METHODS OF SYNTHESIZING A PROSTACYCLIN ANALOG

CROSS REFERENCE TO RELATED APPLICATION

[0001] This PCT application claims the benefit of U.S. provisional application serial nos. 61/734,672, filed December 7, 2012, and 61/777,882, filed on March 12, 2013. Both of these documents are hereby incorporated by reference in their entireties.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to processes and intermediates for the preparation of prostacyclin analog that are useful for treating hypertension and other diseases.

BACKGROUND

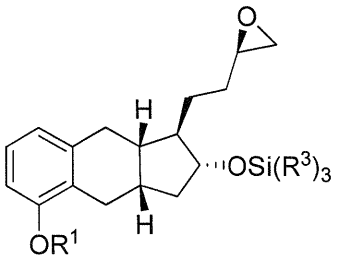
[0003] Prostacyclin derivatives and analogs are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, vasodilation, and bronchodilation.

[0004] Treprostinil is a synthetic prostacyclin derivative currently marketed as an active pharmaceutical ingredient (API) for its ability to inhibit pulmonary arterial hypertension under the trade name Remodulin®. Treprostinil was first described in U.S. patent no. 4,306,075.

[0005] Prostacyclin derivatives are traditionally synthesized using a variety of methods that are described in *J. Org. Chem.* **2004**, *69*, 1890-1902, *Drug of the Future*, **2001**, *26(4)*, 364-374, U.S. patent nos. 4,306,075; 6,441,245; 6,528,688; 6,700,025; 6,765,117; 6,809,223 and U.S. patent application publication nos. 2009/0163738, 2011/0319641 A1, as well as Canadian patent application publication no. 2710726 A1. The entire teachings of these documents are incorporated herein by reference in their entireties. Also disclosed in these publications are processes and intermediates useful for the preparation of Treprostinil. However, the methods of these teachings suffer from one or more problems including toxic oxidation reagents, reduced yields, elevated levels of impurities, poor scalability, and numerous chromatography steps to purify intermediates and final products. Thus, there remains a need for safe, scalable, efficient, and economical processes for the preparation of Treprostinil.

SUMMARY

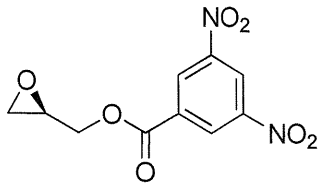
[0005a] In one aspect of the present disclosure, there is provided a compound of Formula **21**



21

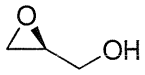
wherein R^1 is C_{1-6} alkyl and each R^3 is independently C_{1-6} alkyl or phenyl.

[0005b] In another aspect of the present disclosure, there is provided a compound of Formula **1a**



1a

[0005c] In a further aspect of the present disclosure, there is provided a method of purifying a compound of Formula **1** comprising:



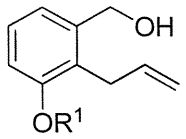
1

xxx) reacting a compound of Formula **1** with a derivatizing reagent to generate a precipitate that is substantially insoluble in dichloromethane or mixtures thereof;

xxxi) collecting the precipitate and refluxing the precipitate in a solvent comprising an alcohol to generate the compound of Formula **1** having a chemical purity of about 98% or greater and an e.e. of about 98% or greater;

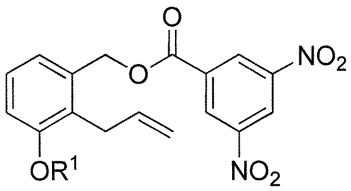
wherein the method excludes the use of any column chromatography.

[0005d] In another aspect of the present disclosure, there is provided a method of purifying a compound of Formula **9** comprising:



9

xl) reacting a compound of Formula **9**, wherein R^1 is C_{1-6} alkyl, with 3,5-dinitrobenzoyl chloride to generate a precipitate comprising a compound of Formula **9A**; and

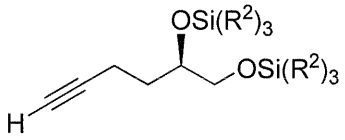


9A

xli) collecting the precipitate and treating the precipitate with a base in the presence of an alcohol to generate the compound of Formula **9** having a chemical purity of about 95% or greater;

wherein the method excludes the use of any column chromatography.

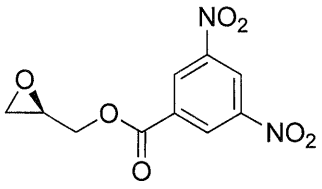
[0005e] In a further aspect of the present disclosure, there is provided a method of generating a compound of Formula **5**



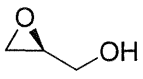
5

wherein each R^2 is independently selected from a C_{1-6} alkyl or phenyl, comprising

iv) refluxing the compound of Formula **1a** in the presence of methanol to generate a compound of Formula **1** having an e.e. of greater than about 98%;

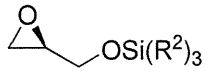


1a



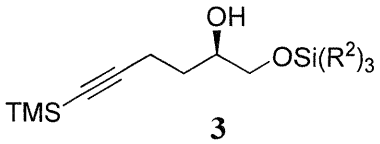
1

v) reacting the compound of Formula **1** with $SiCl(R^2)_3$, wherein each R^2 is independently selected from C_{1-6} alkyl or phenyl, under basic conditions to generate the compound of Formula **2**;



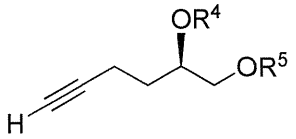
2

vi) reacting the compound of Formula **2** with 1-TMS-1-propyne to generate the compound of Formula **3**;



3

l) deprotecting the compound Formula **3** under basic condition to generate a compound of Formula **4**, wherein each of R^4 and R^5 are H or $-OSi(R^2)_3$; and

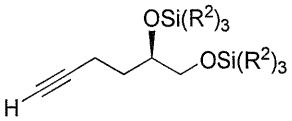


4

li) reacting the compound of Formula **4** with $SiCl(R^2)_3$ under basic conditions to generate the compound of Formula **5**,

wherein the compound of Formula **5** has a chemical purity of about 98% or greater and an e.e. of about 98% or greater.

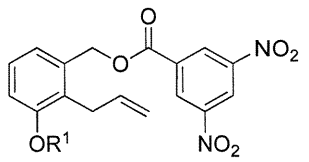
[0005f] In another aspect of the present disclosure, there is provided a compound of Formula **5**



5

wherein each of R^2 is independently selected from a C_{1-6} alkyl or phenyl.

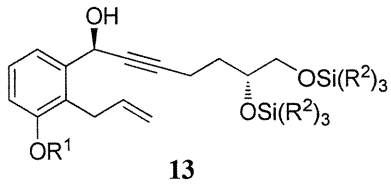
[0005g] In a further aspect of the present disclosure, there is provided a compound of Formula **9a**



9A

wherein R^1 is C_{1-6} alkyl.

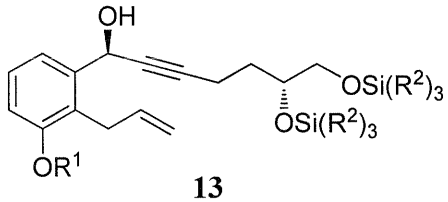
[0005h] In another aspect of the present disclosure, there is provided a compound of Formula **13**



13

wherein R^1 is C_{1-6} alkyl and each R^2 is independently selected from C_{1-6} alkyl or phenyl.

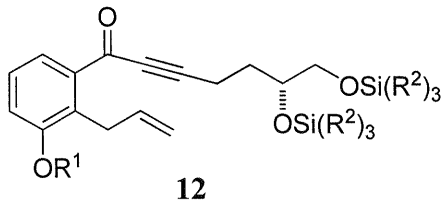
[0005i] In another aspect of the present disclosure, there is provided a method of generating a compound of Formula **13**



13

wherein R^1 is C_{1-6} alkyl and each R^2 is independently selected from C_{1-6} alkyl or phenyl, comprising

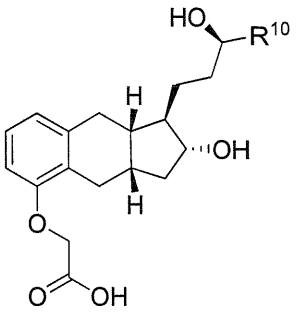
x) reacting a compound of Formula **12** with (R)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-c][1,3,2]oxazaborole in the presence of an organic solvent comprising THF and toluene to generate a compound of Formula **13**



12

wherein the compound of Formula **13** has a chemical purity of about 97% or greater and a d.e. of about 97% or greater.

[0006] As described herein, the present disclosure provides processes for preparing a prostacyclin analogue of Formula **IA**:

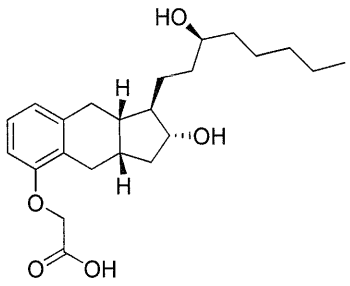


IA

or a pharmaceutically acceptable salt thereof, wherein R^{10} is a linear or branched C_{1-6} alkyl.

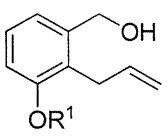
[0007] The processes of the present disclosure comprise steps that generate improved yields and fewer byproducts than traditional methods. The processes of the present disclosure employ reagents (e.g., the oxidizing reagent) that are less toxic that those used in the traditional methods (e.g., oxalyl chloride). Many of the processes of the present disclosure do not require additional chromatography for purification of intermediates and generate intermediates with improved e.e. and chemical purity. And, the processes of the present disclosure are scalable to generate commercial quantities of the final compound.

[0008] The present disclosure provides a method of generating a compound of Formula **I**

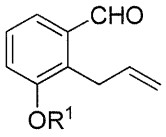


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **i)** reacting a compound of Formula **9** with an oxidizing agent in the presence of an organic solvent to generate a compound of Formula **10**

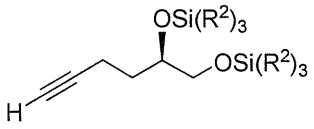


9

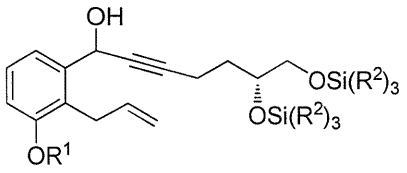


10

wherein R^1 is C_{1-6} alkyl and the oxidizing agent comprises MnO_2 or Dess-Martin periodinane; **ii)** reacting the compound of Formula **10** with a compound of Formula **5** in the presence of a base and an organic solvent to generate a compound of Formula **11**, wherein each R^2 is independently selected from C_{1-6} alkyl or phenyl; and



5



11

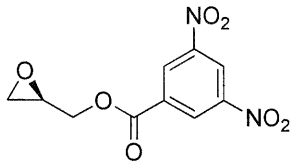
iii) converting the compound of Formula **11** to the compound of Formula **I**.

[0009] In some implementations, the organic solvent of step **i)** comprises a halogenated organic solvent. For example, the organic solvent of step **i)** comprises dichloromethane, chloroform, or any combination thereof.

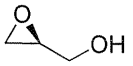
[0010] In some implementations, the base of step **ii)** comprises an alkyllithium reagent. For example, the base of step **ii)** comprises *sec*-butyllithium.

[0011] In some implementations, the organic solvent of step **ii)** comprises pentane, hexane, cyclohexane, heptane, tetrahydrofuran, 1,4-dioxane, diethyl ether, petro ether, methyl-*tert*-butylether, or any combination thereof. For example, the organic solvent of step **ii)** comprises methyl-*tert*-butylether.

[0012] Some methods further comprise the steps of: **iv)** refluxing the compound of Formula **1a** in the presence of methanol to generate a compound of Formula **1** having an e.e. of greater than about 98%;

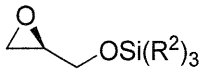


1a



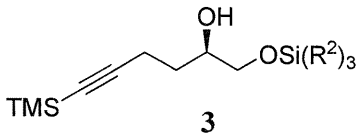
1

v) reacting the compound of Formula **1** with $SiCl(R^2)_3$ under basic conditions to generate the compound of Formula **2**;



2

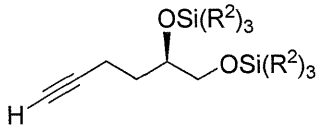
vi) reacting the compound of Formula **2** with 1-TMS-1-propyne to generate the compound of Formula **3**; and



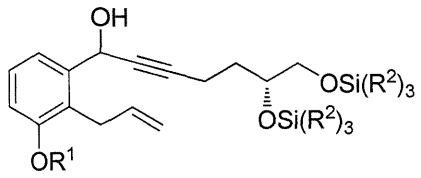
3

vii) converting the compound of Formula **3** to the compound of Formula **5**.

[0013] The present disclosure also provides a method of generating a compound of Formula **I**



5



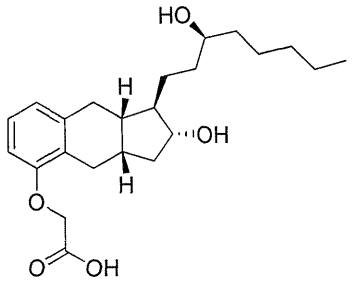
11

in the presence of a base and an organic solvent to generate a compound of Formula **11**.

[0017] In some implementations, the base of step **ii)** comprises an alkyllithium reagent. For example, the alkyllithium reagent of step **ii)** comprises *sec*-butyllithium.

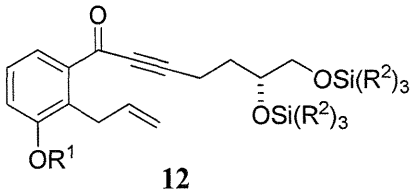
[0018] In some implementations, the organic solvent of step **ii)** comprises pentane, hexane, cyclohexane, heptane, tetrahydrofuran, 1,4-dioxane, diethyl ether, petro ether, methyl-*tert*-butylether, or any combination thereof. For example, the organic solvent of step **ii)** comprises methyl-*tert*-butylether.

[0019] The present disclosure also provides a method of generating a compound of Formula **I**

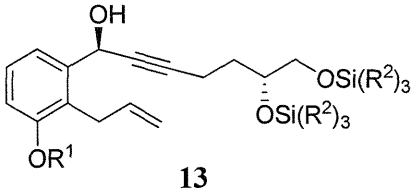


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **x)** reacting a compound of Formula **12** with a reducing agent in the presence of an organic solvent to generate a compound of Formula **13**



12

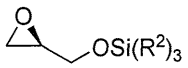


13

wherein the organic solvent comprises THF, R^1 is C_{1-6} alkyl, and each R^2 is independently C_{1-6} alkyl or phenyl; and **xi)** converting the compound of Formula **13** to the compound of Formula **I**.

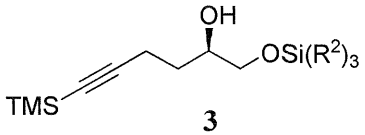
[0020] In some implementations, the reducing agent of step **x)** comprises a chiral borane compound. And, in some examples, the chiral borane compound is selected from (R)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-c][1,3,2]oxazaborole, (R)-3,3-diphenylhexahydropyrrolo[1,2-c][1,3,2]oxazaborole, (R)-1-butyl-3,3-diphenylhexahydropyrrolo[1,2-c][1,3,2]oxazaborole, (R)-tetrahydro-1,3,3-triphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxaborole, (4S)- 2-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine, or any combination thereof.

v) reacting the compound of Formula **1** with $SiCl(R^2)_3$ under basic conditions to generate the compound of Formula **2**;



2

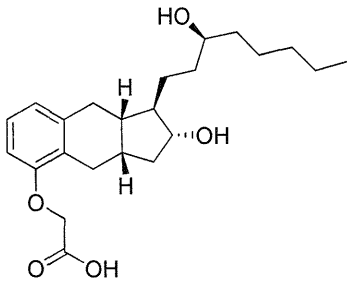
vi) reacting the compound of Formula **2** with 1-TMS-1-propyne to generate the compound of Formula **3**; and



3

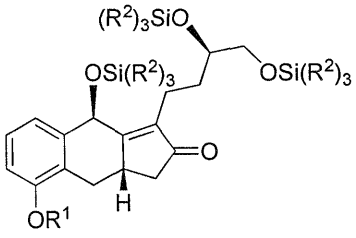
vii) converting the compound of Formula **3** to the compound of Formula **5**.

[0028] The present disclosure also provides a method of generating a compound of Formula **I**

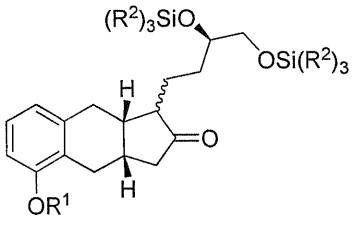


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **xii)** hydrogenating a compound of Formula **15** in the presence of an organic solvent (e.g., an alcohol (e.g., methanol, ethanol, or any combination thereof), an optionally substituted THF (e.g., 2-methyl-THF or THF), EtOAc, or any combination thereof) to generate the compound of Formula **16**



15



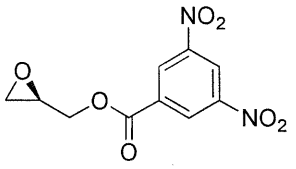
16

wherein R^1 is C_{1-6} alkyl and each R^2 is independently selected from C_{1-6} alkyl or phenyl; and **xiii)** converting the compound of Formula **16** to the compound of Formula **I**.

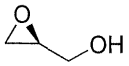
[0029] Some methods further comprise the steps of: **x)** reacting a compound of Formula **12** with a reducing agent in the presence of an organic solvent to generate a compound of Formula **13**

[0035] In some implementations, the organic solvent of step **ii)** comprises pentane, hexane, cyclohexane, heptane, tetrahydrofuran, 1,4-dioxane, diethyl ether, petro ether, methyl-*tert*-butylether, or any combination thereof. For example, the organic solvent of step **ii)** comprises methyl-*tert*-butylether.

[0036] Some methods further comprise the steps of: **iv)** refluxing the compound of Formula **1a** in the presence of methanol to generate a compound of Formula **1** having an e.e. of greater than about 98%;

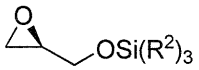


1a



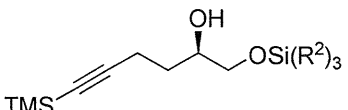
1

v) reacting the compound of Formula **1** with $SiCl(R^2)_3$ under basic conditions to generate the compound of Formula **2**;



2

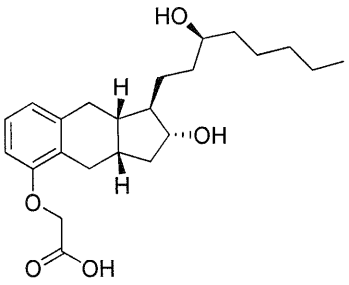
vi) reacting the compound of Formula **2** with 1-TMS-1-propyne to generate the compound of Formula **3**; and



3

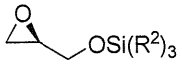
vii) converting the compound of Formula **3** to the compound of Formula **5**.

[0037] The present disclosure also provides a method of generating a compound of Formula **I**



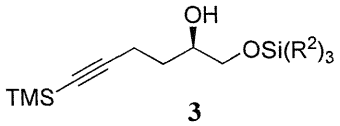
I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **xv)** reacting a compound of Formula **21** with n-butyllithium in the presence of an organic solvent and a transition metal catalyst to generate a compound of Formula **22**



2

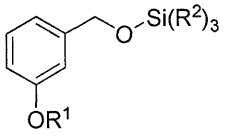
vi) reacting the compound of Formula **2** with 1-TMS-1-propyne to generate the compound of Formula **3**; and



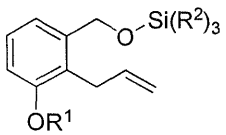
3

vii) converting the compound of Formula **3** to the compound of Formula **5**.

[0051] Some methods further comprise the steps of: **xxii)** reacting a compound of Formula **7** with a 3-haloprop-1-ene in the presence of a base and an organic solvent to generate a compound of Formula **8**; and



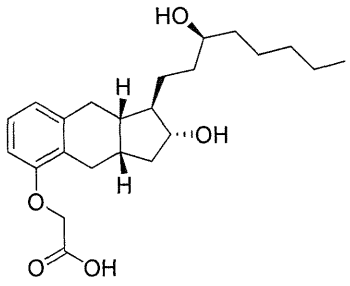
7



8

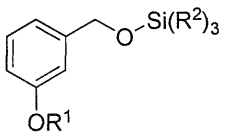
xxiii) deprotecting the compound of Formula **8** to generate the compound of Formula **9**.

[0052] The present disclosure also provides a method of generating a compound of Formula **I**

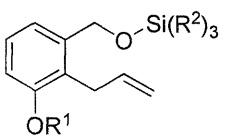


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **xxii)** reacting a compound of Formula **7**, wherein R^1 is C_{1-6} alkyl and each R^2 is independently selected from C_{1-6} alkyl or phenyl, with a 3-haloprop-1-ene in the presence of a base and an organic solvent to generate a compound of Formula **8**;

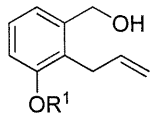


7



8

xxiii) deprotecting the compound of Formula **8** to generate the compound of Formula **9**, and

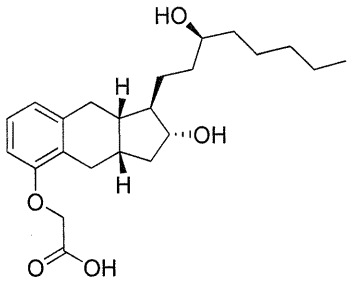


9

xxiv) converting the compound of Formula **9** to the compound of Formula **I,**

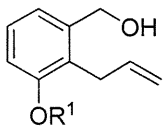
wherein the base of step **xxii)** comprises sec-butyl lithium.

[0053] The present disclosure also provides a method of generating a compound of Formula **I**

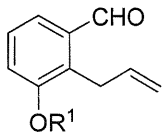


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **i)** reacting a compound of Formula **9** with an oxidizing agent in the presence of an organic solvent to generate a compound of Formula **10**

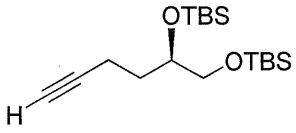


9

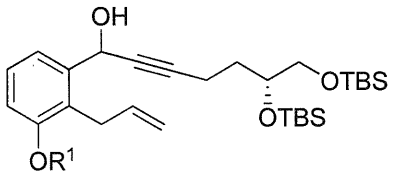


10

wherein R^1 is $C_{1\text{-}6}$ alkyl and the oxidizing agent comprises MnO_2 or Dess-Martin periodinane; **ii)** reacting the compound of Formula **10** with a compound of Formula **5a** in the presence of a base and an organic solvent to generate a compound of Formula **11a**; and



5a



11a

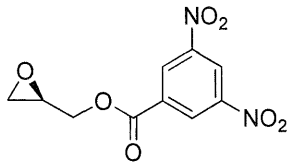
iii) converting the compound of Formula **11a** to the compound of Formula **I.**

[0054] In some implementations, the organic solvent of step **i)** comprises a halogenated organic solvent. For example, the organic solvent of step **i)** comprises dichloromethane, chloroform, or any combination thereof.

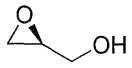
[0055] In some implementations, the base of step **ii)** comprises an alkyllithium reagent. For example, the base of step **ii)** comprises *sec*-butyllithium.

[0056] In some implementations, the organic solvent of step **ii)** comprises pentane, hexane, cyclohexane, heptane, tetrahydrofuran, 1,4-dioxane, diethyl ether, petro ether, methyl-*tert*-butylether, or any combination thereof. For example, the organic solvent of step **ii)** comprises methyl-*tert*-butylether.

[0057] Some methods further comprise the steps of: **iv)** refluxing the compound of Formula **1a** in the presence of methanol to generate a compound of Formula **1** having an e.e. of greater than about 98%;

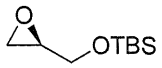


1a



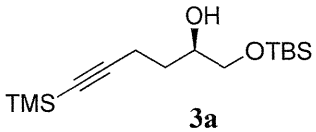
1

v) reacting the compound of Formula **1** with TBSCl under basic conditions to generate the compound of Formula **2a**;



2a

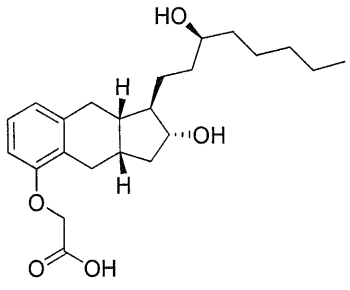
vi) reacting the compound of Formula **2a** with 1-TMS-1-propyne to generate the compound of Formula **3a**; and



3a

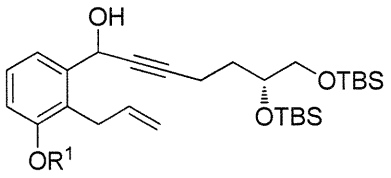
vii) converting the compound of Formula **3a** to the compound of Formula **5a**.

[0058] The present disclosure also provides a method of generating a compound of Formula **I**

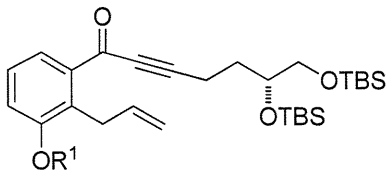


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **viii)** reacting a compound of Formula **11a** with an oxidizing agent in the presence of an organic solvent to generate a compound of Formula **12a**



11a

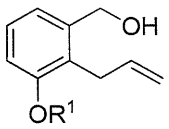


12a

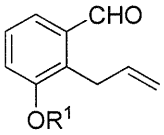
wherein R^1 is $C_{1\text{-}6}$ alkyl and the oxidizing agent comprises MnO_2; and **ix)** converting the compound of Formula **12a** to the compound of Formula **I**.

[0059] In some implementations, the organic solvent of step **viii)** comprises a halogenated organic solvent. For example, the halogenated organic solvent of step **viii)** comprises dichloromethane, chloroform, or any combination thereof.

[0060] Some methods further comprise the steps of: **i)** reacting a compound of Formula **9** with an oxidizing agent in the presence of an organic solvent to generate a compound of Formula **10**

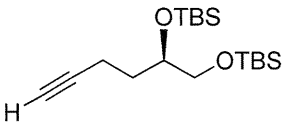


9

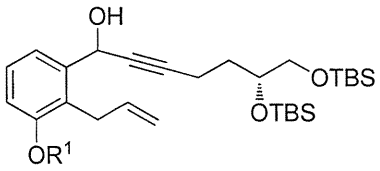


10

wherein the oxidizing agent comprises MnO_2 or Dess-Martin periodinane; and **ii)** reacting the compound of Formula **10** with a compound of Formula **5a**



5a



11a

in the presence of a base and an organic solvent to generate a compound of Formula **11a**.

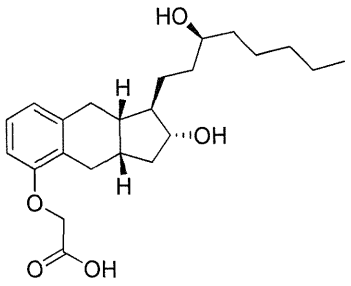
[0061] In some implementations, the organic solvent of step **i)** comprises a halogenated organic solvent. For example, the organic solvent of step **i)** comprises dichloromethane, chloroform, or any combination thereof.

[0062] In some implementations, the base of step **ii)** comprises an alkyllithium reagent. For example, the base of step **ii)** comprises *sec*-butyllithium.

[0063] In some implementations, the organic solvent of step **ii)** comprises pentane, hexane, cyclohexane, heptane, tetrahydrofuran, 1,4-dioxane, diethyl ether, petro ether, methyl-*tert*-butylether, or any combination thereof. For example, the organic solvent of step **ii)** comprises methyl-*tert*-butylether.

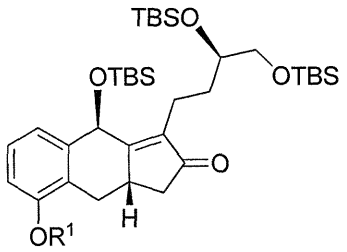
[0064] The present disclosure also provides a method of generating a compound of Formula **I**

[0074] The present disclosure also provides a method of generating a compound of Formula **I**

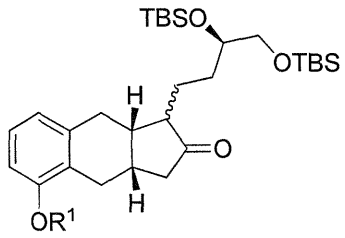


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **xii)** hydrogenating a compound of Formula **15a** in the presence of an organic solvent (e.g., an alcohol (e.g., methanol, ethanol, or any combination thereof), an optionally substituted THF (e.g., 2-methyl-THF or THF), EtOAc, or any combination thereof) to generate the compound of Formula **16a**



15a

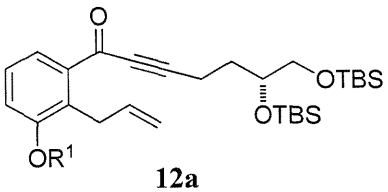


16a

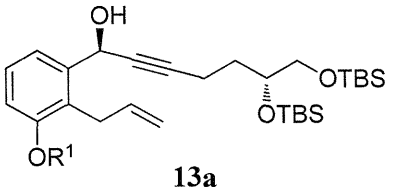
wherein R^1 is C_{1-6} alkyl; and **xiii)** converting the compound of Formula **16a** to the compound of Formula **I**.

[0075] In some implementations, the hydrogenation of the compound of Formula **15a** also occurs in the presence of a base (e.g., potassium carbonate or potassium bicarbonate).

[0076] Some methods further comprise the steps of: **x)** reacting a compound of Formula **12a** with a reducing agent in the presence of an organic solvent to generate a compound of Formula **13a**



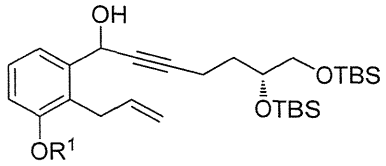
12a



13a

wherein the organic solvent comprises THF; and **xiv)** converting the compound of Formula **13a** to the compound of Formula **15a**.

[0077] Some methods further comprise the steps of: **viii)** reacting a compound of Formula **11a** with an oxidizing agent to generate the compound of Formula **12a**, wherein the oxidizing agent comprises MnO_2



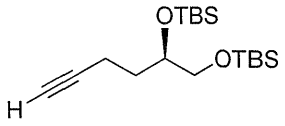
11a

[0078] Some methods further comprise the steps of: **i)** reacting a compound of Formula **9** with an oxidizing agent to generate a compound of Formula **10**; and



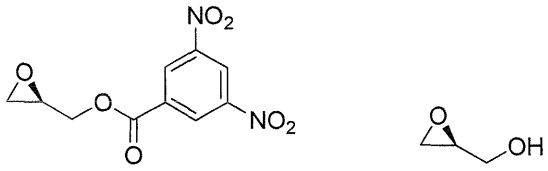
9 **10**

ii) reacting the compound of Formula **10** with a compound of Formula **5a** in the presence of a base and an organic solvent to generate a compound of Formula **11a**



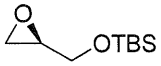
5a

[0079] Some methods further comprise the steps of: **iv)** refluxing the compound of Formula **1a** in the presence of methanol to generate a compound of Formula **1** having an e.e. of greater than about 98%;



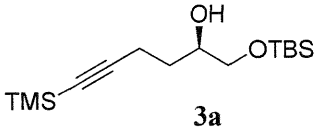
1a **1**

v) reacting the compound of Formula **1** with TBSCl under basic conditions to generate the compound of Formula **2a**;



2a

vi) reacting the compound of Formula **2a** with 1-TMS-1-propyne to generate the compound of Formula **3a**; and

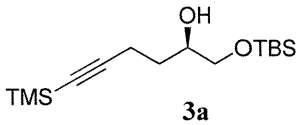


3a

vii) converting the compound of Formula **3a** to the compound of Formula **5a**.

[0080] The present disclosure also provides a method of generating a compound of Formula **I**

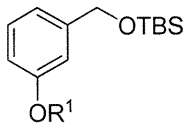
vi) reacting the compound of Formula **2a** with 1-TMS-1-propyne to generate the compound of Formula **3a**; and



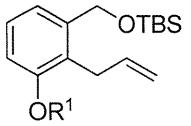
3a

vii) converting the compound of Formula **3a** to the compound of Formula **5a**.

[0091] Some methods further comprise the steps of: **xxii)** reacting a compound of Formula **7a** with a 3-haloprop-1-ene in the presence of a base and an organic solvent to generate a compound of Formula **8a**; and



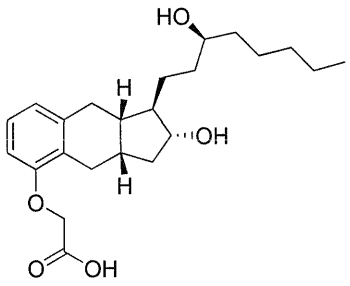
7a



8a

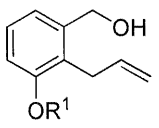
xxiii) deprotecting the compound of Formula **8a** to generate the compound of Formula **9**.

[0092] The present disclosure also provides a method of generating a compound of Formula **I**

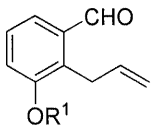


I

or a pharmaceutically acceptable salt thereof, comprising the steps of: **i)** reacting a compound of Formula **9** with an oxidizing agent to generate a compound of Formula **10**;

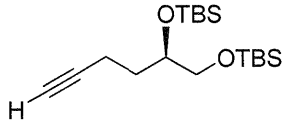


9

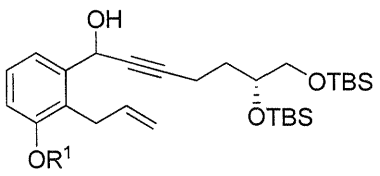


10

ii) reacting the compound of Formula **10** with a compound of Formula **5a** in the presence of a base and an organic solvent to generate a compound of Formula **11a**;

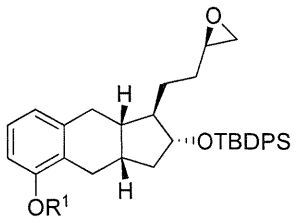


5a



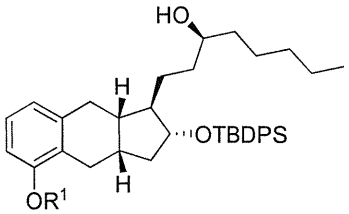
11a

xviii) reacting the compound of Formula **20a** with methanol under basic conditions to generate the compound of Formula **21a**;



21a

xv) reacting a compound of Formula **21a** with n-butyllithium in the presence of an organic solvent and a transition metal catalyst to generate a compound of Formula **22a**; and

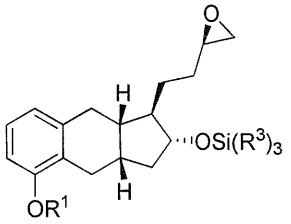


22a

xvi) converting the compound of Formula **22a** to the compound of Formula **I.**

[0093] Some methods further comprise the step of: **xxiv)** reacting the compound of Formula **I** with diethanolamine in the presence of an organic solvent to generate the diethanolamine salt of the compound of Formula **I.**

[0094] The present disclosure also provides a compound of Formula **21**

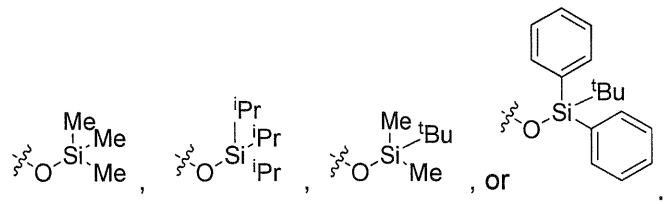


21

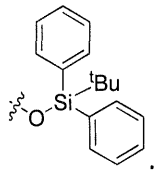
wherein R^1 is $C_{1\text{-}6}$ alkyl and each R^3 is independently $C_{1\text{-}6}$ alkyl or phenyl.

[0095] In some embodiments, R^1 is methyl, ethyl, propyl, *iso*-propyl, butyl, *sec*-butyl, or *tert*-butyl.

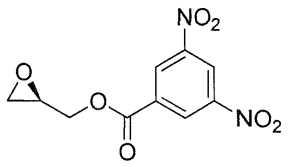
[0096] In other embodiments, the $-OSi(R^3)_3$ group is selected from



[0097] In some embodiments, R^1 is methyl and the $-OSi(R^3)_3$ group is

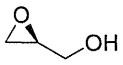


[0098] The present disclosure also provides a compound of Formula **1a**



1a

[0099] The present disclosure also provides a method of purifying a compound of Formula **1**

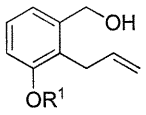


1

comprising the steps of: **xxx)** reacting a compound of Formula **1** with a derivatizing reagent to generate a precipitate that is substantially insoluble in dichloromethane or mixtures thereof (e.g., a mixture of dichloromethane and an alkane (e.g., heptane)); **xxxi)** collecting the precipitate and refluxing the precipitate in a solvent comprising an alcohol to generate the compound of Formula **1** having a chemical purity of about 98% or greater and an e.e. of about 98% or greater; wherein the method excludes the use of any column chromatography.

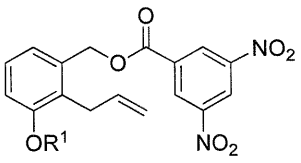
[0100] In some implementations, the derivitizing reagent comprises 3,5-dinitrobenzoyl chloride and the alcohol comprises methanol.

[0101] The present disclosure also provides a method of purifying a compound of Formula **9**



9

comprising the steps of: **xl)** reacting a compound of Formula **9**, wherein R^1 is $C_{1\text{-}6}$ alkyl, with 3,5-dinitrobenzoyl chloride to generate a precipitate comprising a compound of Formula **9A**; and



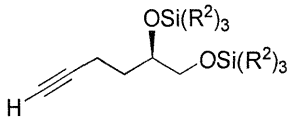
9A

xli) collecting the precipitate and treating the precipitate with a base in the presence of an alcohol to generate the compound of Formula **9** having a chemical purity of about 95% or greater (e.g.,

about 98% or greater, or from about 95% to about 99.9%); wherein the method excludes the use of any column chromatography.

[0102] Some methods further comprise the step of: **xlii)** recrystallizing the precipitate of step **xli)**.

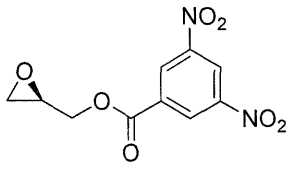
[0103] The present disclosure also provides a method of generating a compound of Formula **5**



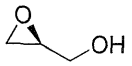
5

wherein each of R^2 is independently selected from a C_{1-6} alkyl or phenyl, comprising the steps of:

iv) refluxing the compound of Formula **1a** in the presence of methanol to generate a compound of Formula **1** having an e.e. of greater than about 98%;

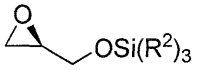


1a



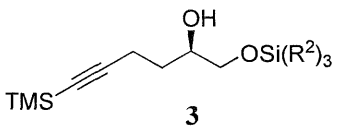
1

v) reacting the compound of Formula **1** with $SiCl(R^2)_3$, wherein each R^2 is independently selected from C_{1-6} alkyl or phenyl, under basic conditions to generate the compound of Formula **2**;



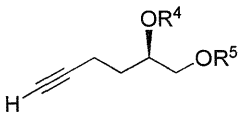
2

vi) reacting the compound of Formula **2** with 1-TMS-1-propyne to generate the compound of Formula **3**;



3

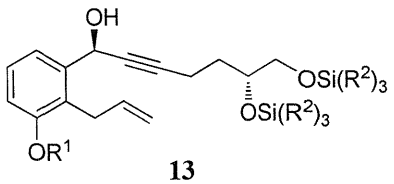
l) deprotecting the compound Formula **3** under basic condition to generate a compound of Formula **4**, wherein each of R^4 and R^5 are H or $-OSi(R^2)_3$; and



4

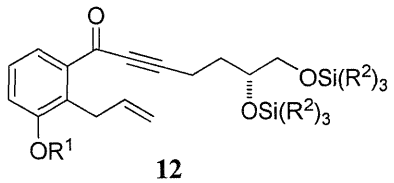
li) reacting the compound of Formula **4** with $SiCl(R^2)_3$ under basic conditions to generate the compound of Formula **5**, wherein the compound of Formula **5** has a chemical purity of about 98% or greater and an e.e. of about 98% or greater (e.g., from about 99% to about 99.99%).

[0104] The present disclosure also provides a method of generating a compound of Formula **13**



13

wherein R^1 is C_{1-6} alkyl and each R^2 is independently selected from C_{1-6} alkyl or phenyl, comprising the step of: **x)** reacting a compound of Formula **12** with (R)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-c][1,3,2]oxazaborole in the presence of an organic solvent comprising THF and toluene to generate a compound of Formula **13**

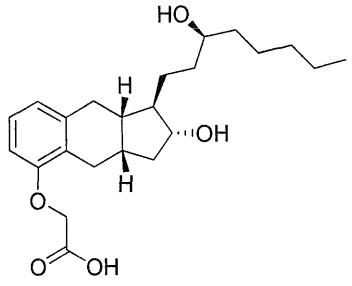


12

wherein the compound of Formula **13** has a chemical purity of about 97% or greater and a d.e. of about 97% or greater.

DETAILED DESCRIPTION OF THE INVENTION

[0105] The present invention provides a method of generating a compound of Formula **I**



I

or a pharmaceutically acceptable salt thereof.

[0106] The present invention also provides novel intermediates that are useful for the synthesis of the compound of Formula **I**.

[0107] I. DEFINITIONS

[0108] As used herein, the following definitions shall apply unless otherwise indicated.

[0109] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry",