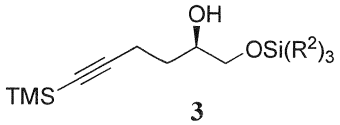


2

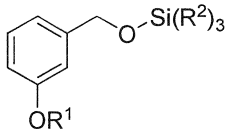
vi) reacting the compound of Formula **2** with 1-TMS-1-propyne to generate the compound of Formula **3**; and



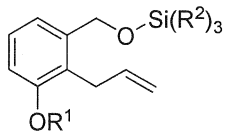
3

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



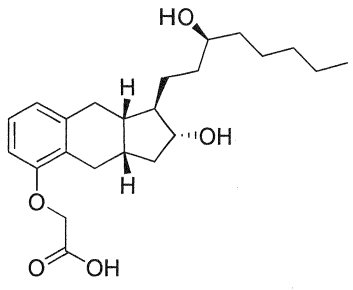
7



8

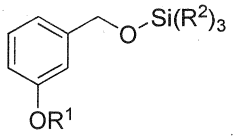
xxiii) deprotecting the compound of Formula **8** to generate the compound of Formula **9**.

[0052] ~~Another aspect of t~~The present disclosure further provides a method of generating a compound of Formula **I**

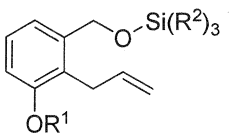


I

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**;

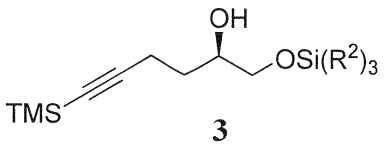


7



8

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

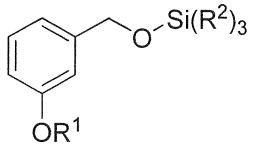


3

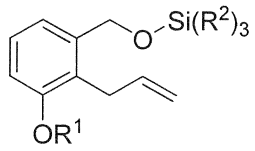
vii) converting the compound of Formula **3** to the compound of Formula **5**.

60. The method of claim 59, further comprising 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



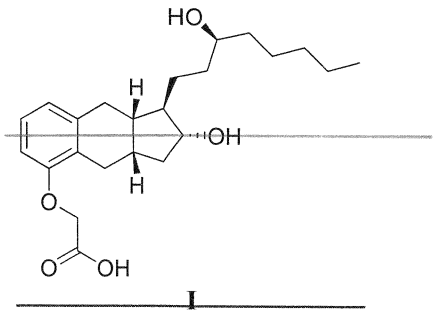
7



8

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

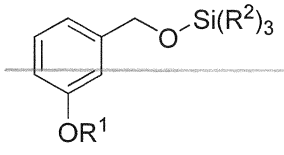
~~61. A method of generating a compound of Formula I~~



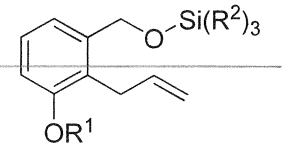
~~I~~

~~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;~~

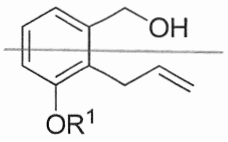


~~7~~



~~8~~

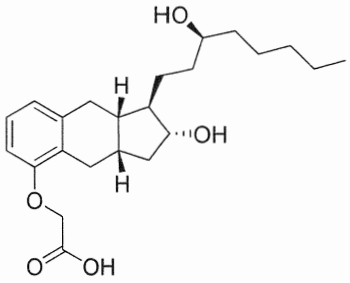
~~**xxiii)** deprotecting the compound of Formula 8 to generate the compound of Formula 9, and~~



~~9~~

~~xxiv) converting the compound of Formula 9 to the compound of Formula I, wherein the base of step xxii) comprises sec-butyl lithium.~~

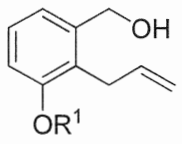
~~62~~61. A method of generating a compound of Formula **I**



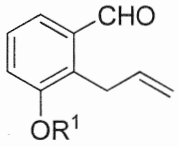
I

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**



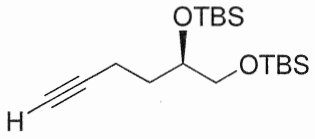
9



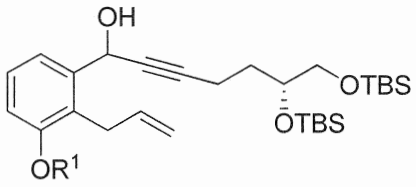
10

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**.

~~63~~62. The method of claim ~~62~~61, wherein the organic solvent of step **i)** comprises a halogenated organic solvent.

6463. The method of claim 6362, wherein the halogenated organic solvent comprises dichloromethane, chloroform, or any combination thereof.

6564. The method of claim 6261, wherein the base of step **ii)** comprises an alkyllithium reagent.

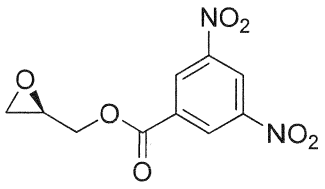
6665. The method of claim 6564, wherein the alkyllithium reagent is *sec*-butyllithium.

6766. The method of claim 6261, wherein 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.

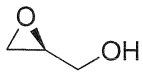
6867. The method of claim 6766, wherein the organic solvent of step **ii)** comprises methyl-*tert*-butylether.

6968. The method of claim 6261, further 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%;

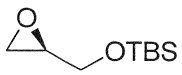


1a



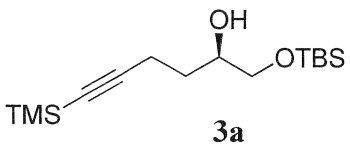
1

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



2a

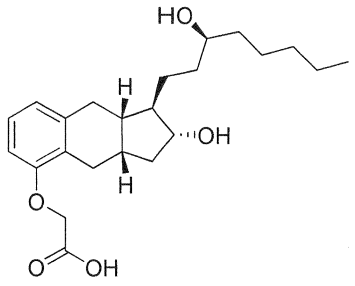
vi) reacting the compound of Formula **2a** with 1-TMS-1-propyne to generate the compound of Formula **3a**; and



3a

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

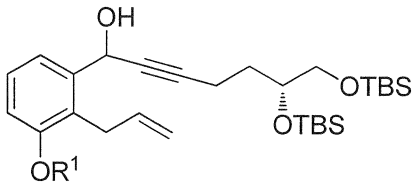
7069. A method of generating a compound of Formula **I**



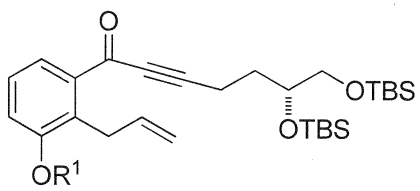
I

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

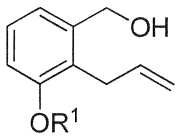
ix) converting the compound of Formula **12a** to the compound of Formula **I**.

~~71~~70. The method of claim ~~70~~69, wherein the organic solvent of step **viii)** comprises a halogenated organic solvent.

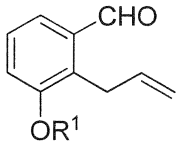
~~72~~71. The method of claim ~~71~~70, wherein the halogenated organic solvent comprises dichloromethane, chloroform, or any combination thereof.

~~73~~72. The method of claim ~~70~~69, further 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**



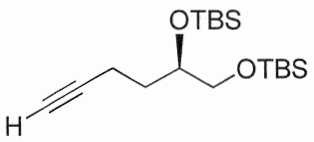
9



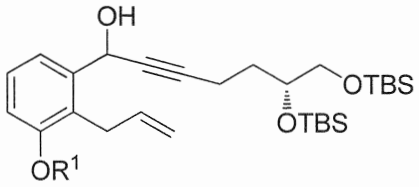
10

wherein 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**.

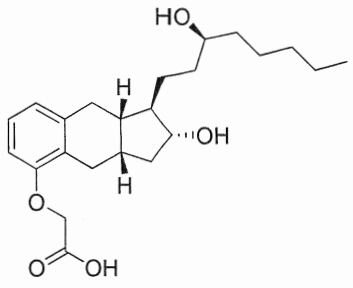
7473. The method of claim ~~73~~72, wherein the base of step **ii)** comprises an alkyllithium reagent.

7574. The method of claim ~~74~~73, wherein the alkyllithium reagent is *sec*-butyllithium.

7675. The method of claim ~~73~~72, wherein 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.

7776. The method of claim ~~76~~75, wherein the organic solvent of step **ii)** comprises methyl-*tert*-butylether.

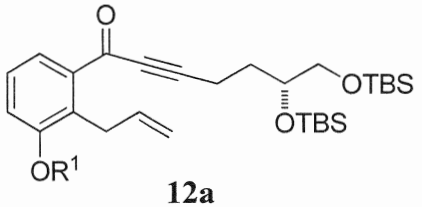
7877. A method of generating a compound of Formula **I**



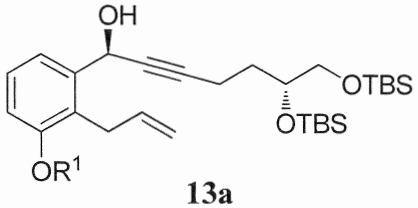
I

or a pharmaceutically acceptable salt thereof, comprising the steps of:

x) reacting a compound of Formula **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, R^1 is C_{1-6} alkyl, and each R^2 is independently selected from C_{1-6} alkyl or phenyl; and

xi) converting the compound of Formula **13** to the compound of Formula **I**.

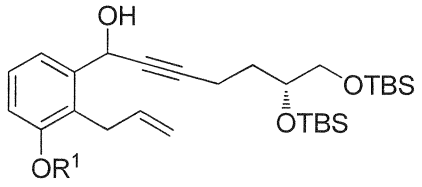
~~79~~78. The method of claim ~~78~~77, wherein the reducing agent of step **x)** comprises a chiral borane compound.

~~80~~79. The method of claim ~~79~~78, wherein 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.

~~81~~80. The method of claim ~~80~~79, wherein the organic solvent of step **x)** further comprises toluene.

~~82~~81. The method of claim ~~78~~77, further comprising the step of:

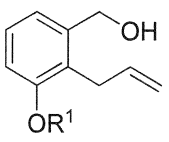
viii) reacting a compound of Formula **11a** with an oxidizing agent to generate the compound of Formula **12a**, wherein the oxidizing agent comprises MnO_2



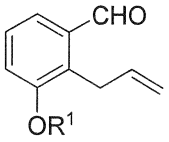
11a

~~82~~81. The method of claim ~~81~~80, further comprising the steps of:

i) reacting a compound of Formula **9** with an oxidizing agent to generate a compound of Formula **10**; and

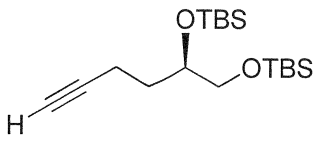


9



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**

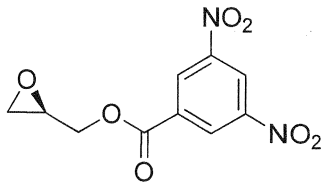


5a

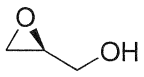
~~84~~83. The method of claim ~~83~~82, wherein the oxidizing agent comprises MnO_2 or Dess-Martin periodinane.

~~85~~84. The method of claim ~~83~~82, further 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%;

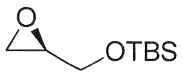


1a



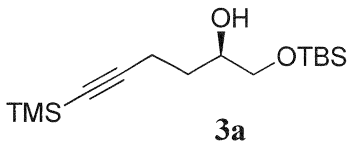
1

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



2a

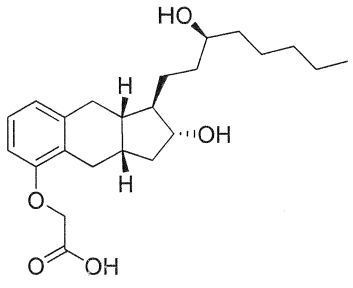
vi) reacting the compound of Formula **2a** with 1-TMS-1-propyne to generate the compound of Formula **3a**; and



3a

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

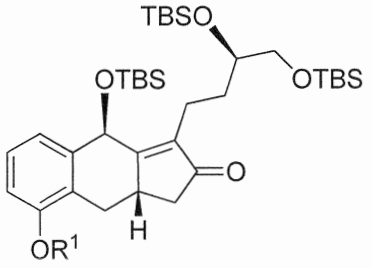
~~86~~85. A method of generating a compound of Formula **I**



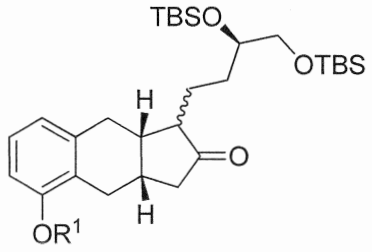
I

or a pharmaceutically acceptable salt thereof, comprising the steps of:

xii) hydrogenating a compound of Formula **15a** in the presence of methanol, ethanol, THF, 2-methyl-THF, or any combination thereof to generate the compound of Formula **16a**



15a



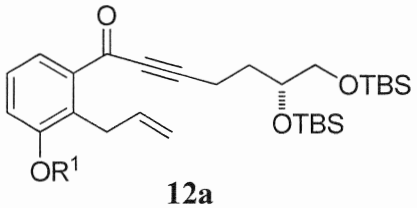
16a

wherein R^1 is C_{1-6} alkyl; and

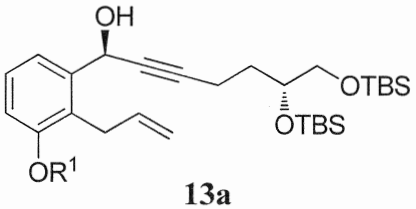
xiii) converting the compound of Formula **16a** to the compound of Formula **I**.

~~87~~86. The method of claim ~~86~~85, further comprising 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



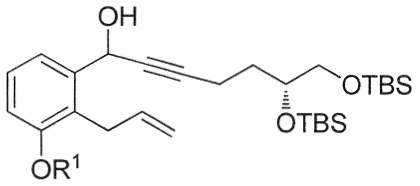
13a

wherein the organic solvent comprises THF; and

xiv) converting the compound of Formula **13a** to the compound of Formula **15a**.

~~88~~87. The method of claim ~~87~~86, further comprising the steps of:

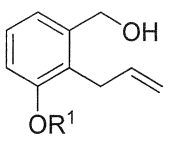
viii) reacting a compound of Formula **11a** with an oxidizing agent to generate the compound of Formula **12a**, wherein the oxidizing agent comprises MnO_2



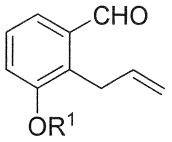
11a .

~~89~~88. The method of claim ~~87~~86, further comprising the steps of:

i) reacting a compound of Formula **9** with an oxidizing agent to generate a compound of Formula **10**; and

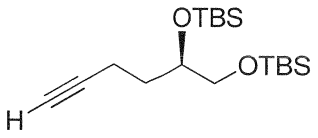


9



10

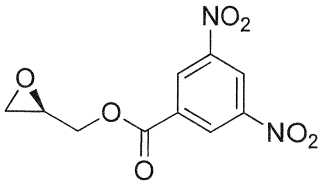
ii) reacting the compound of Formula **10** with a compound of Formula **5a** in the presence of a base and an organic solvent to generate a compound of Formula **11a**



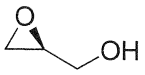
5a

~~90~~89. The method of claim ~~89~~88, further 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%;

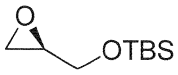


1a



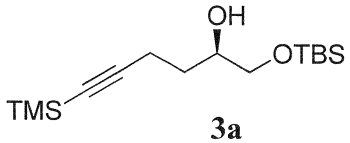
1

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



2a

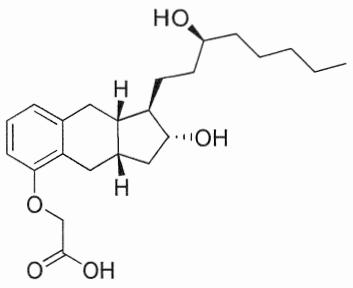
vi) reacting the compound of Formula **2a** with 1-TMS-1-propyne to generate the compound of Formula **3a**; and



3a

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

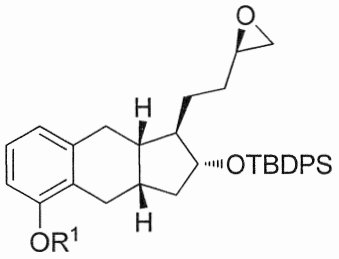
~~91~~90. A method of generating a compound of Formula **I**



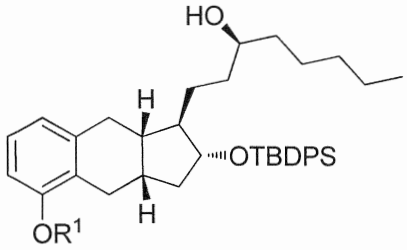
I

or a pharmaceutically acceptable salt thereof, comprising the steps of:

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



21a



22a

wherein R^1 is $C_{1\text{-}6}$ alkyl; and

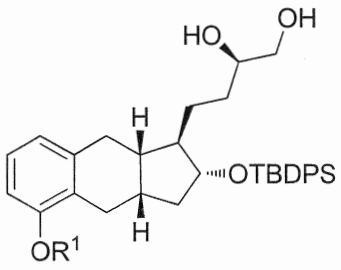
xvi) converting the compound of Formula **22a** to the compound of Formula **I**.

~~92~~91. The method of claim ~~91~~90, wherein the transition metal catalyst comprises a compound or complex either of which comprises copper having a +1 oxidation state.

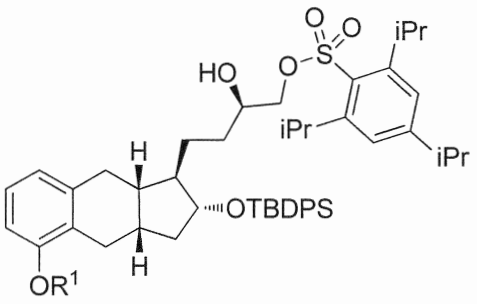
~~93~~92. The method of claim ~~92~~91, wherein the transition metal catalyst comprises CuI.

~~94~~93. The method of claim ~~91~~90, further comprising the steps of:

xvii) reacting a compound of Formula **19a** with triisopropylbenzenesulfonyl chloride under basic conditions to generate a compound of Formula **20a**; and



19a

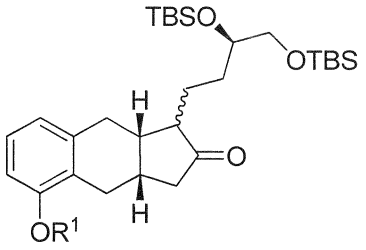


20a

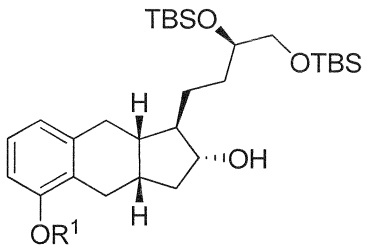
xviii) reacting the compound of Formula **20a** with methanol under basic conditions to generate the compound of Formula **21a**.

~~95~~94. The method of claim ~~94~~93, further comprising the steps of

xix) reacting a compound of Formula **16a** with a reducing agent to generate a compound of Formula **17a**;

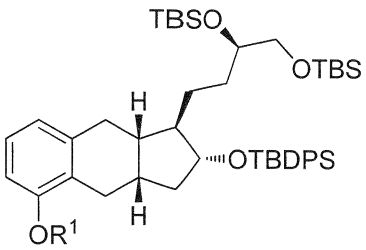


16a



17a

xx) reacting the compound of Formula **17a** with TBDPSCl under basic conditions to generate a compound of Formula **18a**; and

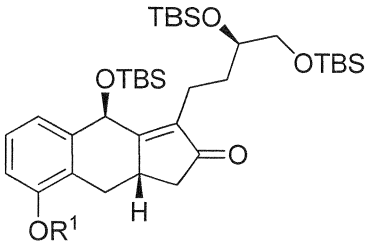


18a

xxi) selectively deprotecting the compound of Formula **18a** to generate the compound of Formula **19a**.

~~96~~95. The method of claim ~~95~~94, further comprising the steps of:

xii) hydrogenating a compound of Formula **15a**

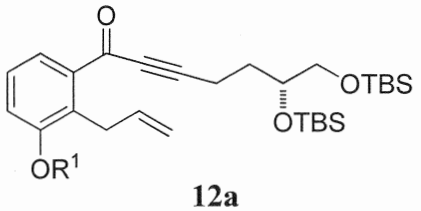


15a

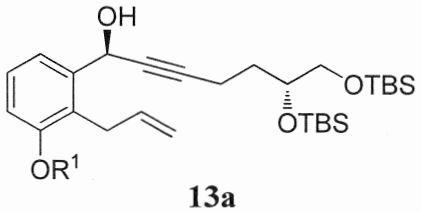
in the presence of an alcohol, optionally substituted THF, or any combination thereof to generate the compound of Formula **16a**.

~~97~~96. The method of claim ~~96~~95, further comprising the steps of:

x) reacting a compound of Formula **12a** with a reducing agent to generate a compound of Formula **13a**; and



12a

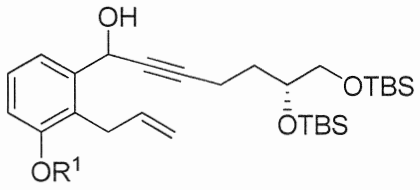


13a

xiv) converting the compound of Formula **13a** to the compound of Formula **15a**.

~~98~~97. The method of claim ~~97~~96, further comprising the step of:

viii) reacting a compound of Formula **11a**

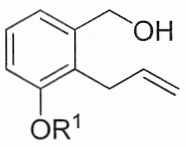


11a

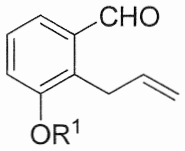
with an oxidizing agent to generate the compound of Formula **12a**, wherein the oxidizing agent comprises MnO_2.

~~99~~98. The method of claim ~~97~~96, further comprising the steps of:

i) reacting a compound of Formula **9** with an oxidizing agent to generate a compound of Formula **10**; and

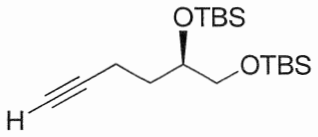


9



10

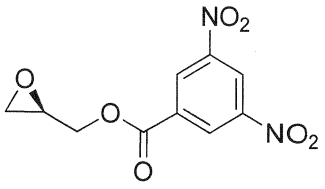
ii) reacting the compound of Formula **10** with a compound of Formula **5a** in the presence of a base and an organic solvent to generate a compound of Formula **11a**



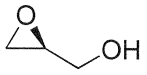
5a

~~100~~99. The method of claim ~~99~~98, further 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%;

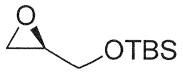


1a



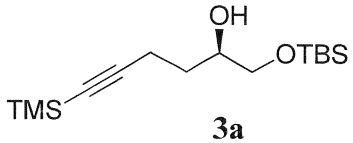
1

v) reacting the compound of Formula **1** with 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

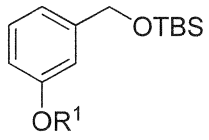


3a

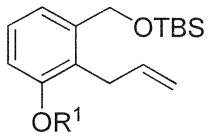
vii) converting the compound of Formula **3a** to the compound of Formula **5a**.

~~101~~100. The method of claim ~~100~~99, further comprising 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



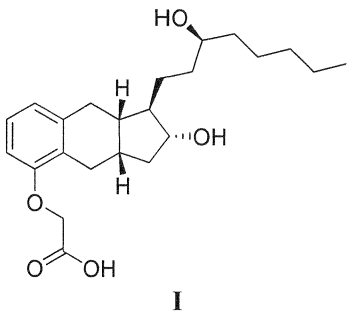
7a



8a

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

~~102~~101. A method of generating a compound of Formula **I**



I

or a pharmaceutically acceptable salt thereof, comprising the steps of:

~~103~~102. The method of claim ~~102~~101, further comprising 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**.