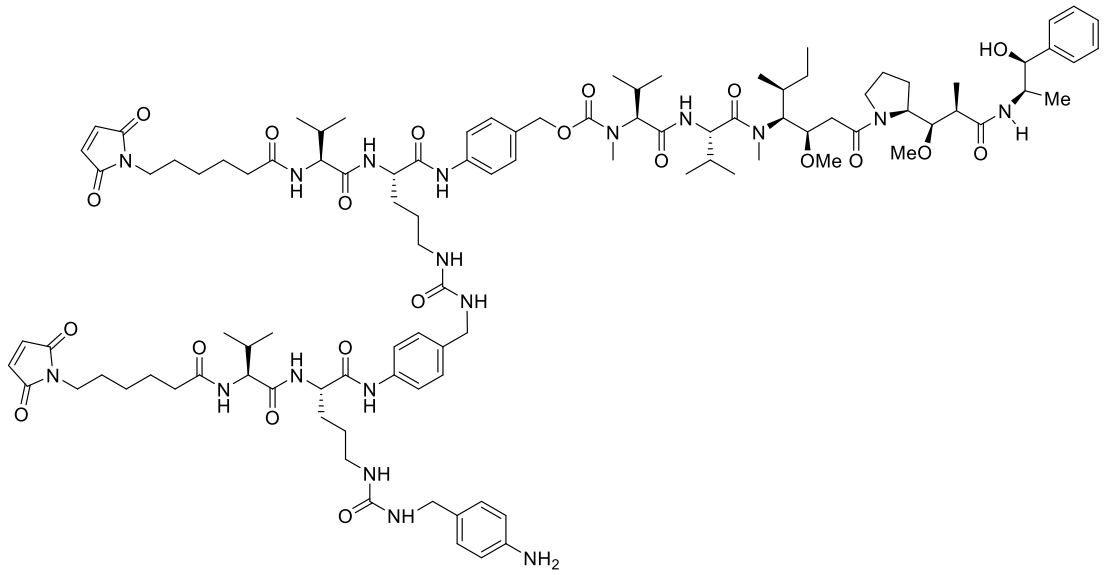


(5),

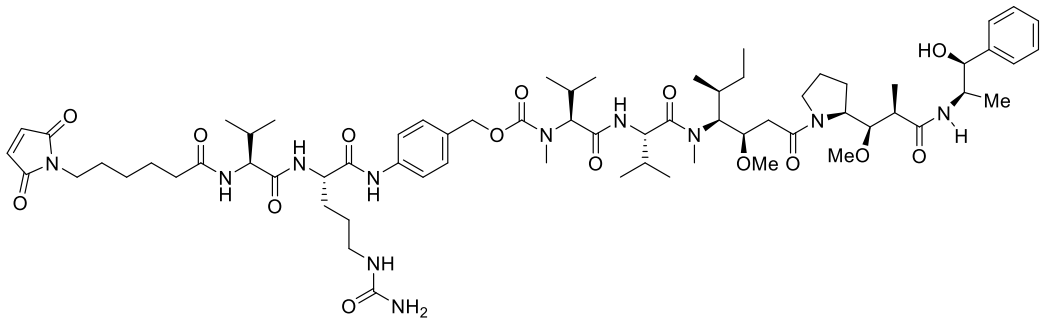
or a pharmaceutically acceptable salt thereof, wherein Ab and p are as defined herein.

[0009] In another aspect, provided herein is a compound of Formula (4):



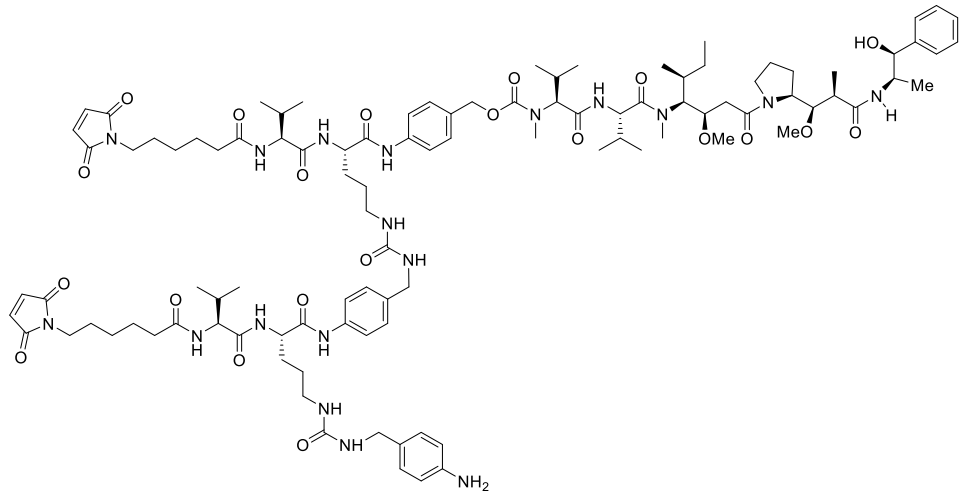
(4).

[0009a] In another aspect, there is provided a composition comprising a compound of Formula (3),



(3),

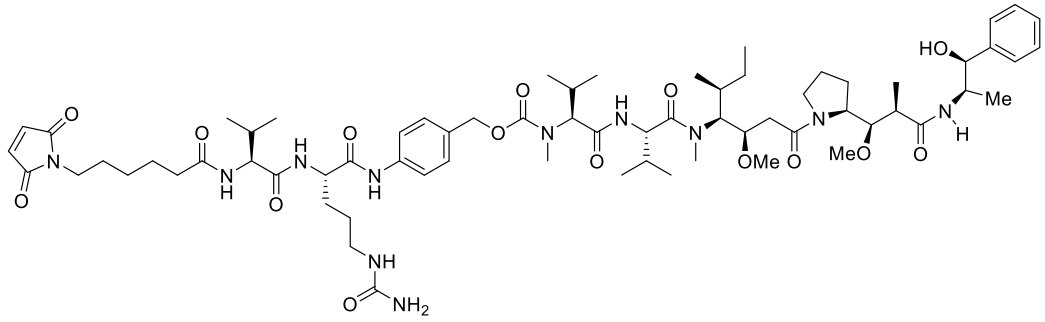
and a compound of Formula (4):



(4),

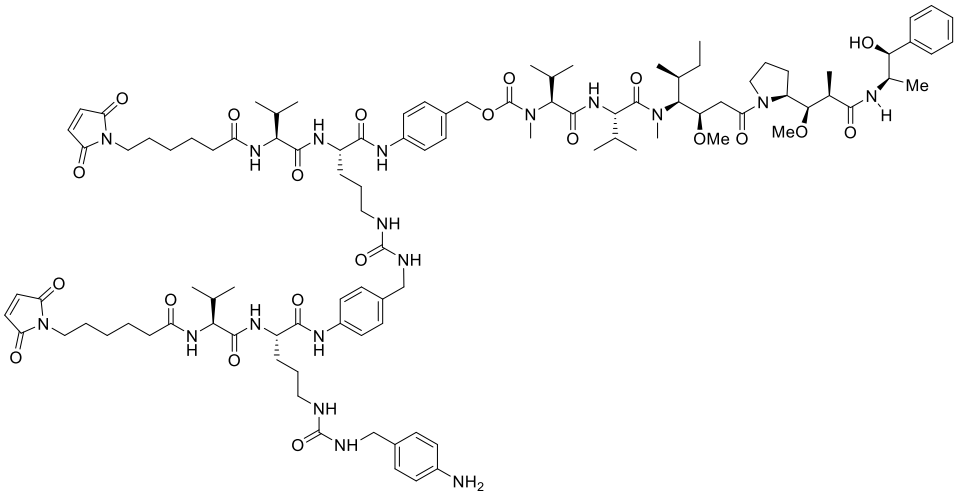
wherein the molar ratio of the compound of Formula (4) to the compound of Formula (3) is no more than 0.1%.

[0010] In another aspect, provided herein is a composition comprising a compound of Formula (3):



(3).

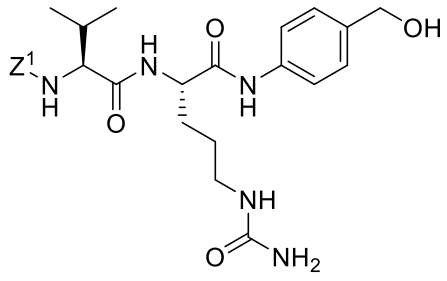
wherein the composition is substantially free of the compound of Formula (4):



(4).

CLAIMS

1. A method of preparing a compound of Formula (1A):

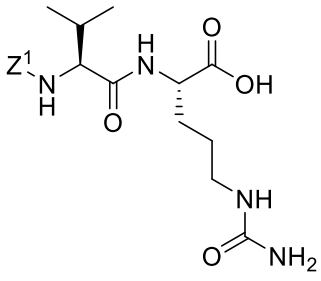


(1A),

or a salt thereof,

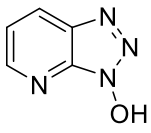
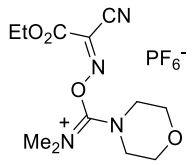
wherein Z^1 is a protecting group;

the method comprising reacting a compound of Formula (1B) or a salt thereof:



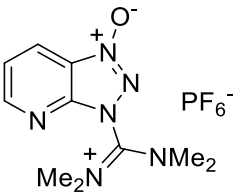
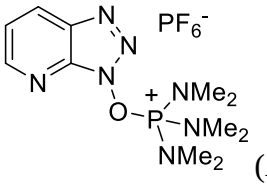
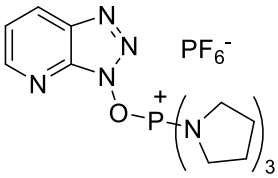
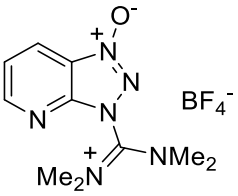
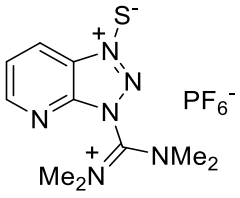
(1B)

with *p*-aminobenzyl alcohol (PABOH) in the presence of a peptide coupling reagent, wherein

the peptide coupling reagent comprises  (HOAt),  (COMU), or an HOAt derivative.

2. The method of claim 1, wherein Z^1 is an alkoxy-carbonyl or aryloxy-carbonyl group.

3. The method of claim 1 or 2, wherein Z^1 is fluorenylmethyloxycarbonyl (Fmoc).

4. The method of any one of claims 1-3, wherein the peptide coupling reagent comprises a compound selected from the group consisting of HOAt,  (HATU),  (AOP),  (PyAOP),  (TATU), COMU, and  (HATTU).

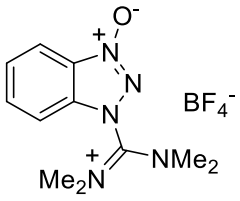
5. The method of any one of claims 1-4, wherein the peptide coupling reagent comprises a compound selected from the group consisting of HOAt, HATU, COMU, and PyAOP.

6. The method of any one of claims 1-5, wherein the peptide coupling reagent comprises HOAt.

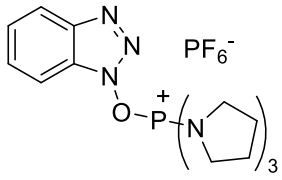
7. The method of any one of claims 1-5, wherein the peptide coupling reagent comprises HATU.

8. The method of any one of claims 1-5, wherein the peptide coupling reagent comprises PyAOP.

9. The method of any one of claims 1-5, wherein the peptide coupling reagent comprises COMU.

10. The method of claim 6, wherein the peptide coupling reagent further comprises  (TBTU).

11. The method of claim 6, wherein the peptide coupling reagent further comprises


(PyBOP).

12. The method of any one of claims 1-11, wherein the reaction of the compound of Formula (1B) or a salt thereof with the PABOH is performed in the presence of a base.

13. The method of claim 12, wherein the base is N,N-Diisopropylethylamine (DIPEA).

14. The method of any one of claims 1-13, wherein the reaction of the compound of Formula (1B) or a salt thereof with the PABOH is performed in an organic solvent.

15. The method of claim 14, wherein the organic solvent comprises N,N-Dimethylformamide (DMF).

16. The method of claim 15, wherein the organic solvent further comprises ethyl acetate.

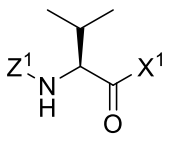
17. The method of claim 16, wherein the volume ratio of the DMF to the ethyl acetate is about 1:1.

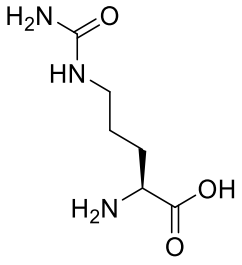
18. The method of any one of claims 1-17, wherein the reaction of the compound of Formula (1B) or a salt thereof with the PABOH is performed at a temperature of no more than about 5 °C.

19. The method of claim 13, wherein the PABOH is mixed with the compound of Formula (1B) or a salt thereof before addition of the DIPEA.

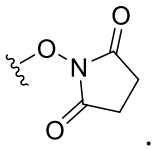
20. The method of claim 19, wherein the DIPEA is added within 5 minutes after the PABOH is mixed with the compound of Formula (1B) or a salt thereof.

21. The method of any one of claims 1-20, wherein the compound of formula (1B) or a salt thereof is obtained by reacting a compound of Formula (1C) or a salt thereof,

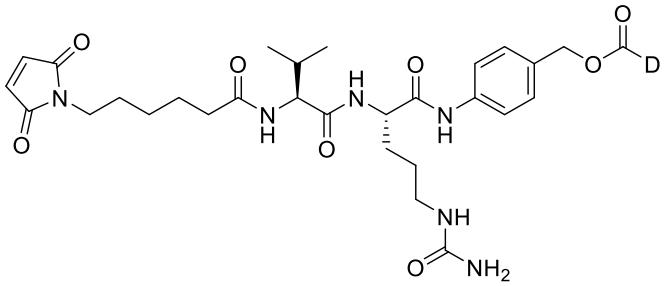

(1C),



wherein X^1 is a carboxyl-activating group, with or a salt thereof to form the compound of Formula (1B) or a salt thereof.

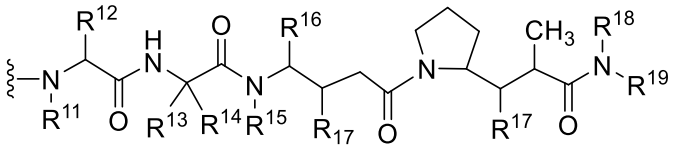
22. The method of claim 21, wherein X^1 is .

23. The method of any one of claims 1-22, further comprising converting the compound of Formula (1A) or a salt thereof to a compound of Formula (1D) or a salt thereof:



(1D),

wherein D is a moiety of Formula (D):



(D),

wherein the wavy line indicates covalent bonding of D to the remainder of the compound;

R^{11} is selected from the group consisting of H and C_1-C_8 alkyl;

R^{12} is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl, and C_1-C_8 alkyl-(C_3-C_8 heterocyclyl);

R^{13} is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl, and C_1-C_8 alkyl-(C_3-C_8 heterocyclyl);

R^{14} is selected from the group consisting of H and methyl;

or R^{13} and R^{14} jointly form a carbocyclic ring and have the formula -$(CR^aR^b)_n$-, wherein R^a and R^b are independently selected from the group consisting of H, C_1-C_8 alkyl and C_3-C_8 carbocyclyl, and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R^{15} is selected from the group consisting of H and C_1-C_8 alkyl;

R^{16} is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl, and C_1-C_8 alkyl-(C_3-C_8 heterocyclyl);

each R^{17} is independently selected from the group consisting of H, OH, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, and -O-(C_1-C_8 alkyl);

R^{18} is selected from the group consisting of H and C_1-C_8 alkyl;

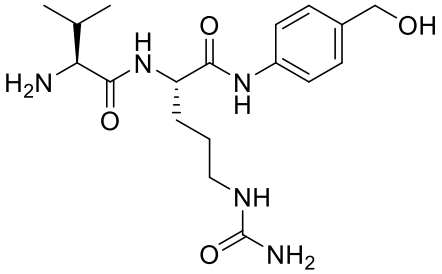
R^{19} is selected from the group consisting of $–C(R^{17})_2–C(R^{17})_2–$aryl, $–C(R^{17})_2–C(R^{17})_2–(C_3$-$C_8$ heterocyclyl), $–C(R^{17})_2–C(O)–ZR^{20}$, and $–C(R^{17})_2–C(R^{17})_2–(C_3$-$C_8$ carbocyclyl);

R^{20} is selected from the group consisting of H, C_1-C_8 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_5-C_{10} heteroaryl and C_3-C_8 heterocyclyl; and

Z is –O-, or –NH-, or

Z- is –O- and R^{20} is C_1-C_4 alkyl or Z is –NH- and R^{20} is optionally substituted phenyl or optionally substituted C_5-C_6 heteroaryl.

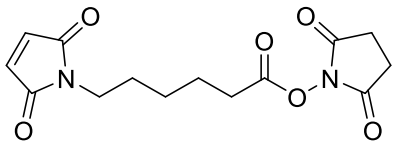
24. The method of claim 23, wherein the conversion of the compound of Formula (1A) or a salt thereof to the compound of Formula (1D) or a salt thereof comprises converting the compound of Formula (1A) or a salt thereof to a compound of Formula (1E) or a salt thereof:



(1E),

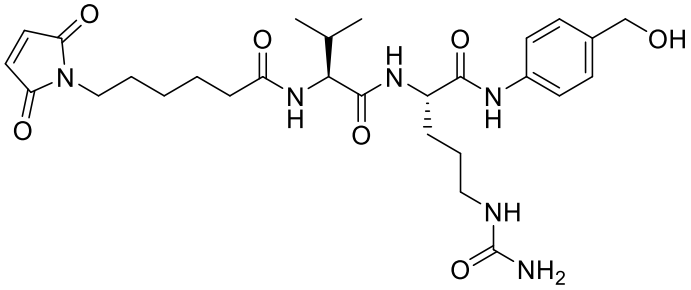
and converting the compound of Formula (1E) or a salt thereof to the compound of Formula (1D) or a salt thereof.

25. The method of claim 24, wherein the conversion of the compound of Formula (1A) or a salt thereof to the compound of Formula (1D) or a salt thereof further comprises reacting the compound of Formula (1E) or a salt thereof with a compound of Formula (1F):



(1F),

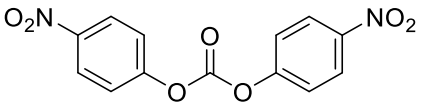
to form a compound of Formula (1G) or a salt thereof:



(1G),

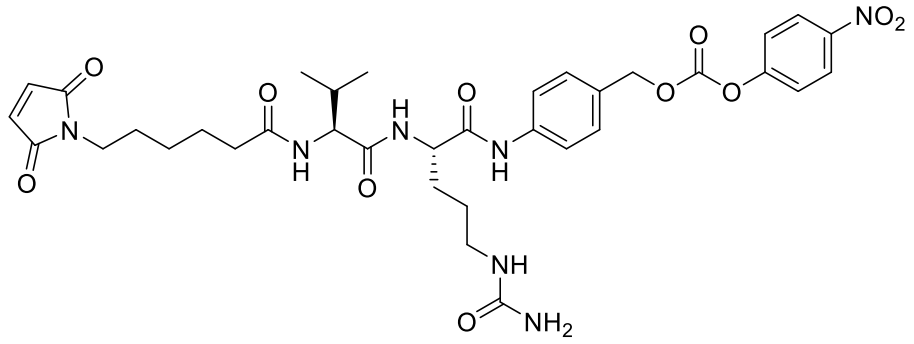
and converting the compound of Formula (1G) or a salt thereof to the compound of Formula (1D) or a salt thereof.

26. The method of claim 25, wherein the conversion of the compound of Formula (1A) or a salt thereof to the compound of Formula (1D) or a salt thereof further comprises reacting the compound of Formula (1G) or a salt thereof with a compound of Formula (1H):



(1H),

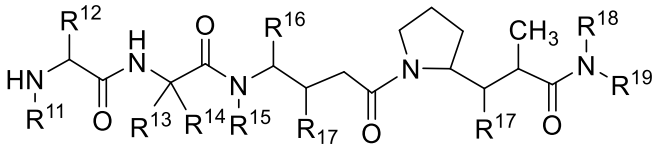
to form a compound of Formula (1I) or a salt thereof:



(1I),

and converting the compound of Formula (1I) or a salt thereof to the compound of Formula (1D) or a salt thereof.

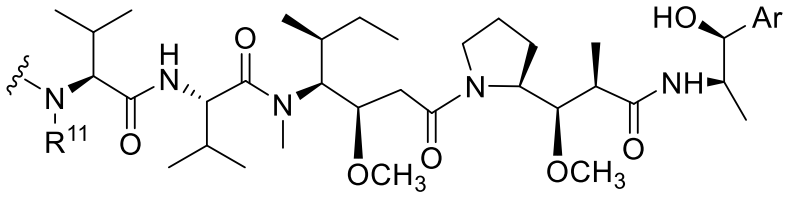
27. The method of claim 26, wherein the conversion of the compound of Formula (1A) or a salt thereof to the compound of Formula (1D) or a salt thereof further comprises reacting the compound of Formula (1I) or a salt thereof with a compound of Formula (1J) or a salt thereof:



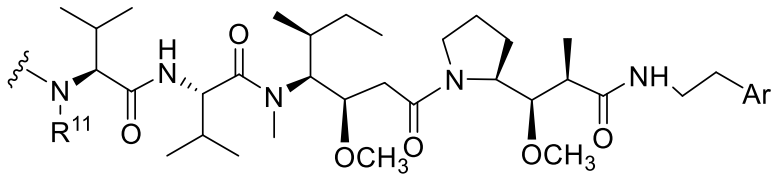
(1J)

to form the compound of Formula (1D) or a salt thereof.

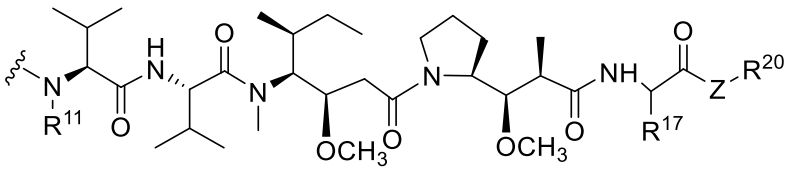
28. The method of any one of claims 23-27, wherein D is a moiety of any one of Formulae **D_{E-1}**, **D_{E-2}**, **D_{F-1}** and **$D_{F/E-3}$**:



(**D_{E-1}**),

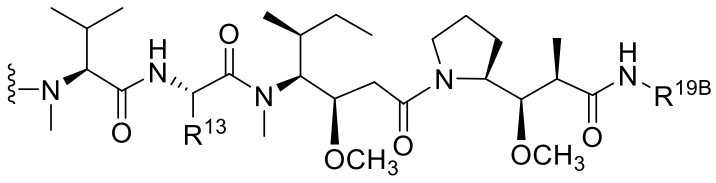


(**D_{E-2}**),



(**D**$_{F-1}$),

and



(**D**$_{F/E-3}$),

wherein the wavy line indicates covalent bonding of D to the remainder of the compound;

R^{11} is selected from the group consisting of H and C_1-C_8 alkyl;

R^{13} is isopropyl or $–CH_2$-$CH(CH_3)_2$;

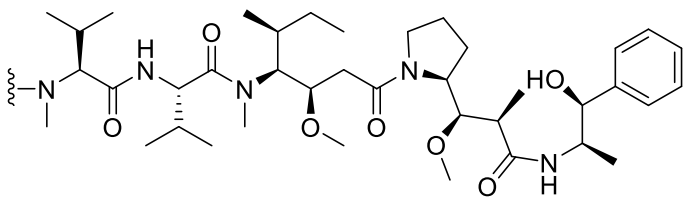
R^{17} is selected from the group consisting of H, OH, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, and -O-(C_1-C_8 alkyl);

R^{19B} is $–CH(CH_3)$-CH(OH)Ph, -$CH(CO_2H)CH_2$Ph, -$CH(CH_2Ph)$-2-thiazole, -$CH(CH_2Ph)$-2-pyridyl, -$CH(CH_2$-p-Cl-Ph), -$CH(CO_2Me)$-CH_2Ph, -$CH(CO_2Me)$-$CH_2CH_2SCH_3$, $CH(CH_2CH_2SCH_3)C(=O)$NH-3-quinolyl, or -$CH(CH_2Ph)C(=O)$NH-p-Cl-Ph;

R^{20} is selected from the group consisting of H, C_1-C_8 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_5-C_{10} heteroaryl and C_3-C_8 heterocyclyl; and

Ar is optionally substituted C_6-C_{10} aryl or optionally substituted C_3-C_8 heterocyclyl.

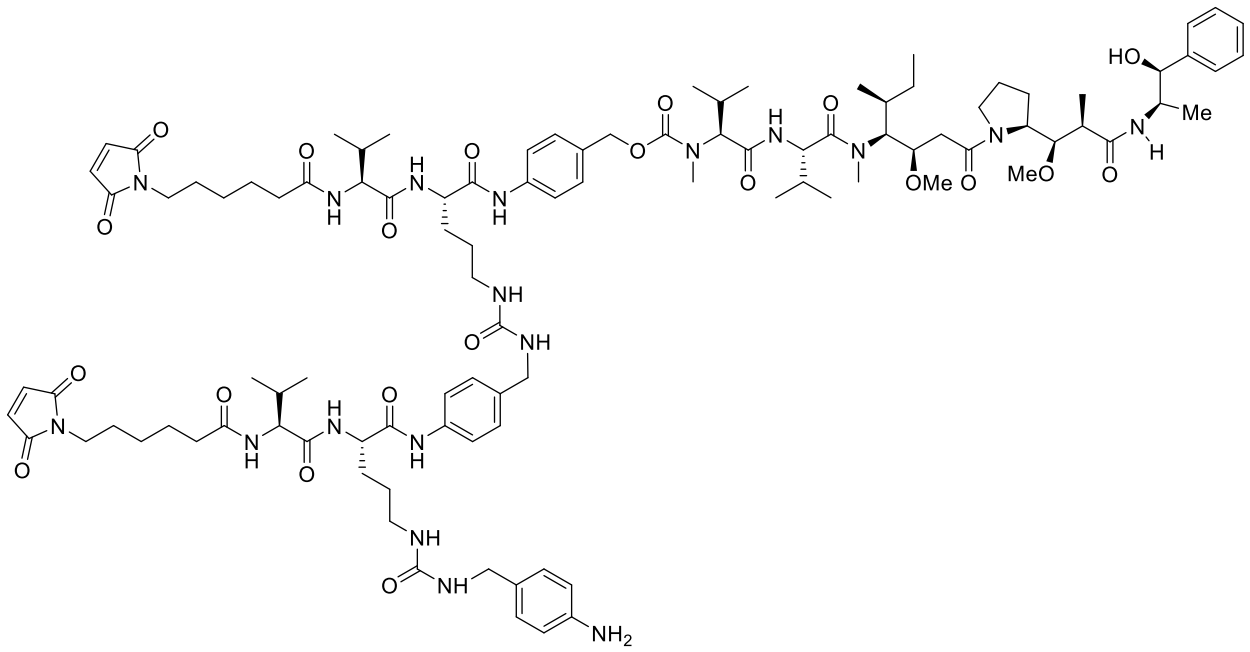
29. The method of any one of claims 23-27, wherein D is a moiety of Formula (D1):



(D1),

wherein the wavy line indicates covalent bonding of D to the remainder of the compound.

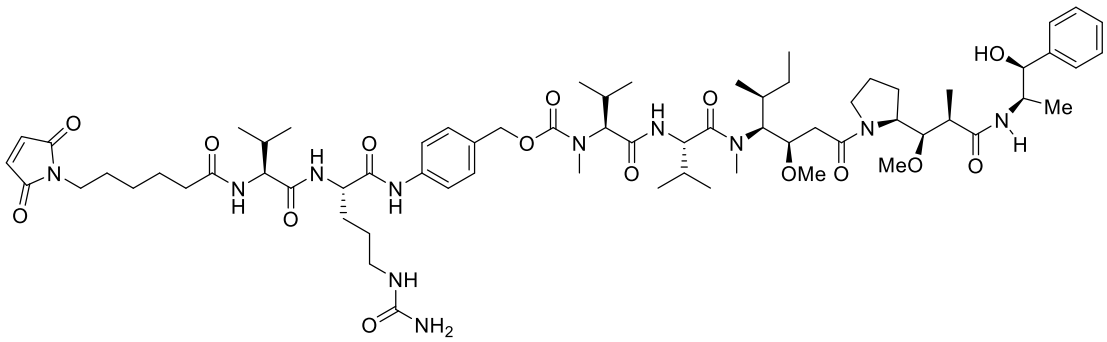
30. A compound of Formula (4):



(4).

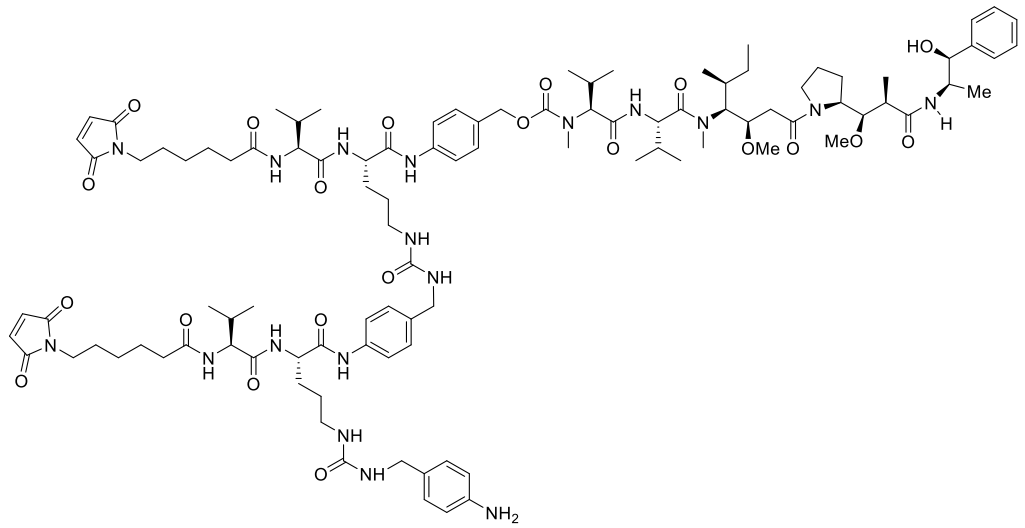
31. The compound of claim 30, wherein the compound is isolated.

32. A composition comprising a compound of Formula (3),



(3),

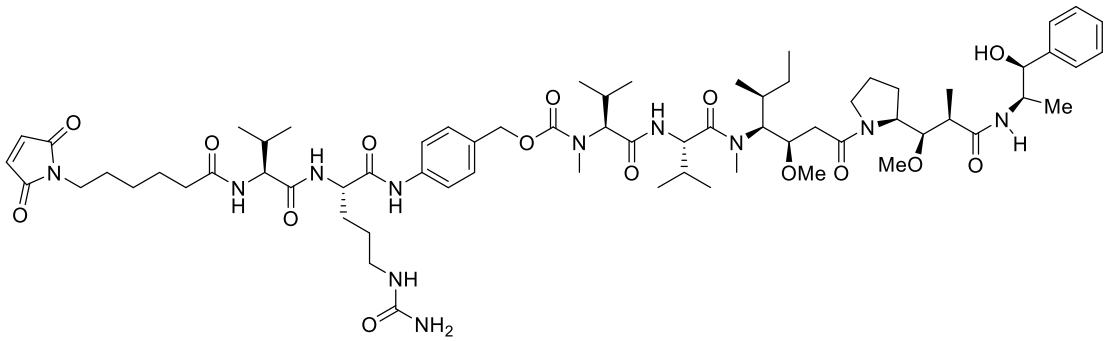
and a compound of Formula (4):



(4),

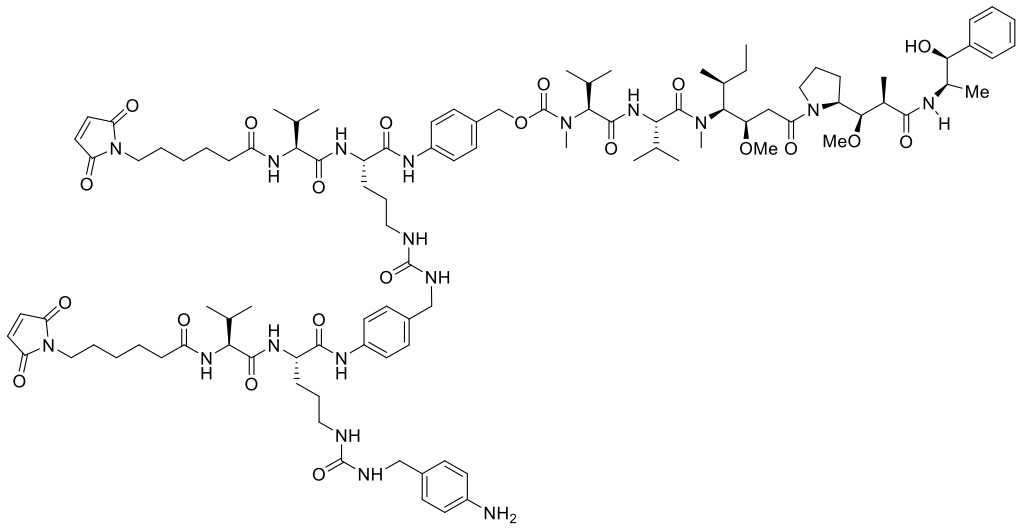
wherein the molar ratio of the compound of Formula (4) to the compound of Formula (3) is no more than 0.1%.

33. A composition comprising a compound of Formula (3):



(3),

wherein the composition is substantially free of a compound of Formula (4):



(4).

34. The composition of claim 32 or 33, further comprising a pharmaceutically acceptable carrier or excipient.