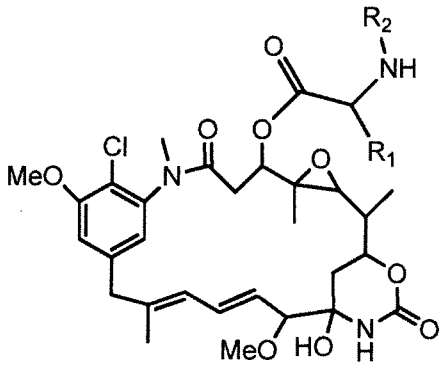
Claims

What is claimed is:

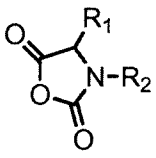
1. A method of preparing a compound represented by the following formula:



(I),

wherein R_1 is hydrogen, an optionally substituted C1-C10 alkyl group or an amino acid side chain, provided that, if the amino acid side chain has a reactive functional group, the reactive functional group is optionally protected; and R_2 is hydrogen or an optionally substituted C1-C10 alkyl group, the method comprising:

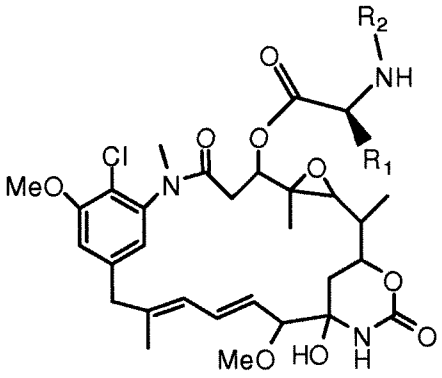
reacting maytansinol with an *N*-carboxyanhydride in a reaction mixture additionally comprising a base and a drying agent, wherein the *N*-carboxyanhydride is represented by the following formula:



(II),

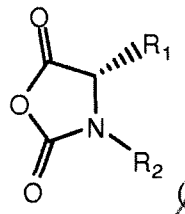
thereby forming the compound of Formula (I).

2. The method of claim 1, wherein the compound of Formula (I) is represented by the following formula:



(Ia);

and the *N*-carboxyanhydride is represented by the following formula:



(IIa).

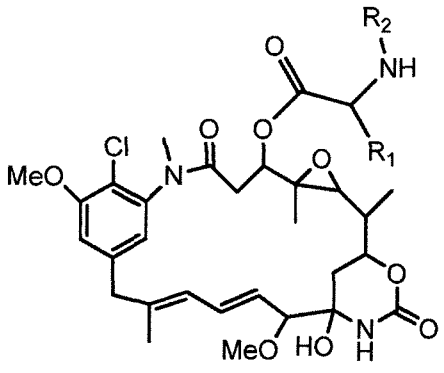
3. The method of claim 1 or 2, wherein the reaction mixture further comprises a Lewis acid.

4. The method of claim 3, wherein the Lewis acid is selected from the group consisting of zinc triflate, zinc chloride, magnesium bromide, magnesium triflate, copper triflate, copper (II) bromide, copper (II) chloride, and magnesium chloride.

5. The method of claim 3, wherein the Lewis acid is zinc triflate.

6. The method of any one of claims 1-5, wherein further comprising contacting the reaction mixture after the reaction of maytansinol and the N-carboxyanhydride with an aqueous solution containing bicarbonate or carbonate or contacting the reaction mixture with a metal scavenger.

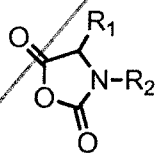
7. A method of preparing a compound represented by the following formula:



(I),

wherein R_1 is hydrogen, an optionally substituted C1-C10 alkyl group or an amino acid side chain, provided that, if the amino acid side chain has a reactive functional group, the reactive functional group is optionally protected; and R_2 is hydrogen, or an optionally substituted C1-C10 alkyl group, the method comprising:

a) reacting maytansinol with an *N*-carboxyanhydride in a reaction mixture additionally comprising a base, wherein the *N*-carboxyanhydride is represented by the following formula:

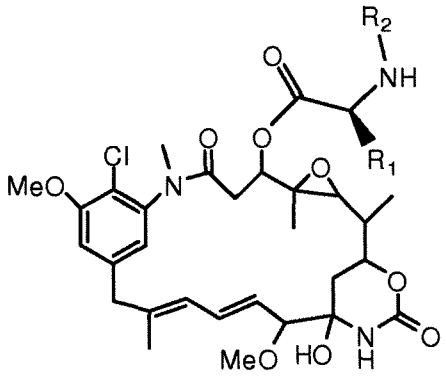


(II)

thereby forming the compound of Formula (I);

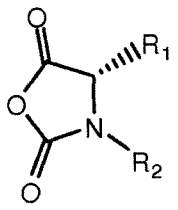
b) reacting unreacted *N*-carboxyanhydride from the reaction mixture in step a) with a nucleophilic reagent.

8. The method of claim 7, wherein the compound of Formula (I) is represented by the following formula:



(Ia);

and the *N*-carboxyanhydride is represented by the following formula:



(IIa).

9. The method of claim 7 or 8, wherein the reaction mixture in step a) further comprises a Lewis acid.

10. The method of claim 9, wherein the Lewis acid is selected from the group consisting of zinc triflate, zinc chloride, magnesium bromide, magnesium triflate, copper triflate, copper (II) bromide copper (II) chloride, and magnesium chloride.

11. The method of claim 10, wherein the Lewis acid is zinc triflate.

12. The method of any one of claims 7-11, wherein the reaction mixture in step a) further comprises a drying agent.

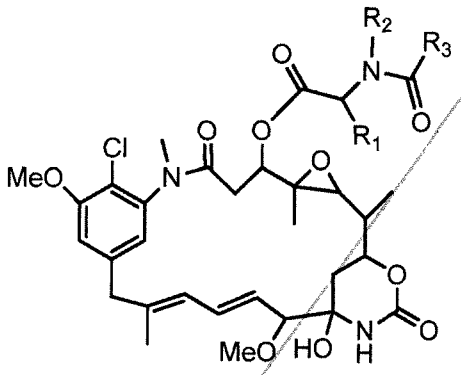
13. The method of any one of claims 7-12, wherein the nucleophilic reagent is water or an alcohol.

14. The method of claim 13, wherein the nucleophilic reagent is an alcohol.

15. The method of claim 14, wherein the alcohol is methanol, ethanol, n-propanol, isopropanol, or tert-butanol.

16. The method of any one of 9-15, wherein the method further comprises contacting the reaction mixture after step b) with an aqueous solution containing bicarbonate or carbonate or contacting the reaction mixture with a metal scavenger.

17. The method of any one of claims 1-16, further comprising the step of reacting the compound of formula (I) with a carboxylic acid having the formula R_3COOH in the presence of a condensing agent or with an activated carboxylic acid having the formula R_3COX, to form a compound represented by the following formula:



(III)

wherein R_3 is an alkyl group or a substituted alkyl group, and X is a leaving group.

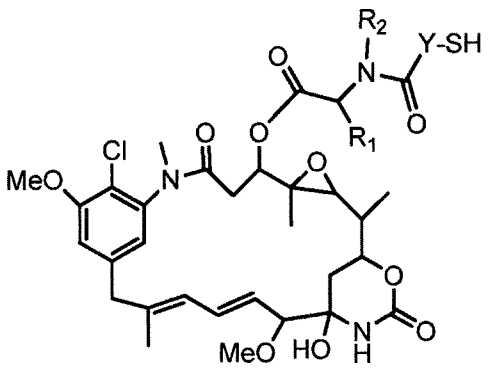
18. The method of claim 17, wherein X is a halide, an alkoxy group, an aryloxy group, an imidazole, –S-phenyl optionally substituted with nitro or chloride, or –OCOR, in which R is a linear C1-C10 alkyl group, a branched C1-C10 alkyl group, a cyclic C3-C10 alkyl group, or a C1-C10 alkenyl group.

19. The method of claim 17, wherein -COX is a reactive ester.

20. The method of claim 17, wherein R_3 is -Y–S-SR_4, in which Y is C1-C10 alkylene and R_4 is C1-C10 alkyl, aryl, or heteroaryl (pyridyl).

21. The method of claim 20, wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2C(CH_3)_2-$ and R_4 is $-CH_3$.

22. The method of claim 20 or 21, further comprising reacting the compound of formula (III) with a reducing agent to form a compound represented by the following formula:

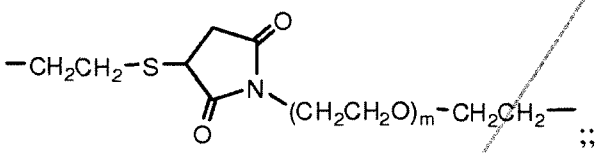


(IV)

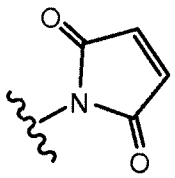
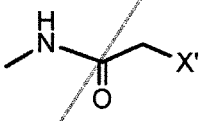
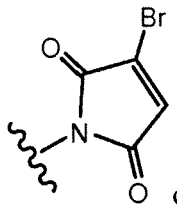
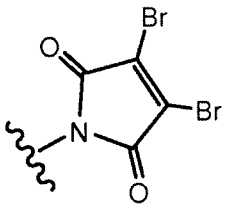
23. The method of 17, wherein R_3 is –L-E;

L is $-(CH_2)_n-\left(\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2CH_2O)_mCH_2CH_2\right)_q$, or

$-(CH_2CH_2O)_mCH_2CH_2NHC(=O)CH_2CH_2-$ or



;;

E is  or  or  or  ;;

X' is a halide;

n is 2, 3, 4, 5 or 6;

m is 0 or an integer from 1 to 20; and

q is 0 or 1.

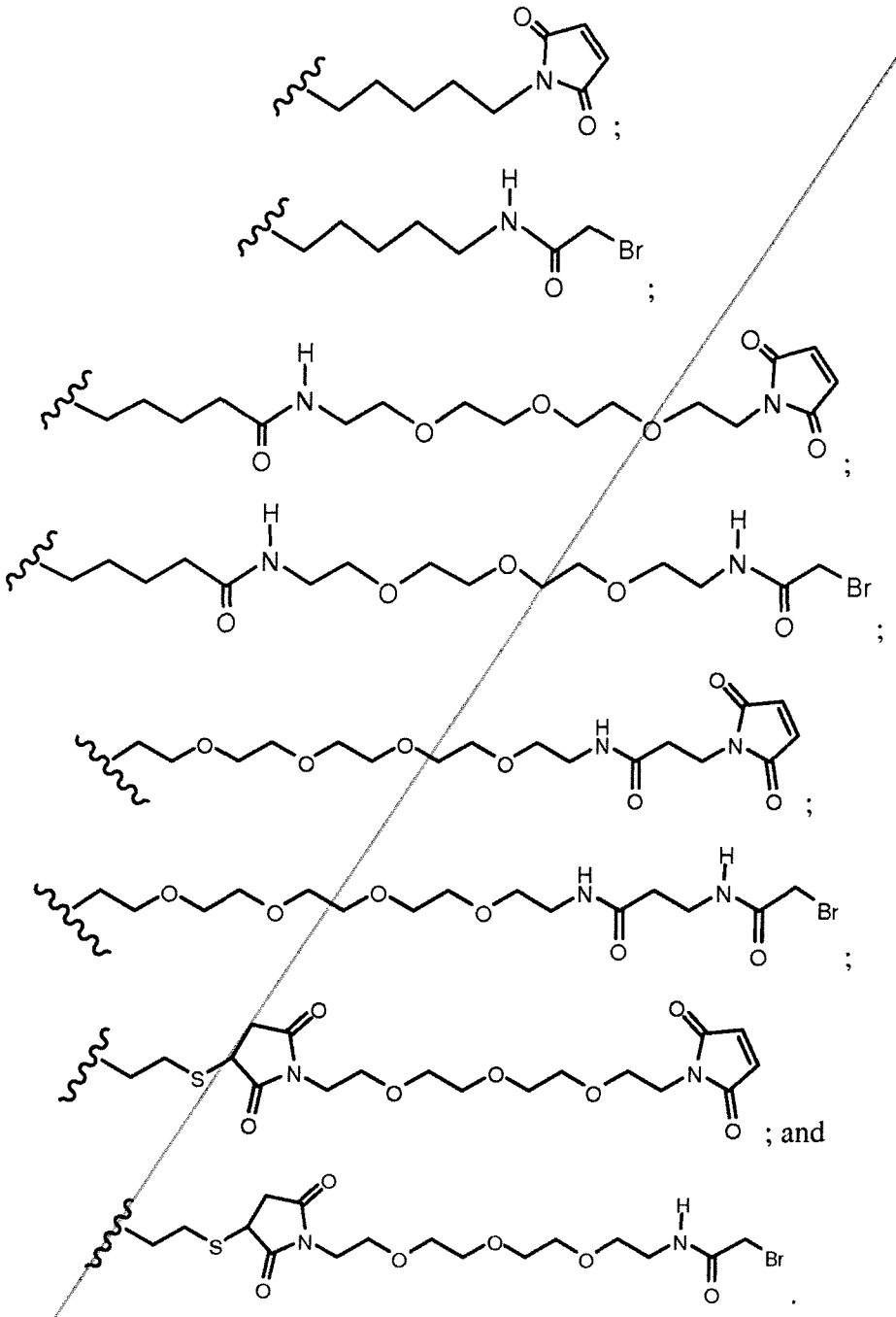
24. The method of claim 23, wherein L is $-(CH_2)_n-$.

25. The method of claim 24, wherein n is 5.

26. The method of claim 23, wherein L is $-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2CH_2O)_mCH_2CH_2-$.

27. The method of claim 26, wherein n is 4 and m is 3.

28. The method of claim 23, wherein R_3 is represented by one of the following:



; and

.

29. The method of any one of claims 17-28, wherein the condensing agent is a carbodiimide, a uronium, an active ester, a phosphonium, 2-alkyl-1-alkylcarbonyl-1,2-dihydroquinoline, 2-alkoxy-1-alkoxycarbonyl-1,2-dihydroquinoline, or alkylchloroformate.

30. The method of claim 29, wherein the condensing agent is a carbodiimide.

31. The method of claim 30, wherein the condensing agent is *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride.

32. The method of any one of claims 1-31, wherein R_1 is the side chain of a naturally occurring amino acid, provided that, if the side chain has a functional group, the functional group is optionally protected; and R_2 is methyl.

33. The method of claim 32, wherein R_1 is methyl.

34. The method of claims 1-33, wherein the base is a trialkylamine, a metal alkoxide, an alkyl metal, an aryl metal, a metal hydride, a metal amide, or a silicon-based amide.

35. The method of claim 34, wherein the base is a trialkylamine.

36. The method of claim 35, wherein the trialkylamine is diisopropylethylamine.

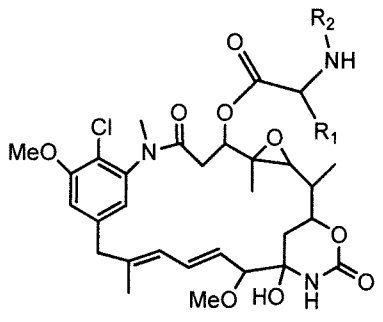
37. The method of any one of claims 1-6 and 12-36, wherein the drying agent is a molecular sieve, sodium sulfate, calcium sulfate, calcium chloride, or magnesium sulfate.

38. The method of claim 37, wherein the drying agent is a molecular sieve.

39. The method of claim 37 or 38, wherein the drying agent is in the form of granular beads or powders.

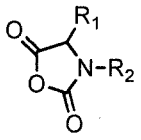
Claims

1. A method of preparing a compound represented by the following formula:


(I),

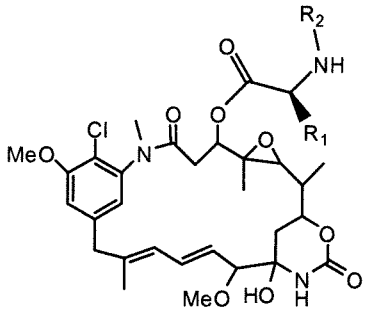
wherein R_1 is methyl; and R_2 is methyl, the method comprising:

reacting maytansinol with an *N*-carboxyanhydride in a reaction mixture additionally comprising a base, a drying agent and a Lewis acid, wherein the *N*-carboxyanhydride is represented by the following formula:

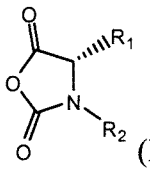

(II),

thereby forming the compound of Formula (I).

2. The method of claim 1, wherein the compound of Formula (I) is represented by the following formula:


(Ia);

and the *N*-carboxyanhydride is represented by the following formula:

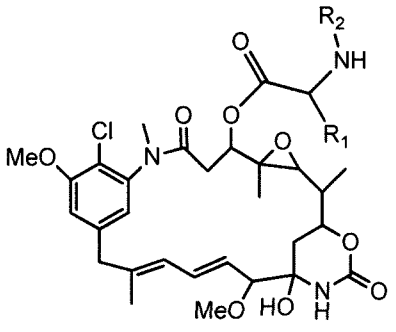

(IIa).

3. The method of claim 2, wherein the Lewis acid is selected from the group consisting of zinc triflate, zinc chloride, magnesium bromide, magnesium triflate, copper triflate, copper (II) bromide, copper (II) chloride, and magnesium chloride.

4. The method of claim 2, wherein the Lewis acid is zinc triflate.

5. The method of claim 1, further comprising contacting the reaction mixture, after the reaction of maytansinol and the N-carboxyanhydride, with an aqueous solution containing bicarbonate or carbonate, or contacting the reaction mixture with a metal scavenger.

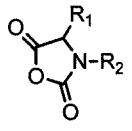
6. A method of preparing a compound represented by the following formula:



(I),

wherein R_1 is methyl, the method comprising:

a) reacting maytansinol with an *N*-carboxyanhydride in a reaction mixture additionally comprising a base and a Lewis acid, wherein the *N*-carboxyanhydride is represented by the following formula:

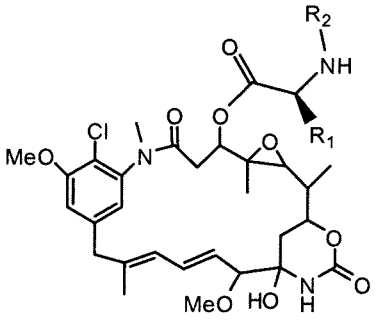


(II)

thereby forming the compound of Formula (I);

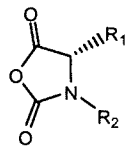
b) reacting unreacted *N*-carboxyanhydride from the reaction mixture in step a) with a nucleophilic reagent.

7. The method of claim 6, wherein the compound of Formula (I) is represented by the following formula:



(Ia);

and the *N*-carboxyanhydride is represented by the following formula:



(IIa).

8. The method of claim 7, wherein the Lewis acid is selected from the group consisting of zinc triflate, zinc chloride, magnesium bromide, magnesium triflate, copper triflate, copper (II) bromide copper (II) chloride, and magnesium chloride.

9. The method of claim 8, wherein the Lewis acid is zinc triflate.

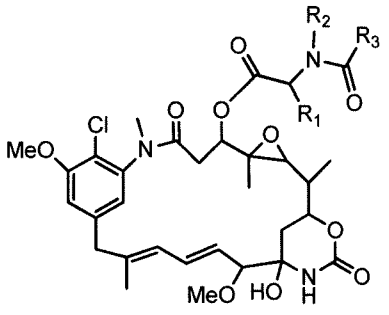
10. The method of claim 6, wherein the reaction mixture in step a) further comprises a drying agent.

11. The method of any one of claims 6, 7, and 8-10, wherein the nucleophilic reagent is water or an alcohol.

12. The method of claim 11, wherein the alcohol is methanol, ethanol, n-propanol, isopropanol, or tert-butanol.

13. The method of claim 6, wherein the method further comprises contacting the reaction mixture after step b) with an aqueous solution containing bicarbonate or carbonate, or contacting the reaction mixture with a metal scavenger.

14. The method of claim 1 or 6, further comprising the step of reacting the compound of formula (I) with a carboxylic acid having the formula R_3COOH in the presence of a condensing agent, or with an activated carboxylic acid having the formula R_3COX, to form a compound represented by the following formula:



(III)

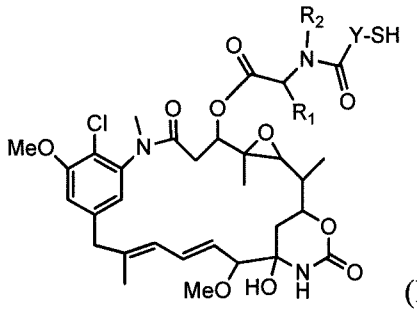
wherein R_3 is -Y-S-SR_4, Y is C_1-C_{10} alkylene, R_4 is C_1-C_{10} alkyl, aryl, or heteroaryl,

X is a halide, an alkoxy group, an aryloxy group, an imidazole, -S-phenyl optionally substituted with nitro or chloride, or -OCOR, in which R is a linear C_1-C_{10} alkyl group, a branched C_1-C_{10} alkyl group, a cyclic C_3-C_{10} alkyl group, or a C_1-C_{10} alkenyl group, and,

-COX is a reactive ester.

15. The method of claim 14, wherein Y is -CH_2CH_2- or -$CH_2CH_2C(CH_3)_2$-, and R_4 is -CH_3.

16. The method of claim 15, further comprising reacting the compound of formula (III) with a reducing agent to form a compound represented by the following formula:



(IV).

17. The method of claim 14, wherein the condensing agent is a carbodiimide, a uronium, an active ester, a phosphonium, 2-alkyl-l-alkylcarbonyl-l,2-dihydroquinoline, 2-alkoxy-l-alkoxycarbonyl-l,2-dihydroquinoline, or alkylchloroformate.

18. The method of claim 17, wherein the condensing agent is *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride.

19. The method of claim 1, 2, 3, 4, 5, 6, 7, or 8, wherein the base is a trialkylamine, a metal alkoxide, an alkyl metal, an aryl metal, a metal hydride, a metal amide, or a silicon-based amide.

20. The method of claim 19, wherein the trialkylamine is diisopropylethylamine.

21. The method of any one of claims 1, 2, 3, 4, and 10, wherein the drying agent is a molecular sieve, sodium sulfate, calcium sulfate, calcium chloride, or magnesium sulfate.

22. The method of claim 21, wherein the drying agent is a molecular sieve.