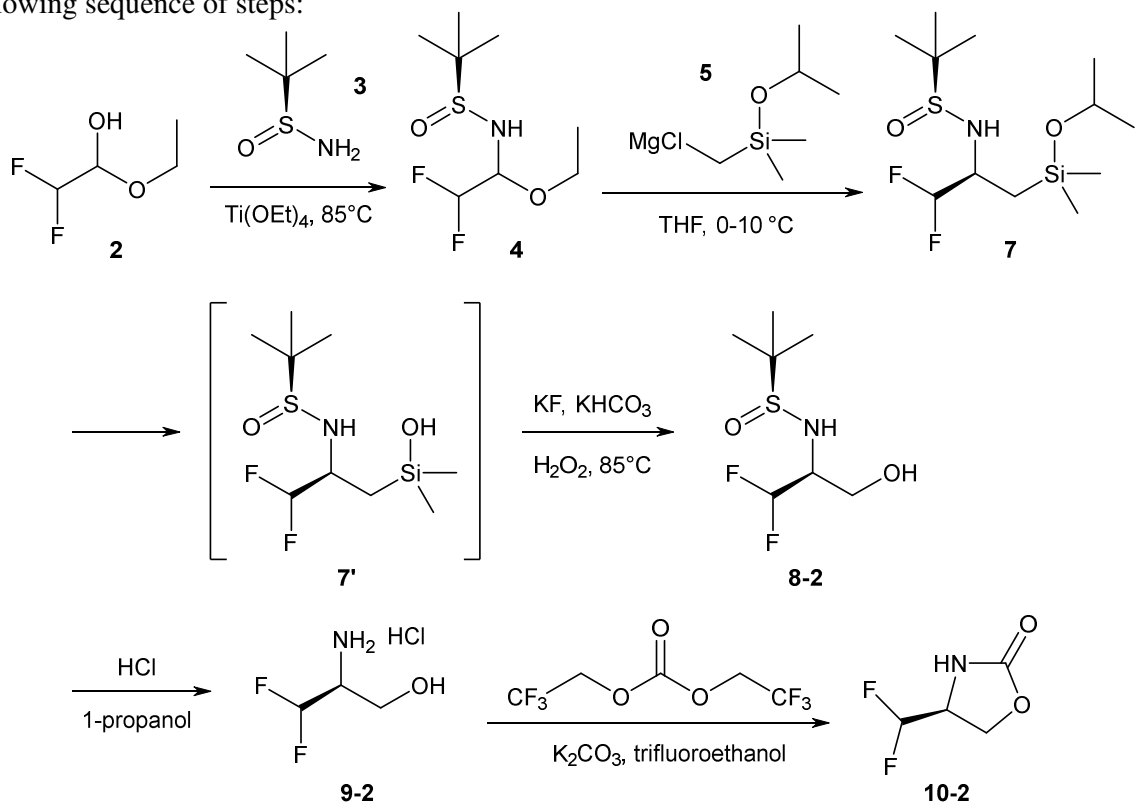
and

(iv) reacting the compound of formula (7) with potassium fluoride, potassium bicarbonate, and hydrogen peroxide in a solvent (e.g., methanol) to form a compound of formula (8-2):



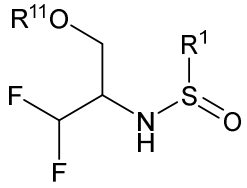
(8-2).

In one aspect, provided is a process of making a compound of formula (10-2) according to the following sequence of steps:



.

In yet another example, provided is a process for the preparation of a compound of Formula (8A):



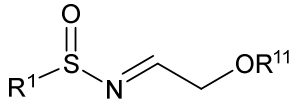
(8A), or a salt thereof,

wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and

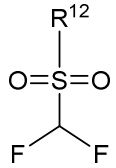
R^{11} is a hydroxyl protecting group, the process comprising the steps of:

(b) reacting a compound of Formula (12A):



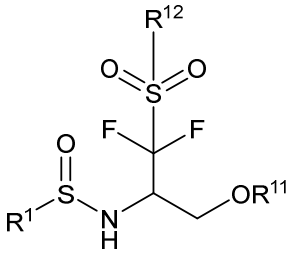
(12A),

with a compound of Formula (13A):



(13A),

wherein R^{12} is optionally substituted C_{6-14} aryl and a base at a temperature below 0°C to form a compound of Formula (14A):

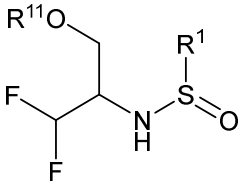


(14A);

and

(c) reacting the compound of Formula (14A) with magnesium in the presence of an acetate buffer to thereby form the compound of Formula (8A).

In one aspect, provided is a process of preparing a compound of Formula (8A):



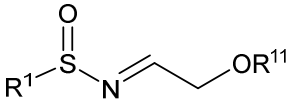
(8A), or a salt thereof,

wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and

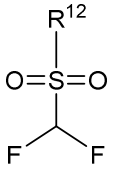
R^{11} is a hydroxyl protecting group, the process comprising the steps of:

(b) reacting a compound of Formula (12A):



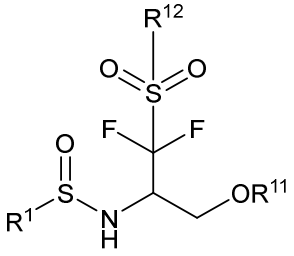
(12A),

with a compound of Formula (13A):



(13A),

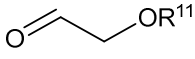
wherein R^{12} is optionally substituted C_{6-14} aryl and a base at a temperature below 0°C to form a compound of Formula (14A):

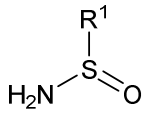


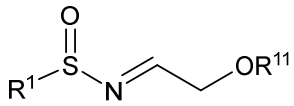
(14A);

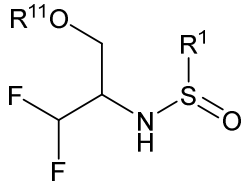
and

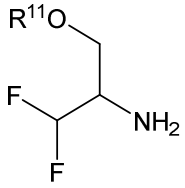
(c) reacting the compound of Formula (14A) with magnesium in the presence of an acetate buffer to thereby form the compound of Formula (8A).

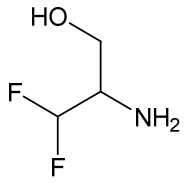
In some of these examples, the process further comprises the step of: (a) reacting a compound of Formula (11A): , with a sulfonamide compound of Formula (3A):

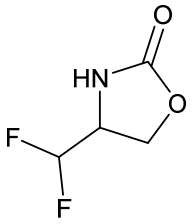

, in the presence of a dehydrating reagent to form the compound of Formula (12A):

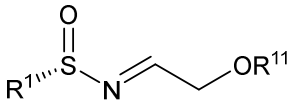

, wherein R^1 and R^{11} are as defined above. In some examples, the process further comprises the step of: (d) reacting the compound of Formula (8A):

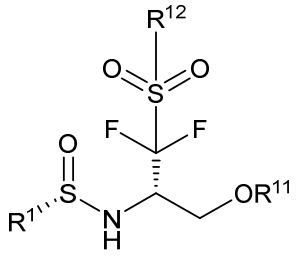

, or a salt thereof, with an acid to yield an amine compound of


Formula (9A): , or an acid addition salt thereof, wherein R^1 and R^{11} are as defined above. In some examples, the process further comprises the steps of: (e) removing the hydroxyl protecting group of the compound of Formula (9A) to form a compound of Formula (9-1):

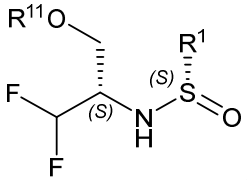

, or an acid addition salt thereof; and (f) reacting the compound of Formula (9-1), or an acid addition salt thereof, with an acylating reagent to form a compound of Formula (10-1):

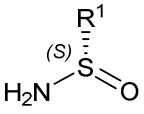
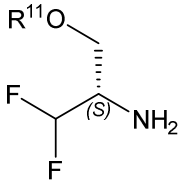

. In some of these examples, the compound of Formula (12A) is of Formula (12B):

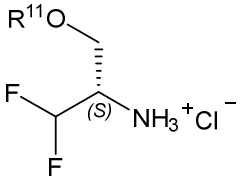

, the compound of Formula (14A) is of Formula (14B):

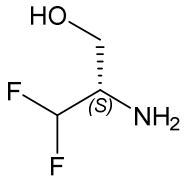
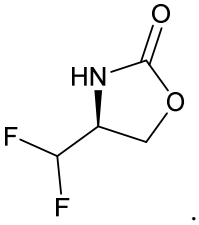


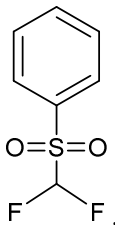
, and the compound of Formula (8A) is of Formula (8B):

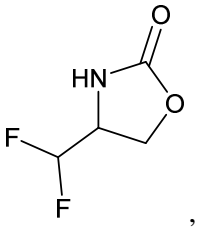
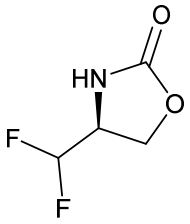
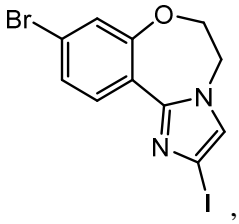
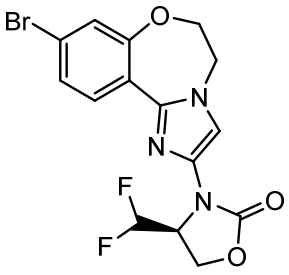


, or a salt thereof, wherein R^1, R^{11}, and R^{12} are as defined above. In some examples, where applicable, the compound of Formula (3A) is of Formula (3B): , wherein R^1 is as defined above. In some examples, where applicable, the compound of Formula (9A) is of Formula (9B): , or a salt thereof, wherein R^{11} is as defined above. In some examples, where applicable, the acid in step (d) is HCl and the acid addition salt of the compound of Formula (9A) or (9B) is a hydrochloride salt having the structure (9C):

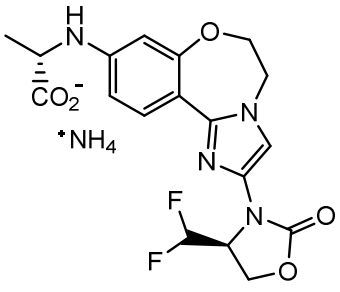


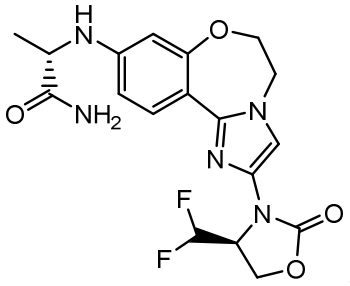
. In some examples, where applicable, the compound of Formula (9-1) is of Formula (9-3): , or the acid addition salt thereof; and the compound of Formula (10-1) is of Formula (10-2): . In some examples, R^1 is *tert*-butyl. In some examples, R^{11} is benzyl. In some examples, R^{12} is phenyl, and the compound of

Formula (13A) has the structure (13):  . In some examples, the base in step (b) is NaHMDS, and step (b) is performed at a temperature of about -70 °C. In some examples, the acetate buffer in step (c) comprises HOAc and NaOAc. In some examples, the dehydrating reagent in step (a) comprises $CuSO_4$.

In some of these examples, the process further comprises reacting a compound of Formula (10-1) having the structures:  , or Formula (10-2) having the structures:  ; with compound **15**, having the structure:  , a copper salt and a ligand to form compound **16**, having the structure:  . In some of these examples, the copper salt is copper(II) acetate. In some of these examples, the copper salt is copper (I) iodide. In some examples, the ligand is *trans*-*N*,*N*-dimethylcyclohexane-1,2-diamine.

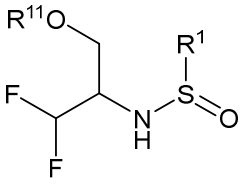
In some of these examples, the process further comprises reacting compound **16** with (*S*)-2-aminopropanoic acid and a copper (I) catalyst to form compound **17**, having the structure:



. In some examples, the copper (I) catalyst is copper(I) oxide. In some of these examples, the process further comprises reacting compound **17** with ammonia (or an ammonia equivalent) and a peptide coupling reagent to form compound **18**, having the structure: 

.

In yet another example, provided is a process for the preparation of a compound of Formula (8A):



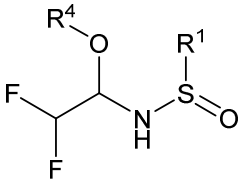
(8A), or a salt thereof,

wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and

R^{11} is a hydroxyl protecting group, the process comprising the steps of:

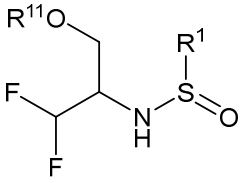
(ii) reacting a compound of Formula (4A):



(4A), or a salt thereof,

wherein R^4 is an optionally substituted C_{1-6} alkyl or hydrogen;

with a Grignard reagent, to thereby prepare the compound having formula (8-A). In some of these examples, the Grignard reagent is prepared by reacting iodomethyl pivalate with *sec*-butylmagnesium chloride. In one aspect, provided is a process of preparing a compound of Formula (8A):



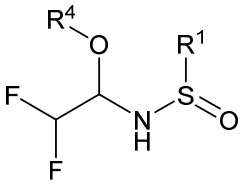
(8A), or a salt thereof,

wherein:

R^1 is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{3-14} cycloalkyl, or an optionally substituted C_{6-14} aryl; and

R^{11} is a hydroxyl protecting group, the process comprising the steps of:

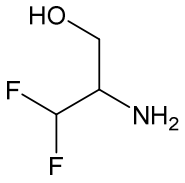
(ii) reacting a compound of Formula (4A):



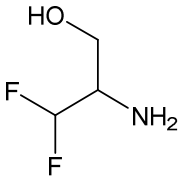
(4A), or a salt thereof,

wherein R^4 is an optionally substituted C_{1-6} alkyl or hydrogen;

with a Grignard reagent, to thereby prepare the compound having formula (8-A). In some examples, the process further comprises a step of

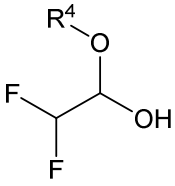
(iii) hydrolyzing the compound having formula (8-A) using an acid to thereby yield an amine compound of Formula (9-1):  , or an acid addition salt thereof.

In another example, provided is a process for the preparation of a compound of Formula (9-1):

 (9-1), or an acid addition salt thereof;

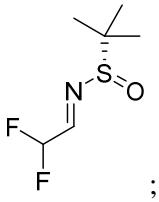
the process comprising:

(i) reacting a compound of Formula (2A):

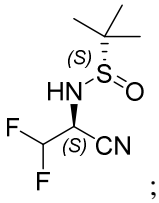
 (2A), or a salt thereof;

wherein R^4 is an optionally substituted C_{1-6} alkyl or hydrogen;

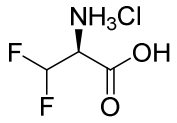
with (S)-2-methylpropane-2-sulfinamide to thereby prepare (S,E)-N-(2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide having structure:

 ;

(ii) reacting (S,E)-N-(2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide with trimethylsilyl-cyanide to give the aminonitrile (S)-N-((S)-1-cyano-2,2-difluoroethyl)-2-methylpropane-2-sulfinamide having the structure:

 ;

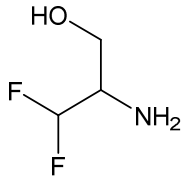
(iii) hydrolyzing (S)-N-((S)-1-cyano-2,2-difluoroethyl)-2-methylpropane-2-sulfinamide in acid to give the product (S)-2-(chloro-λ^5-azaneyl)-3,3-difluoropropanoic acid:



; and

(iv) reducing (S)-2-(chloro-λ^5-azaneyl)-3,3-difluoropropanoic acid to provide the intermediate compound of Formula (9-1) or the acid addition salt thereof.

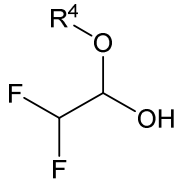
In one aspect, provided is a process for preparing a compound of Formula (9-1):



(9-1), or an acid addition salt thereof;

the process comprising:

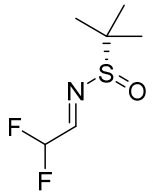
(i) reacting a compound of Formula (2A)



(2A), or a salt thereof;

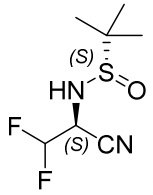
wherein R^4 is an optionally substituted $C_{1\text{-}6}$ alkyl or hydrogen;

with (S)-2-methylpropane-2-sulfinamide to thereby prepare (*S*,*E*)-N-(2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide having structure:



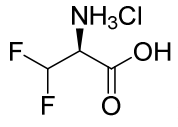
;

(ii) reacting (*S*,*E*)-N-(2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide with trimethylsilyl-cyanide to give the aminonitrile (S)-N-((S)-1-cyano-2,2-difluoroethyl)-2-methylpropane-2-sulfinamide having the structure:



;

(iii) hydrolyzing (S)-N-((S)-1-cyano-2,2-difluoroethyl)-2-methylpropane-2-sulfinamide in acid to give the product (S)-2-(chloro-λ^5-azaneyl)-3,3-difluoropropanoic acid:



; and

(iv) reducing (S)-2-(chloro-λ^5-azaneyl)-3,3-difluoropropanoic acid to provide the intermediate compound of Formula (9-1) or the acid addition salt thereof.

Compounds of Formulae (7A) and (8A) are useful intermediates for the synthesis of 4-(difluoromethyl)oxazolidin-2-one, which is a key building block in the synthesis of a variety of compounds such as (*S*)-2-((2-((*S*)-4-(difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[*f*]imidazo[1,2-d][1,4]oxazepin-9-yl)amino)propanamide (inavolisib). The process of making 4-(difluoromethyl)oxazolidin-2-one is highly complex because of being a small chiral molecule with a challenging difluoromethyl group. Provided herein are efficient processes for making (*S*)-4-(difluoromethyl)oxazolidin-2-one with high stereo-specificity and optical purity. Also provided is a process of making inavolisib using the (*S*)-4-(difluoromethyl)oxazolidin-2-one product as a key intermediate.

DETAILED DESCRIPTIONS OF THE INVENTION

Definitions

The articles “a” and “an” are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise. The use of the term "or" is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

As used herein, the term “about” is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value. In certain embodiments, the term “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of a stated value, unless otherwise stated or otherwise evident from the context (e.g., where such number would exceed 100% of a possible value).