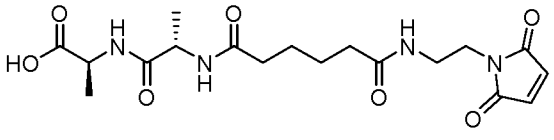
CLAIMS

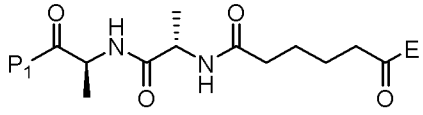
1. A method of preparing a compound of formula (IIIa):



(IIIa),

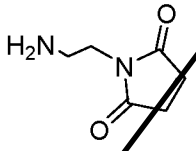
or a salt thereof, comprising the steps:

(a) reacting a compound of formula (Ia):



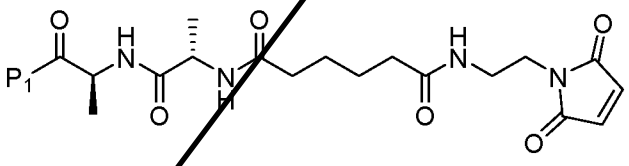
(Ia),

or a salt thereof, with a compound of formula (a):



(a),

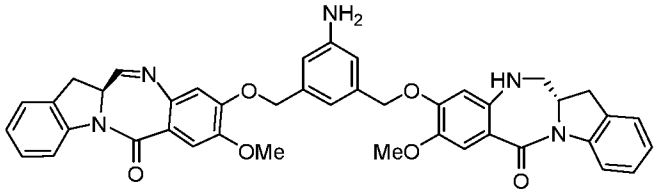
or a salt (*e.g.*, HCl salt) thereof, to form a compound of formula (IIa):



(IIa), and

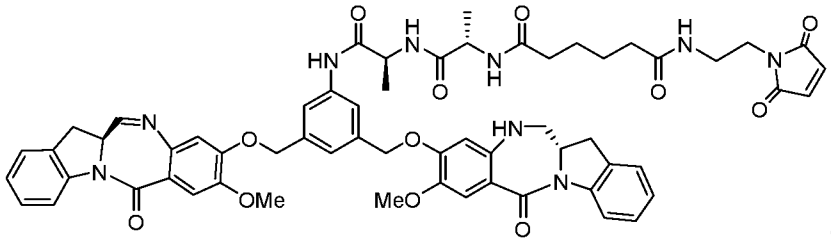
(b) reacting the compound of formula (IIa) with a carboxylic acid deprotecting agent to form the compound of formula (IIIa), wherein E is –OH, halide or -C(=O)E_1 is an activated ester; and P_1 is a carboxylic acid protecting group.

2. The method of claim 1, wherein the method further comprises reacting the compound of formula (IIIa) with a compound of formula (IV):



(IV),

to form a compound of formula (Va):



(Va).

3. The method of claim 1 or 2, wherein P_1 is $-O^tBu$, -OMe, -OBn, or -O-silyl.

4. The method of claim 3, wherein P_1 is $-O^tBu$.

5. The method of any one of claims 1-4, wherein E is –OH and the reaction between the compound of formula (Ia) and the compound of formula (a) is carried out in the presence of an activating agent.

6. The method of claim 5, wherein the activating agent is a 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide, carbodiimide, a uronium, an activated ester, a phosphonium, 2-alkyl-l-alkylcarbonyl-l,2-dihydroquinoline, 2-alkoxy-l-alkoxycarbonyl-l,2-dihydroquinoline, or alkylchloroformate.

7. The method of claim 6, wherein the activating agent is 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide.

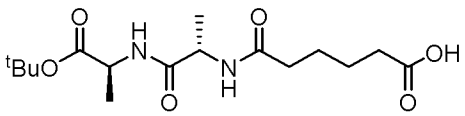
8. The method of claim 7, wherein the activating agent is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide.

9. The method of any one of claims 1-8, wherein the carboxylic acid deprotecting agent in step (b) is an acid.

10. The method of claim 9, wherein the acid is trifluoroacetic acid (TFA).

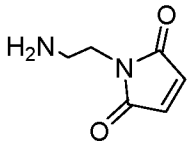
11. The method of claim 1, wherein the method comprises the steps of:

(a) reacting a compound of formula (Ia1):



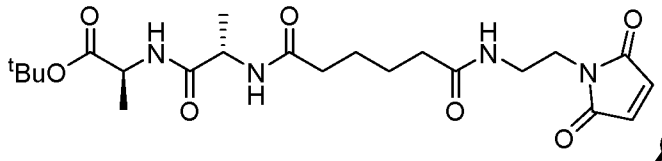
(Ia1),

or a salt thereof, with a compound of formula (a):



(a),

or a salt (*e.g.*, HCl or TFA salt) thereof, in the presence of an activating agent to form a compound of formula (IIa1):



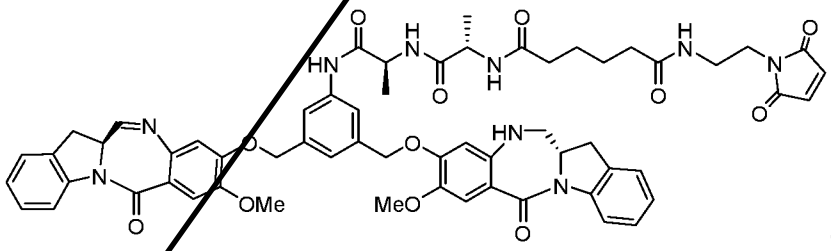
(IIa1), and

(b) reacting the compound of formula (IIa1) with a carboxylic acid deprotecting agent to form the compound of formula (IIIa).

12. The method of claim 11, wherein the activating agent in step (a) is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide.

13. The method of claim 11 or 12, wherein the carboxylic acid deprotecting agent in step (b) is trifluoroacetic acid (TFA).

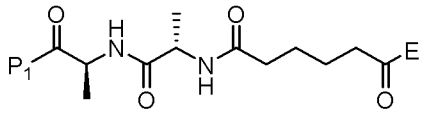
14. A method of preparing a compound of formula (Va):



(Va),

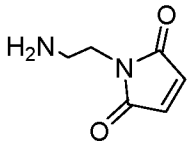
comprising the steps of:

(a) reacting a compound of formula (Ia):



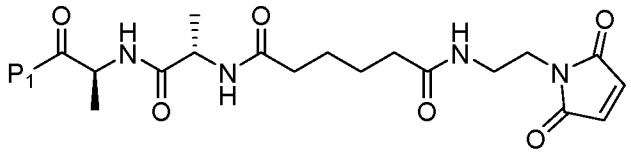
(Ia),

or a salt thereof, with a compound of formula (a):



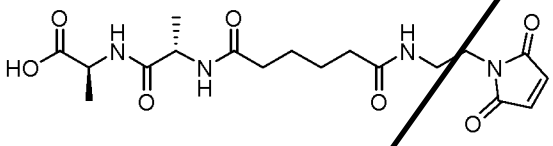
(a),

or a salt (*e.g.*, HCl or TFA salt) thereof, to form a compound of formula (IIa):



(IIa),

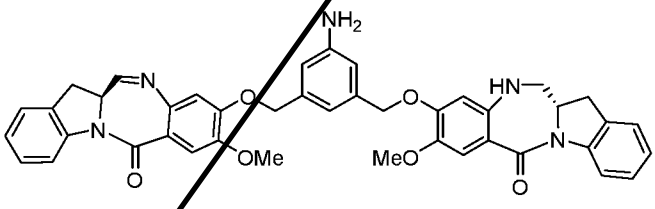
(b) reacting the compound of formula (IIa) with a carboxylic acid deprotecting agent to form the compound of formula (IIIa):



(IIIa),

or a salt thereof; and

(c) reacting the compound of formula (IIIa) with a compound of formula (IV):



(IV)

to form the compound of formula (Va), wherein E is –OH, halide or -C(=O)E_1 is an activated ester; and P_1 is a carboxylic acid protecting group.

15. The method of claim 14, wherein P_1 is –O^{t}Bu, -OMe, -OBn, or -O-silyl.

16. The method of claim 15, wherein P_1 is –O^{t}Bu.

17. The method of any one of claims 14-16, wherein E is –OH and the reaction between the compound of formula (Ia) and the compound of formula (a) is carried out in the presence of an activating agent.

18. The method of claim 17, wherein the activating agent is a 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide, carbodiimide, a uronium, an activated ester,

a phosphonium, 2-alkyl-l-alkylcarbonyl-l,2-dihydroquinoline, 2-alkoxy-l-alkoxycarbonyl-l,2-dihydroquinoline, or alkylchloroformate.

19. The method of claim 18, wherein the activating agent is 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide.

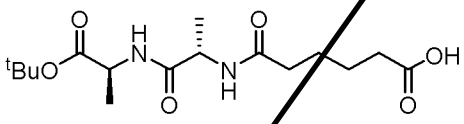
20. The method of claim 19, wherein the activating agent is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide.

21. The method of any one of claims 14-20, wherein the carboxylic acid deprotecting agent in step (b) is an acid.

22. The method of claim 21, wherein the acid is trifluoroacetic acid (TFA).

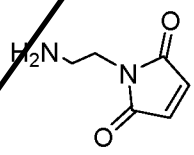
23. The method of claim 14, wherein the method comprises the steps of:

(a) reacting a compound of formula (Ia1):



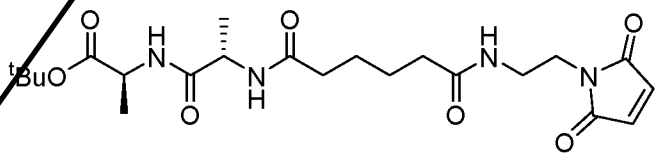
(Ia1),

or a salt thereof, with a compound of formula (a):



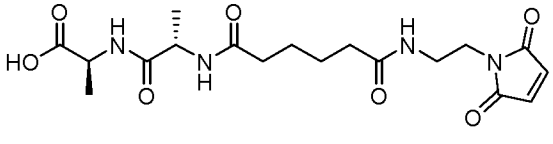
(a),

or a salt (*e.g.*, HCl or TFA salt) thereof, in the presence of an activating agent to form a compound of formula (IIa1):



(IIa1),

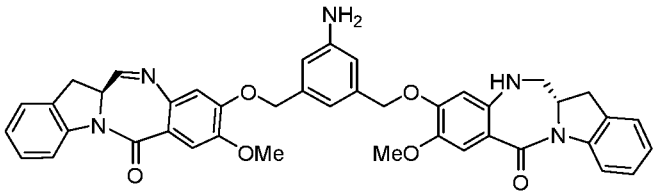
(b) reacting the compound of formula (IIa1) with a carboxylic acid deprotecting agent to form a compound of formula (IIIa):



(IIIa),

or a salt thereof; and

(c) reacting the compound of formula (IIIa) with a compound of formula (IV):



(IV),

to form the compound of formula (Va).

24. The method of claim 23, wherein the activating agent in step (a) is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide.

25. The method of claim 23 or 24, wherein the carboxylic acid deprotecting agent in step (b) is trifluoroacetic acid (TFA).

26. The method of any one of claims 1-25, wherein E, when present, is –OH and the reaction in step (a) is carried out in the presence of an activating agent that is HATU and HOAt.

27. The method of claim 26, wherein the reaction in step (a) is carried out in the presence of a base.

28. The method of claim 27, wherein the base is triethylamine or diisopropylethylamine.

29. The method of any one of claims 2-28, wherein E is –OH and the reaction between the compound of formula (IIIa) and the compound of formula (IV) is carried out in the presence of an activating agent.

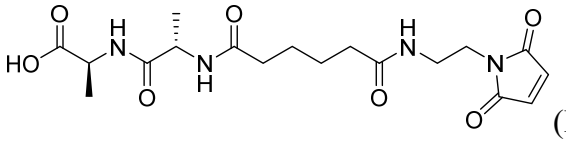
30. The method of claim 29, wherein the activating agent is HATU and HOAt.

31. The method of claim 29 or 30, wherien the reaction between the compound of formula (IIIa) and the compound of formula (IV) is carried out in the presence of a base.

32. The method of claim 31, wherien the base is triethylamine or diisopropylethylamine.

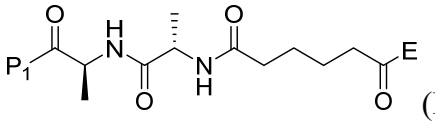
CLAIMS

1. A method of preparing a compound of formula (IIIa):

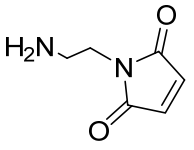

(IIIa),

or a salt thereof, comprising the steps:

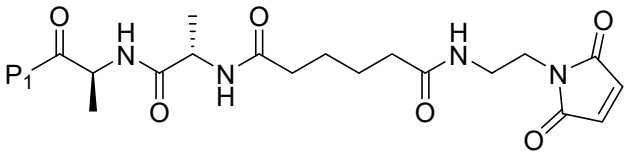
(a) reacting a compound of formula (Ia):


(Ia),

or a salt thereof, with a compound of formula (a):

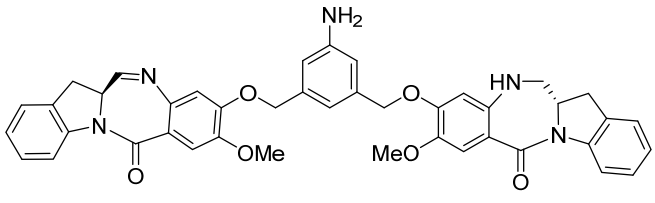

(a),

or a salt thereof, to form a compound of formula (IIa):

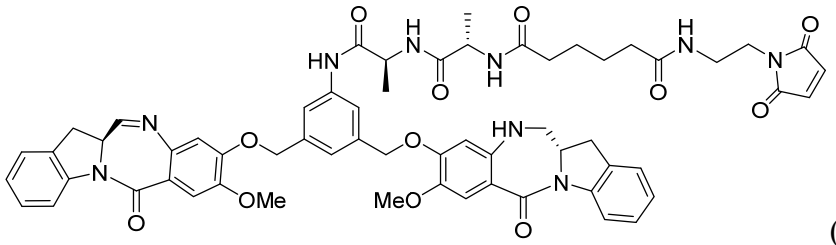

(IIa), and

(b) reacting the compound of formula (IIa) with a carboxylic acid deprotecting agent to form the compound of formula (IIIa), wherein E is –OH, halide or -C(=O)E is an activated ester; and P_1 is a carboxylic acid protecting group.

2. The method of claim 1, wherein the method further comprises reacting the compound of formula (IIIa) with a compound of formula (IV):


(IV),

to form a compound of formula (Va):


(Va).

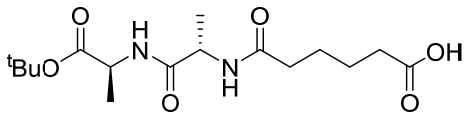
3. The method of claim 1 or 2, wherein (i) P_1 is –O^{t}Bu, -OMe, -OBn, or -O-silyl; or (ii) P_1 is –O^{t}Bu.

4. The method of any one of claims 1-3, wherein E is –OH and the reaction between the compound of formula (Ia) and the compound of formula (a) is carried out in the presence of an activating agent; optionally wherein (i) the activating agent is a 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide, carbodiimide, a uronium, an activated ester, a phosphonium, 2-alkyl-l-alkylcarbonyl-l,2-dihydroquinoline, 2-alkoxy-l-alkoxycarbonyl-l,2-dihydroquinoline, or alkylchloroformate; (ii) the activating agent is 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide; or (iii) the activating agent is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide.

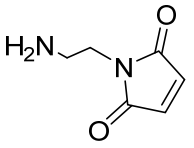
5. The method of any one of claims 1-4, wherein the carboxylic acid deprotecting agent in step (b) is an acid; optionally wherein the acid is trifluoroacetic acid (TFA).

6. The method of claim 1, wherein the method comprises the steps of:

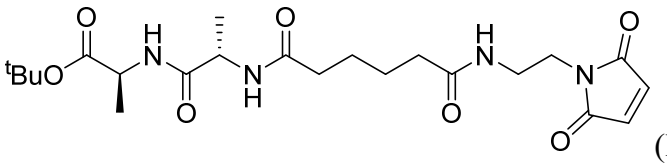
(a) reacting a compound of formula (Ia1):


(Ia1),

or a salt thereof, with a compound of formula (a):


(a),

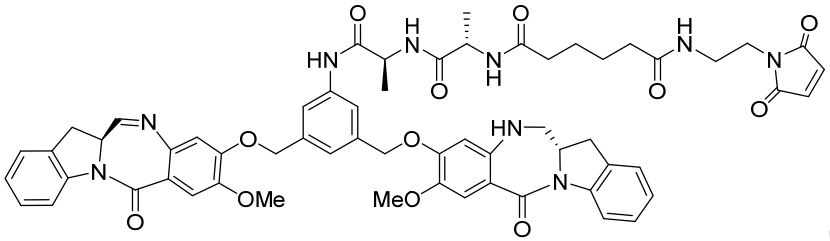
or a salt thereof, in the presence of an activating agent to form a compound of formula (IIa1):


(IIa1), and

(b) reacting the compound of formula (IIa1) with a carboxylic acid deprotecting agent to form the compound of formula (IIIa).

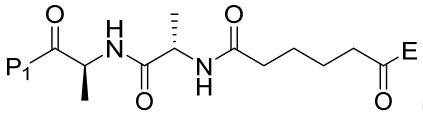
7. The method of claim 6, wherein the activating agent in step (a) is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide and/or the carboxylic acid deprotecting agent in step (b) is trifluoroacetic acid (TFA).

8. A method of preparing a compound of formula (Va):

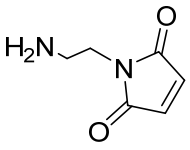

(Va),

comprising the steps of:

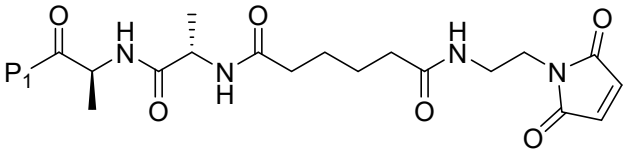
(a) reacting a compound of formula (Ia):


(Ia),

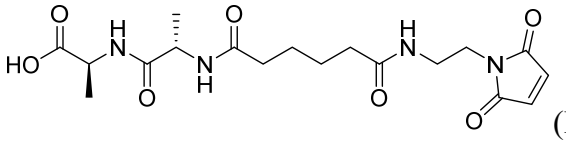
or a salt thereof, with a compound of formula (a):


(a),

or a salt thereof, to form a compound of formula (IIa):

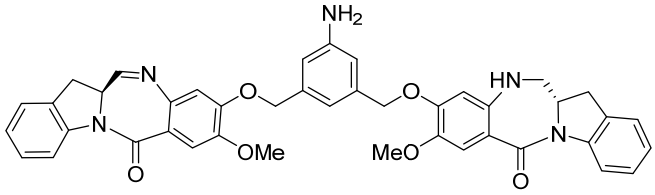

(IIa),

(b) reacting the compound of formula (IIa) with a carboxylic acid deprotecting agent to form the compound of formula (IIIa):


(IIIa),

or a salt thereof; and

(c) reacting the compound of formula (IIIa) with a compound of formula (IV):


(IV)

to form the compound of formula (Va), wherein E is –OH, halide or -C(=O)E is an activated ester; and P_1 is a carboxylic acid protecting group.

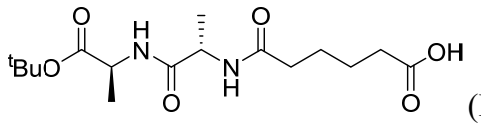
9. The method of claim 8, wherein (i) P_1 is $–O^tBu$, -OMe, -OBn, or -O-silyl; or (ii) P_1 is $–O^tBu$.

10. The method of claim 8 or 9, wherein E is –OH and the reaction between the compound of formula (Ia) and the compound of formula (a) is carried out in the presence of an activating agent; optionally wherein (i) the activating agent is a 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide, carbodiimide, a uronium, an activated ester, a phosphonium, 2-alkyl-l-alkylcarbonyl-l,2-dihydroquinoline, 2-alkoxy-l-alkoxycarbonyl-l,2-dihydroquinoline, or alkylchloroformate; (ii) the activating agent is 2,4,6-trialkyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide; or (iii) the activating agent is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide.

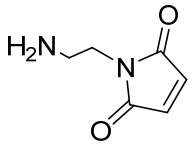
11. The method of any one of claims 8-10, wherein the carboxylic acid deprotecting agent in step (b) is an acid; optionally wherein the acid is trifluoroacetic acid (TFA).

12. The method of claim 8, wherein the method comprises the steps of:

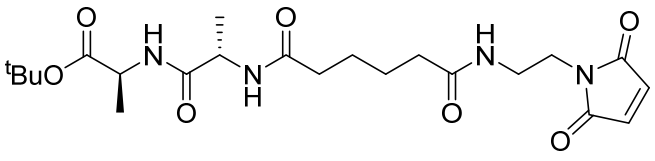
(a) reacting a compound of formula (Ia1):


(Ia1),

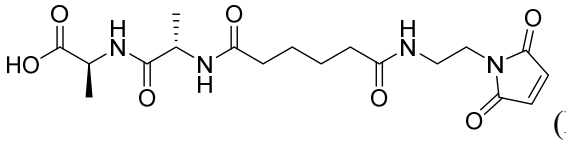
or a salt thereof, with a compound of formula (a):


(a),

or a salt thereof, in the presence of an activating agent to form a compound of formula (IIa1):

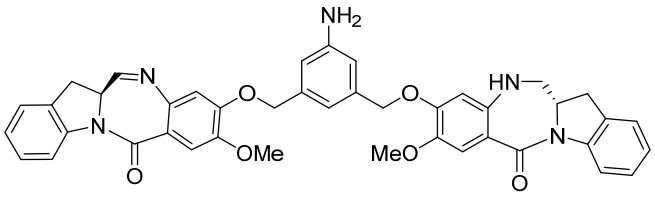

(IIa1),

(b) reacting the compound of formula (IIa1) with a carboxylic acid deprotecting agent to form a compound of formula (IIIa):


(IIIa),

or a salt thereof; and

(c) reacting the compound of formula (IIIa) with a compound of formula (IV):


(IV),

to form the compound of formula (Va).

13. The method of claim 12, wherein the activating agent in step (a) is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide and/or the carboxylic acid deprotecting agent in step (b) is trifluoroacetic acid (TFA).

14. The method of any one of claims 1-13, wherein E, when present, is –OH and the reaction in step (a) is carried out in the presence of an activating agent that is HATU and HOAt.

15. The method of claim 14, wherein the reaction in step (a) is carried out in the presence of a base; optionally wherein the base is triethylamine or diisopropylethylamine.

16. The method of any one of claims 1-15, wherein the salt of the compound of formula (a) is an HCl salt or a TFA salt.