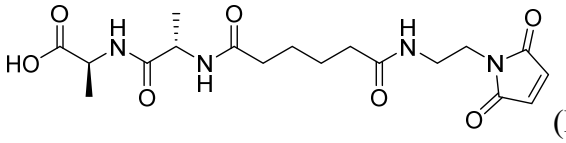
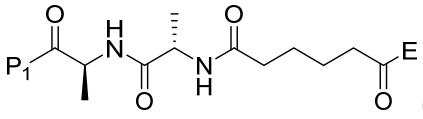
CLAIMS

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

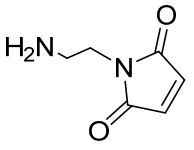

(IIIa),

or a salt thereof, comprising the steps:

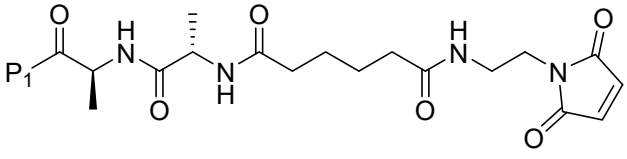
(a) reacting a compound of formula (Ia):


(Ia),

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

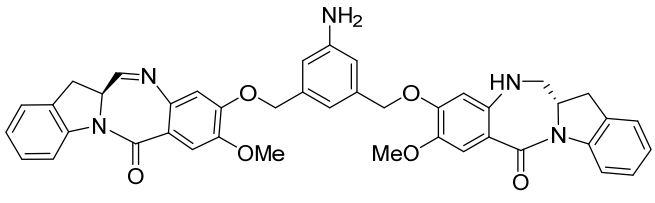

(a),

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

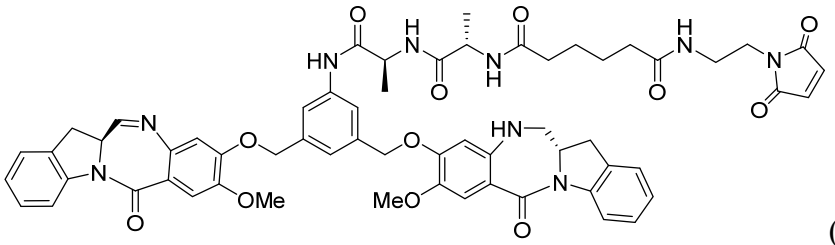

(IIa), and

(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).

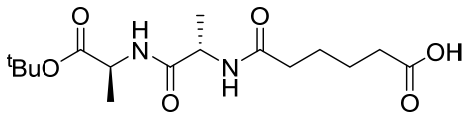
3. The method of claim 1 or 2, wherein (i) P_1 is –O^{t}Bu, -OMe, -OBn, or -O-silyl; or (ii) P_1 is –O^{t}Bu.

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.

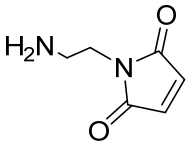
5. The method of any one of claims 1-4, wherein the carboxylic acid deprotecting agent in step (b) is an acid; optionally wherein the acid is trifluoroacetic acid (TFA).

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

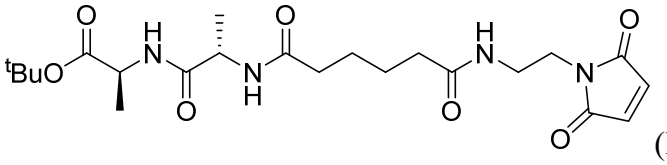
(a) reacting a compound of formula (Ia1):


(Ia1),

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


(a),

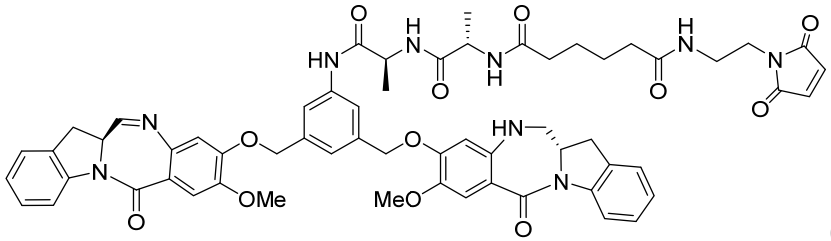
or a salt thereof, in the presence of an activating agent to form a compound of formula (IIa1):


(IIa1), and

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

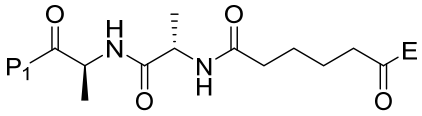
7. The method of claim 6, wherein the activating agent in step (a) is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide and/or the carboxylic acid deprotecting agent in step (b) is trifluoroacetic acid (TFA).

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

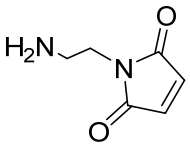

(Va),

comprising the steps of:

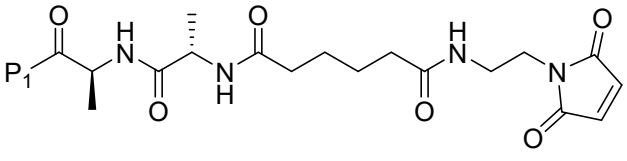
(a) reacting a compound of formula (Ia):


(Ia),

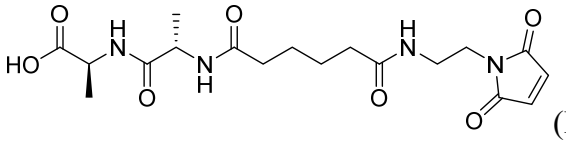
or a salt thereof, with a compound of formula (a):


(a),

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

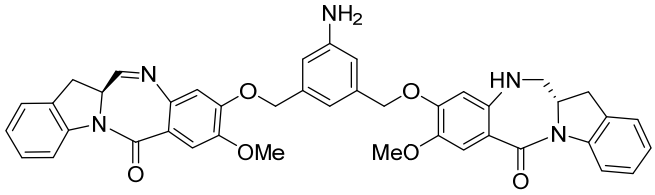

(IIa),

(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.

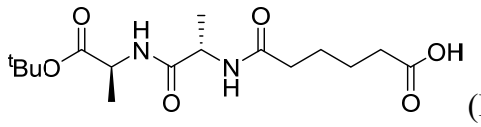
9. The method of claim 8, wherein (i) P_1 is –O^{t}Bu, -OMe, -OBn, or -O-silyl; or (ii) P_1 is –O^{t}Bu.

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.

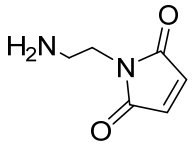
11. The method of any one of claims 8-10, wherein the carboxylic acid deprotecting agent in step (b) is an acid; optionally wherein the acid is trifluoroacetic acid (TFA).

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

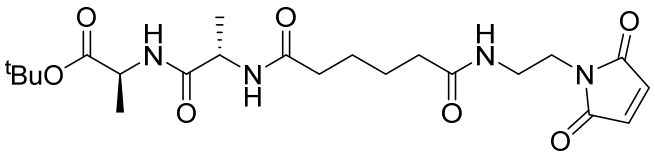
(a) reacting a compound of formula (Ia1):


(Ia1),

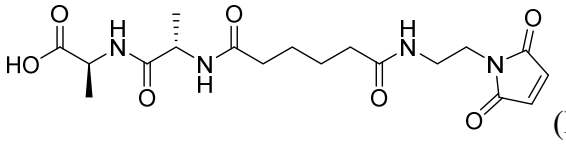
or a salt thereof, with a compound of formula (a):


(a),

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

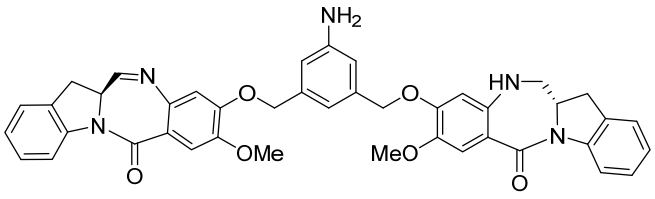

(IIa1),

(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.