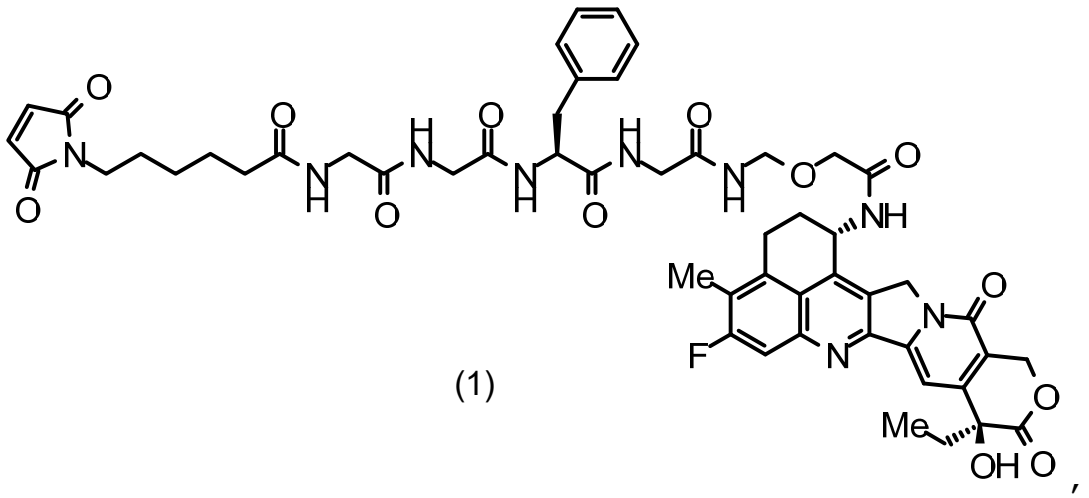
Claims

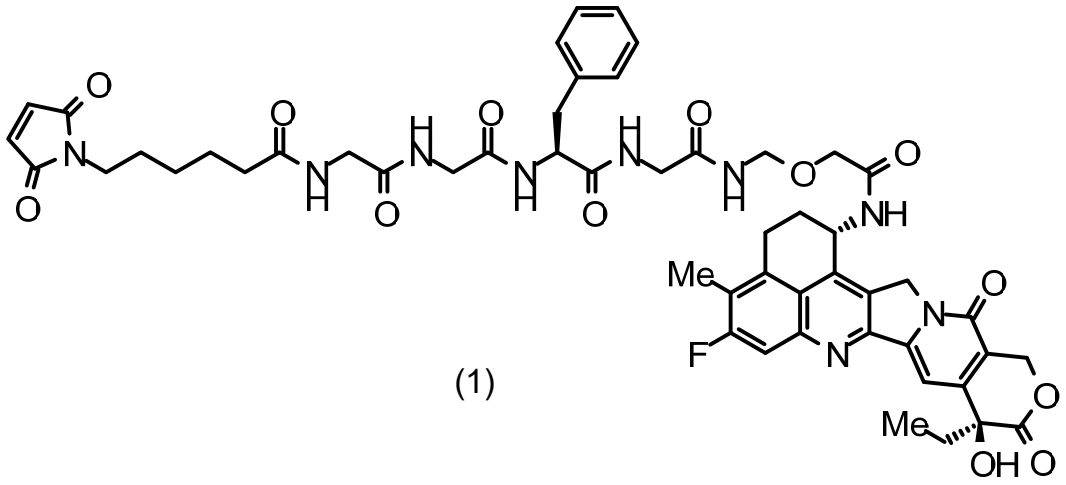
1. Crystals of the compound represented by formula (1):



(1)

wherein the crystals show main peaks at diffraction angles (2θ) of 5.6 ± 0.2°, 15.5 ± 0.2° and 22.0 ± 0.2° in powder X-ray diffraction obtained by irradiation with copper Kα radiation.

2. A method for producing crystals of the compound represented by formula (1):



(1)

comprising the steps of:

preparing a solution comprising a lower ketone and a lower alcohol as solvents in which the compound represented by the formula (1) is dissolved, wherein the lower alcohol is an alcohol having 1 to 4 carbon atoms and the lower ketone is a ketone having 3 to 6 carbon atoms; and then

precipitating crystals of the compound represented by the formula (1) from the solution;

wherein the crystals of the compound represented by the formula (1) show main peaks at diffraction angles (2θ) of 5.6 ± 0.2°, 15.5 ± 0.2° and 22.0 ± 0.2° in powder X-ray diffraction obtained by irradiation with a copper Kα radiation.

3. The production method according to claim 2, wherein the lower ketone is acetone.

4. The production method according to claim 2, wherein the lower ketone is methyl ethyl ketone.

5. The production method according to any one of claims 2 to 4, wherein the lower alcohol is 1-propanol.

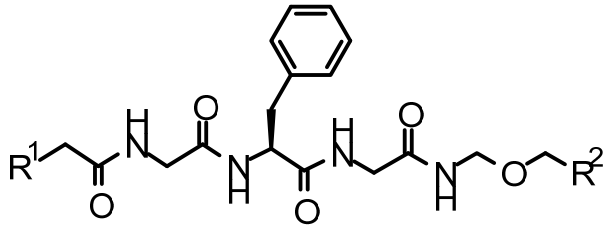
6. The production method according to any one of claims 2 to 4, wherein the lower alcohol is 2-butanol.

7. The production method according to any one of claims 2 to 6, further comprising a step of adding a seed crystal of the crystals of the compound represented by the formula (1).

8. The production method according to any one of claims 2 to 7, further comprising producing the compound represented by the formula (1) by a production method (I),

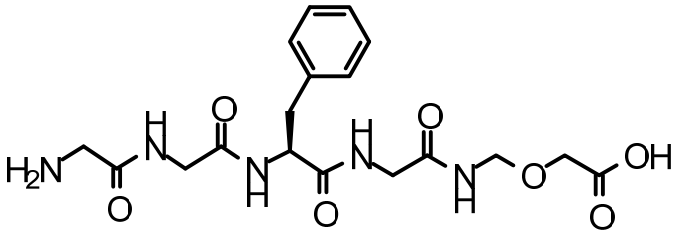
wherein the production method (I) is a production method comprising the steps of:

deprotecting protecting groups for an amino group and a carboxy group of a compound represented by formula (B):



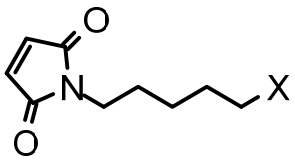
(B)

wherein R^1 represents an amino group protected with a protecting group, and R^2 represents a carboxy group protected with a protecting group, to convert it into the compound represented by formula (8):



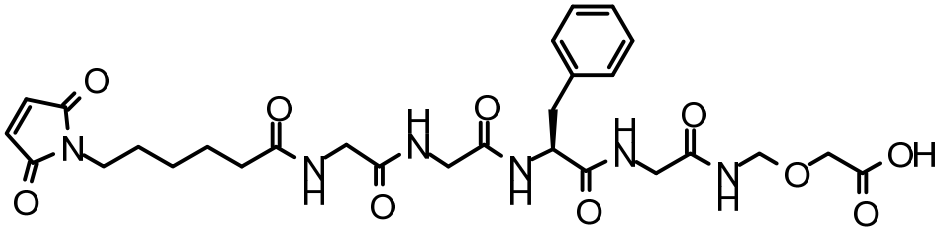
(8) ; then

condensing the compound represented by the formula (8) with a compound represented by formula (C):



(C)

wherein X represents an active ester group or a carboxy group, to convert it into the compound represented by formula (10):

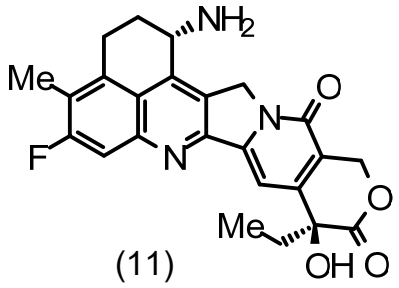


(10)

; and

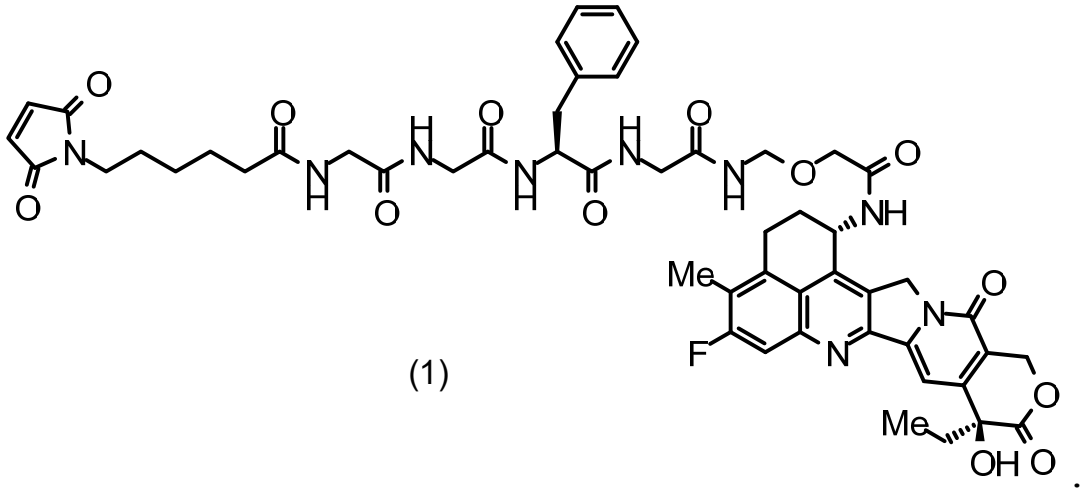
then

condensing the compound represented by the formula (10) with the compound represented by formula (11):



(11)

to convert it into the compound represented by the formula (1):



(1)

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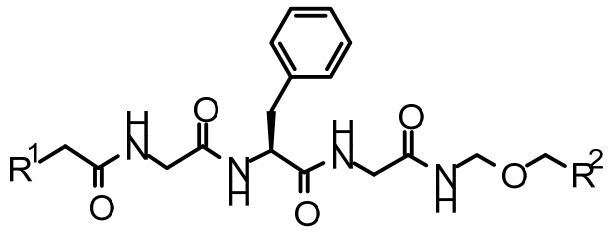
9. The production method according to any one of claims 2 to 7, further comprising producing the compound represented by the formula (1) by a production method (II),

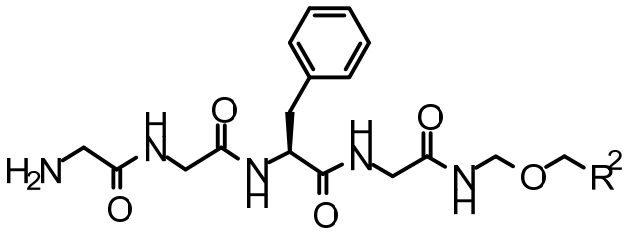
wherein the production method (II) is a production method comprising the steps of:

deprotecting a protecting group for an amino group of a compound represented by formula (B):



(B)

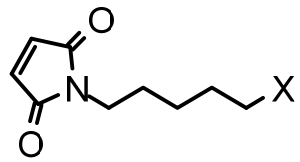
wherein R^1 represents an amino group protected with a protecting group, and R^2 represents a carboxy group protected with a protecting group, to convert it into a compound represented by formula (D):



(D)

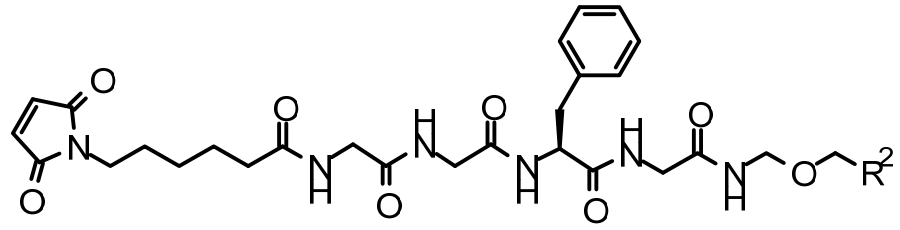
wherein R^2 represents the same meaning as above; then

condensing the compound represented by the formula (D) with a compound represented by formula (C):



(C)

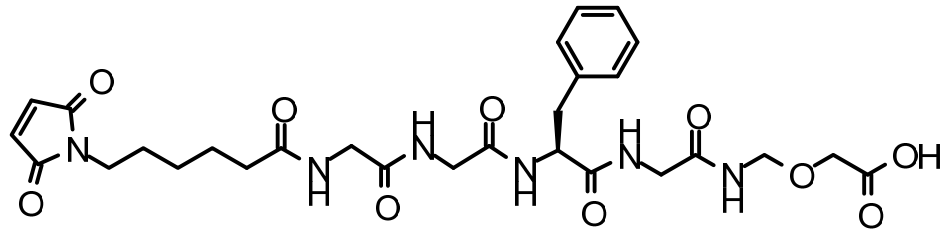
wherein X represents an active ester group or a carboxy group, to convert it into a compound represented by formula (E):



(E)

wherein R^2 represents the same meaning as above; then

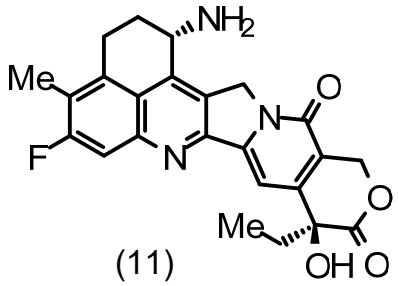
deprotecting the protecting group for the carboxy group of the compound represented by the formula (E) to convert it into the compound represented by formula (10):



(10)

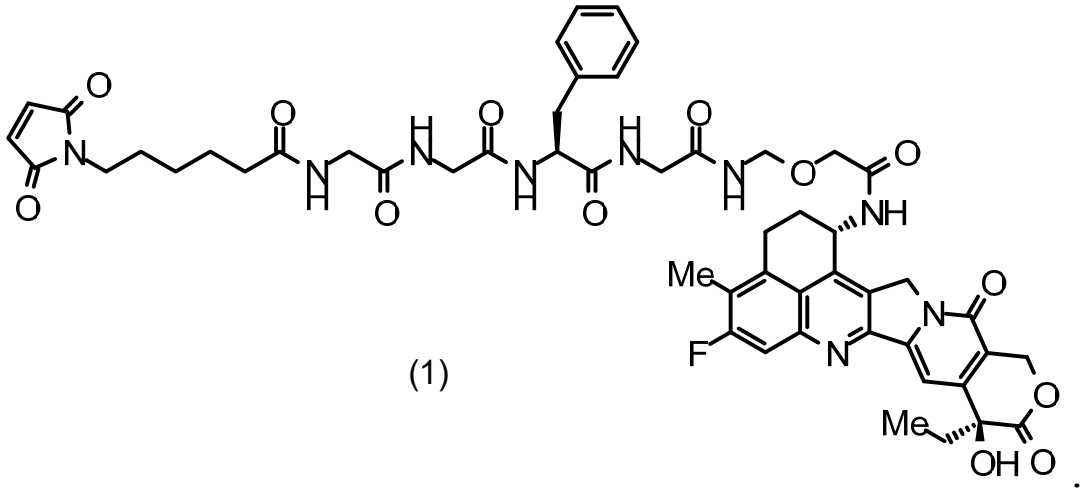
; and then

condensing the compound represented by the formula (10) with the compound represented by formula (11):



(11)

to convert it into the compound represented by the formula (1):



(1)

10. The production method according to claim 8 or 9, further comprising the steps of:

dissolving the compound represented by the formula (10) in a solvent containing 1,2-dimethoxyethane; and then

precipitating crystals of a 1,2-dimethoxyethane adduct of the compound represented by the formula (10).

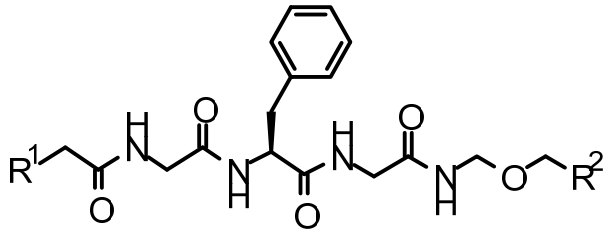
11. The production method according to claim 10, wherein the crystals of the 1,2-dimethoxyethane adduct of the compound represented by the formula (10) show main peaks at diffraction angles (2θ) of 19.0 ± 0.2° and 25.0 ± 0.2° in powder X-ray diffraction obtained by irradiation with a copper Kα radiation.

12. The production method according to any one of claims 8 to 11, wherein the step of condensing the compound represented by the formula (10) and the compound represented by the formula (11) to convert it into the compound represented by the formula (1) is performed in a two-phase system of an aqueous sodium sulfate solution and tetrahydrofuran.

13. The production method according to any one of claims 2 to 7, further comprising producing the compound represented by the formula (1) by a production method (III),

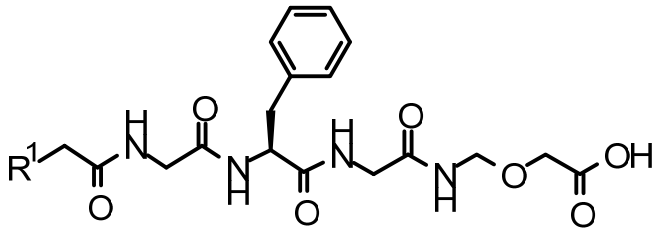
wherein the production method (III) is a production method comprising the steps of:

deprotecting a protecting group for a carboxy group of a compound represented by formula (B):



(B)

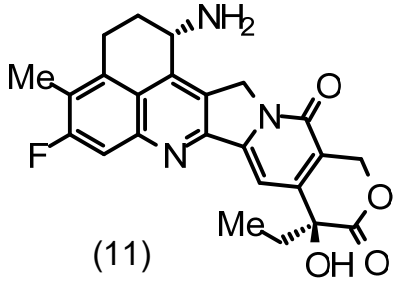
wherein R^1 represents an amino group protected with a protecting group, and R^2 represents a carboxy group protected with a protecting group, to convert it into a compound represented by formula (F):



(F)

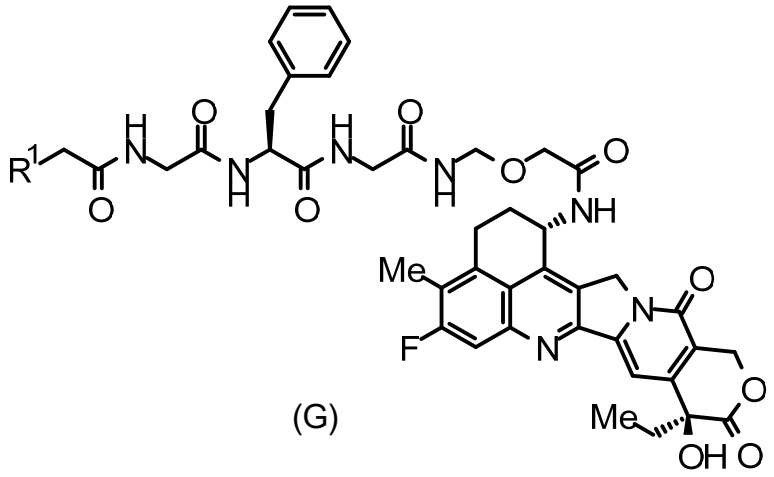
wherein R^1 represents the same meaning as above; then

condensing the compound represented by the formula (F) with the compound represented by formula (11):



(11)

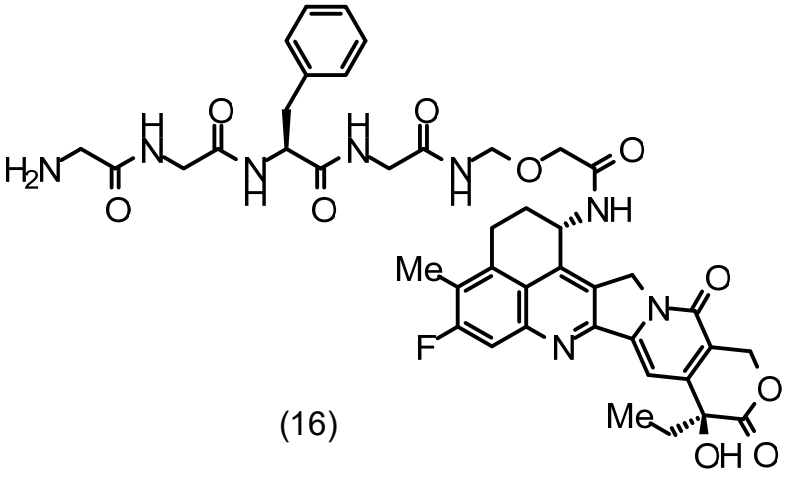
to convert it into a compound represented by formula (G):



(G)

wherein R^1 represents the same meaning as above; then

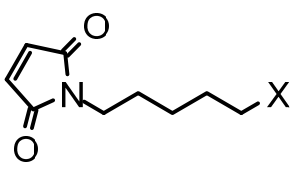
deprotecting the protecting group for the amino group of the compound represented by the formula (G) to convert it into the compound represented by formula (16):



(16)

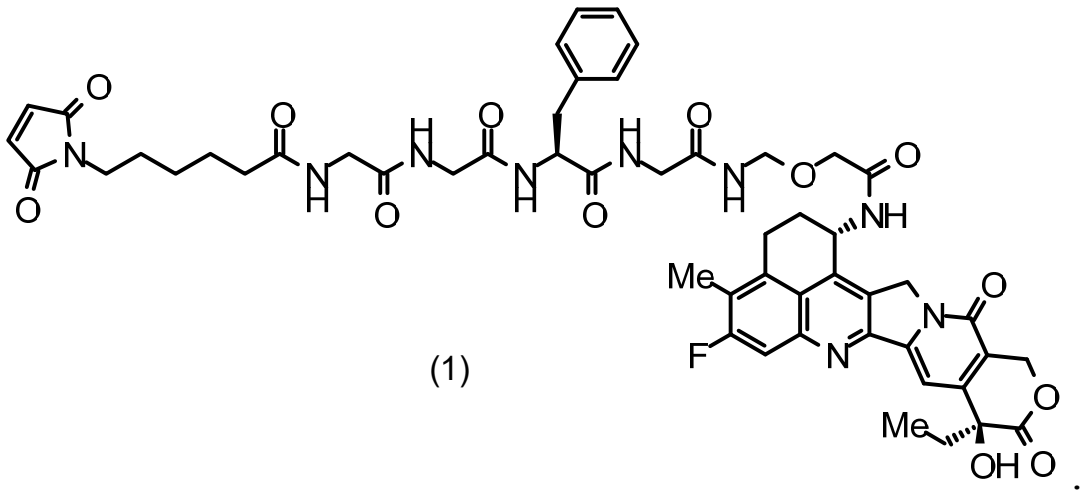
; and then

condensing the compound represented by the formula (16) with a compound represented by formula (C):



(C)

wherein X represents an active ester group or a carboxy group, to convert it into the compound represented by the formula (1):



(1)

14. The production method according to any one of claims 8 to 13, wherein the compound represented by the formula (11) is in the form of a methanesulfonic acid salt.

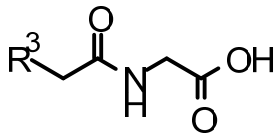
15. The production method according to any one of claims 8 to 13, wherein the compound represented by the formula (11) is in the form of a methanesulfonic acid salt m-hydrate, wherein m is in the range of 0 to 3.

16. The production method according to any one of claims 8 to 13, wherein the compound represented by the formula (11) is in the form of a methanesulfonic acid salt dihydrate.

17. The production method according to any one of claims 8 to 16, further comprising producing the compound represented by the formula (B) by a production method (IV),

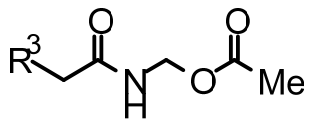
wherein the production method (IV) is a production method comprising the steps of:

reacting a compound represented by formula (H):



(H)

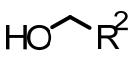
wherein R^3 represents an amino group protected with a protecting group, with lead tetraacetate to convert it into a compound represented by formula (J):



(J)

wherein R^3 represents the same meaning as above; then

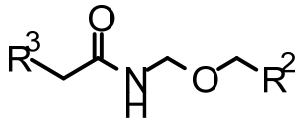
reacting the compound represented by the formula (J) with a compound represented by formula (K):



(K)

wherein R^2 represents the same meaning as the R^2 according to any one of claims 8 to 16, in the presence

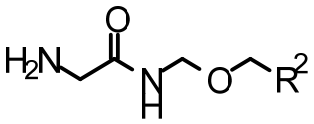
of an acid or a base to convert it into a compound represented by formula (L):



(L)

wherein R^2 and R^3 represent the same meanings as above; then

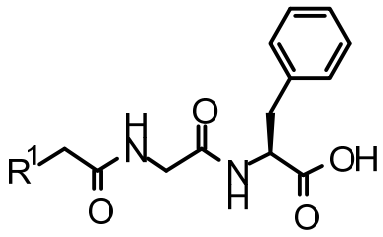
deprotecting the protecting group for the amino group of the compound represented by the formula (L) to convert it into a compound represented by formula (M):



(M)

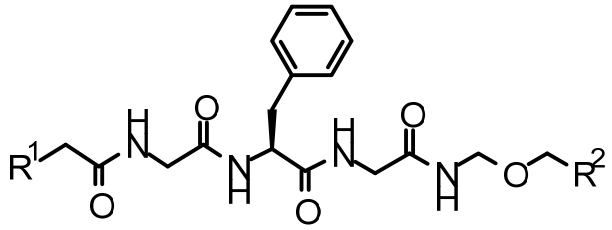
wherein R^2 represents the same meaning as above; and then

condensing the compound represented by the formula (M) with a compound represented by formula (N):



(N)

wherein R^1 represents the same meaning as the R^1 according to any one of claims 8 to 16, to convert it into the compound represented by the formula (B):



(B)

wherein R^1 and R^2 represent the same meanings as above.

18. The production method according to claim 17, wherein the step of reacting the compound represented by the formula (H) with lead tetraacetate to convert it into the compound represented by the formula (J) is performed in the presence of acetic acid.

19. The production method according to claim 17 or 18, wherein the step of reacting the compound represented by the formula (J) with the compound represented by the formula (K) to convert it into the compound represented by the formula (L) is performed in the presence of an aqueous sodium hydroxide solution.

20. The production method according to claim 17 or 18, wherein the step of reacting the compound represented by the formula (J) with the compound represented by the formula (K) to convert it into the compound represented by the formula (L) is performed in the presence of tris(pentafluorophenyl)borane.

21. The production method according to any one of claims 17 to 20, further comprising a step of adding an acid to precipitate a salt of the compound represented by the formula (M) and the acid after the step of deprotecting the protecting group for the amino group of the compound represented by the formula (L) to convert it into the compound represented by the formula (M).

22. The production method according to claim 21, wherein the acid is 1-hydroxybenzotriazole.

23. The production method according to any one of claims 8 to 22, wherein R^1 is an amino group protected with a benzyloxycarbonyl group.

24. The production method according to any one of claims 8 to 22, wherein R^1 is an amino group protected with a (9H-fluoren-9-ylmethoxy)carbonyl group.

25. The production method according to any one of claims 8 to 24, wherein R^2 is a carboxy group protected with a benzyl group.

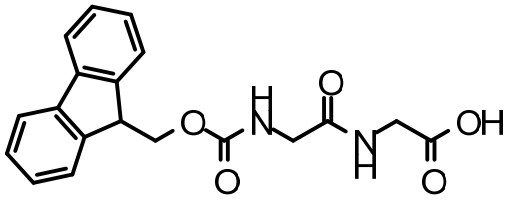
26. The production method according to any one of claims 17 to 25, wherein R^3 is an amino group protected with a (9H-fluoren-9-ylmethoxy)carbonyl group.

27. The production method according to any one of claims 8 to 26, wherein X is a (2,5-dioxopyrrolidin-1-yl)oxycarbonyl group.

28. The production method according to any one of claims 2 to 7, further comprising producing the compound represented by the formula (1) by a production method (V),

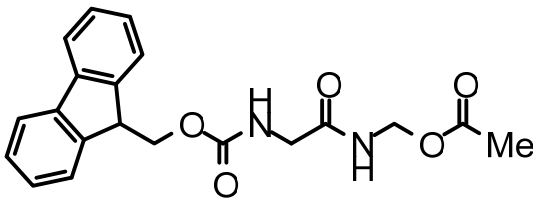
wherein the production method (V) is a production method comprising the steps of:

reacting the compound represented by formula (2):



(2)

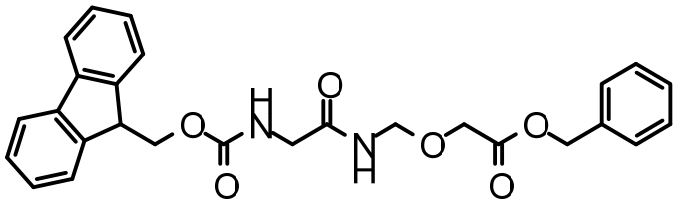
with lead tetraacetate to convert it into the compound represented by formula (3):



(3) ; then

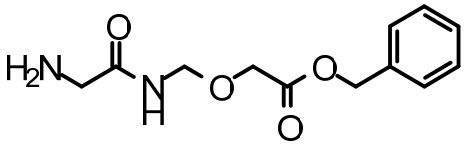
reacting the compound represented by the formula (3) with benzyl glycolate in the presence of an acid or a

base to convert it into the compound represented by formula (4):



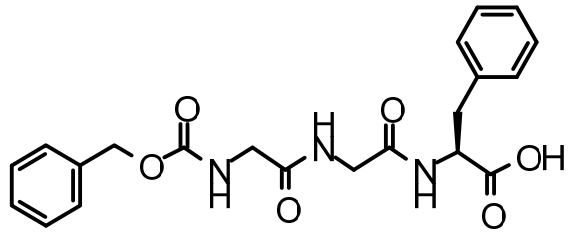
(4) ; then

deprotecting a protecting group for an amino group of the compound represented by the formula (4) to convert it into the compound represented by formula (5):



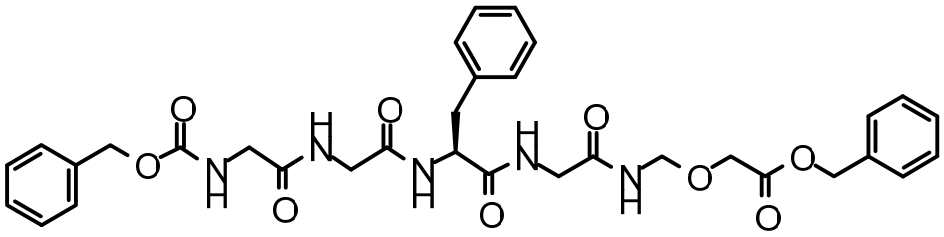
(5) ; then

condensing the compound represented by the formula (5) with the compound represented by formula (6):



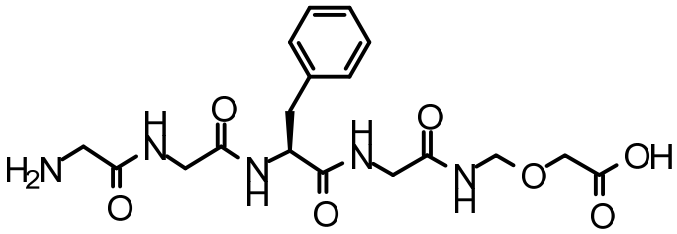
(6)

to convert it into the compound represented by formula (7):



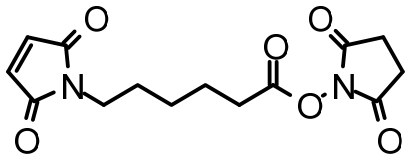
(7) ; then

deprotecting protecting groups for an amino group and a carboxy group of the compound represented by the formula (7) to convert it into the compound represented by formula (8):



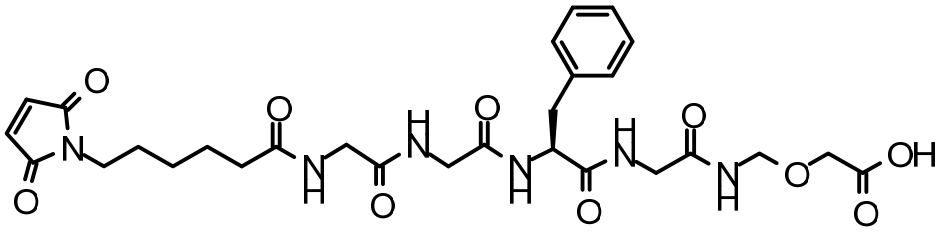
(8) ; then

condensing the compound represented by the formula (8) with the compound represented by formula (9):



(9)

to convert it into the compound represented by formula (10):

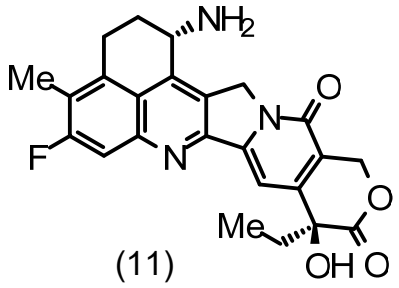


(10)

; and

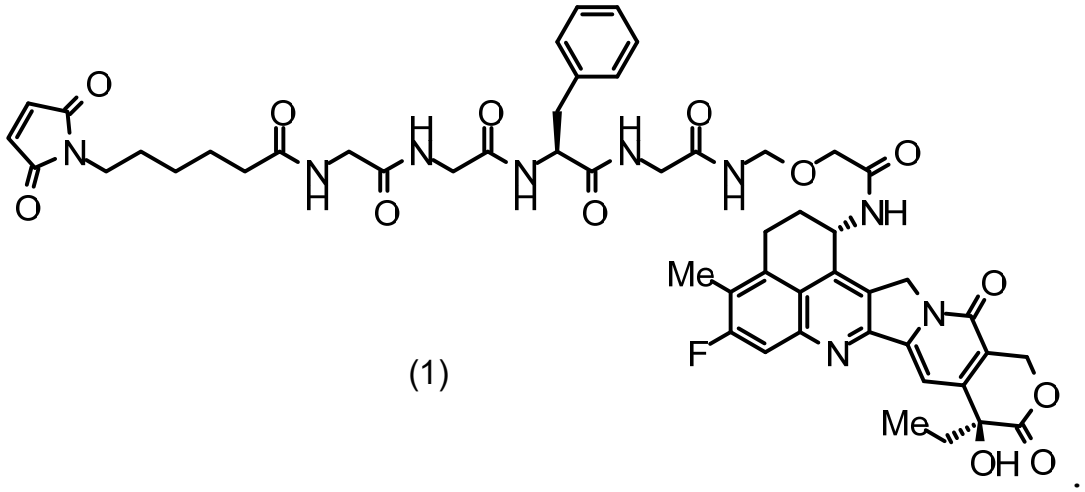
then

condensing the compound represented by the formula (10) with the compound represented by formula (11):



(11)

to convert it into the compound represented by formula (1):



(1)

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29. The production method according to claim 28, further comprising the steps of:

dissolving the compound represented by the formula (10) in a solvent containing 1,2-dimethoxyethane; and then

precipitating crystals of a 1,2-dimethoxyethane adduct of the compound represented by the formula (10).

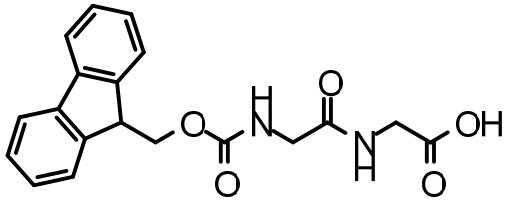
30. The production method according to claim 29, wherein the crystals of the 1,2-dimethoxyethane adduct of the compound represented by the formula (10) show main peaks at diffraction angles (2θ) of 19.0 ± 0.2° and 25.0 ± 0.2° in powder X-ray diffraction obtained by irradiation with a copper Kα radiation.

31. The production method according to any one of claims 28 to 30, wherein the step of condensing the compound represented by the formula (10) with the compound represented by the formula (11) to convert it into the compound represented by the formula (1) is performed in a two-phase system of an aqueous sodium sulfate solution and tetrahydrofuran.

32. The production method according to any one of claims 2 to 7, further comprising producing the compound represented by the formula (1) by a production method (VI),

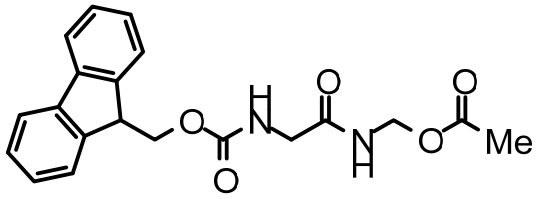
wherein the production method (VI) is a production method comprising the steps of:

reacting the compound represented by formula (2):



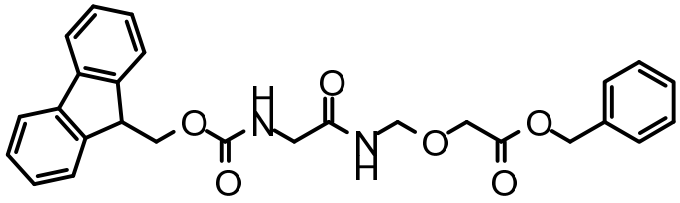
(2)

with lead tetraacetate to convert it into the compound represented by formula (3):



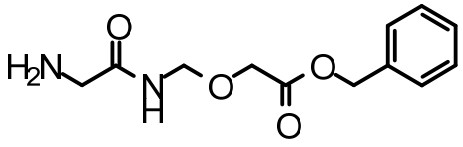
(3) ; then

reacting the compound represented by the formula (3) with benzyl glycolate in the presence of an acid or a base to convert it into the compound represented by formula (4):



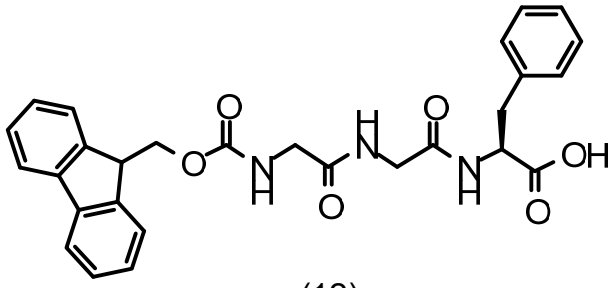
(4) ; then

deprotecting a protecting group for an amino group of the compound represented by the formula (4) to convert it into the compound represented by formula (5):



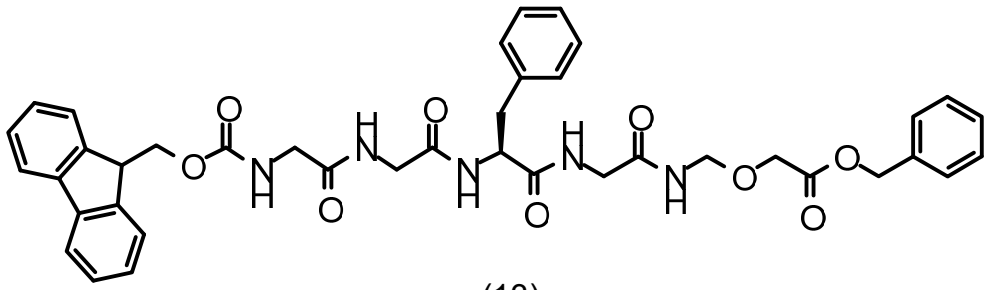
(5) ; then

condensing the compound represented by the formula (5) with the compound represented by formula (12):



(12)

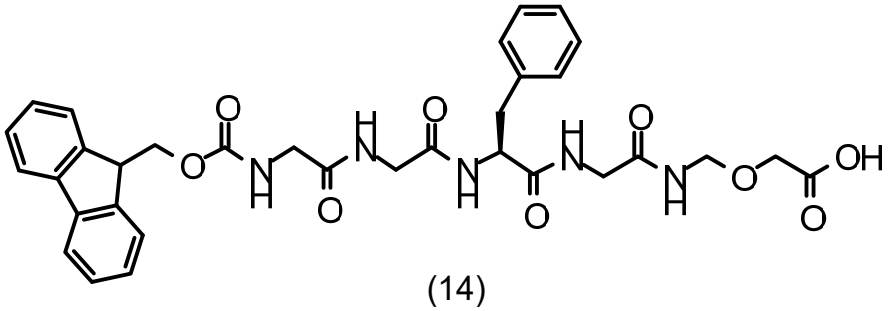
to convert it into the compound represented by formula (13):



(13) ;

then

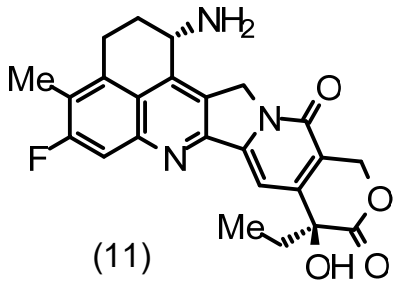
deprotecting a protecting group for a carboxy group of the compound represented by the formula (13) to convert it into the compound represented by formula (14):



(14)

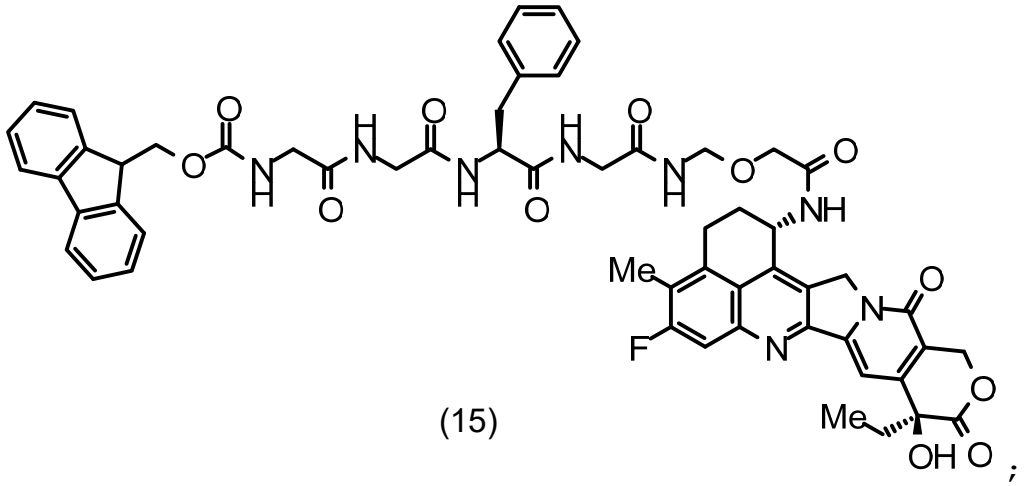
; then

condensing the compound represented by the formula (14) with the compound represented by formula (11):



(11)

to convert it into the compound represented by formula (15):

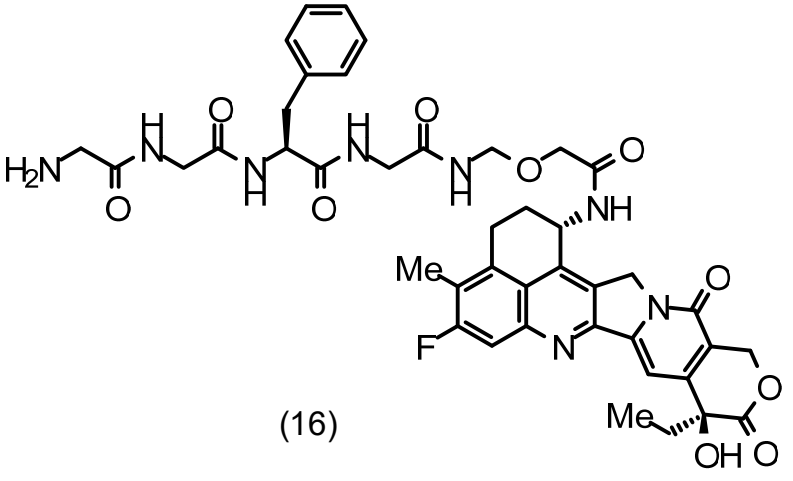


(15)

;

then

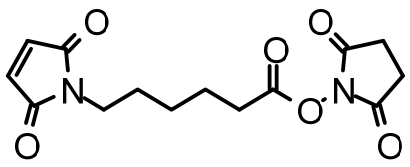
deprotecting a protecting group for an amino group of the compound represented by the formula (15) to convert it into the compound represented by formula (16):



(16)

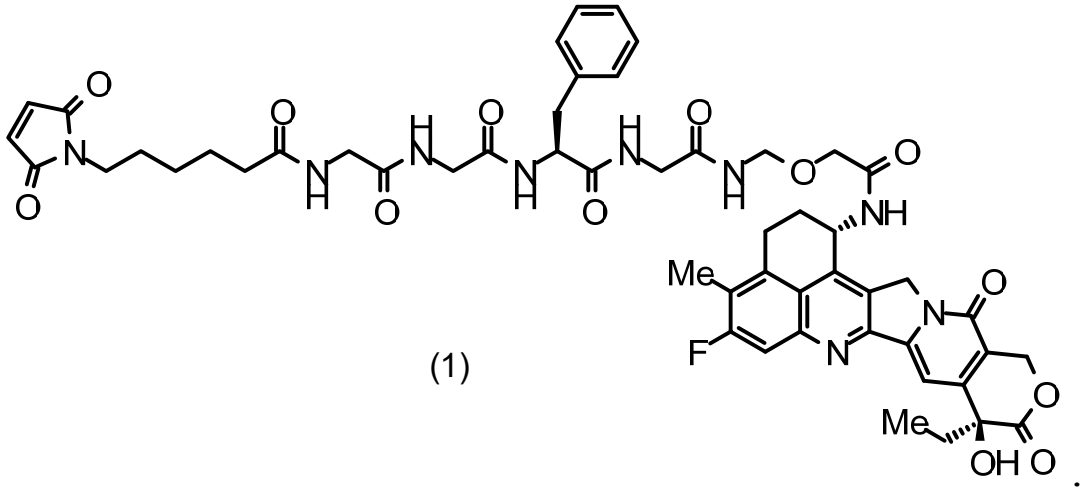
; and then

condensing the compound represented by the formula (16) with the compound represented by formula (9):



(9)

to convert it into the compound represented by the formula (1):



(1)

33. The production method according to any one of claims 28 to 32, wherein the step of reacting the compound represented by the formula (2) with lead tetraacetate to convert it into the compound represented by the formula (3) is performed in the presence of acetic acid.

34. The production method according to any one of claims 28 to 33, wherein the step of converting the compound represented by the formula (3) into the compound represented by the formula (4) is performed in the presence of an aqueous sodium hydroxide solution.

35. The production method according to any one of claims 28 to 33, wherein the step of converting the compound represented by the formula (3) into the compound

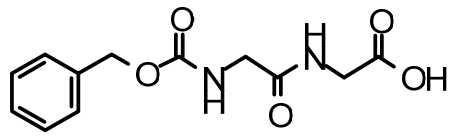
represented by the formula (4) is performed in the presence of tris(pentafluorophenyl)borane.

36. The production method according to any one of claims 28 to 35, further comprising a step of adding an acid to precipitate a salt of the compound represented by the formula (5) and the acid after the step of deprotecting the protecting group for the amino group of the compound represented by the formula (4) to convert it into the compound represented by the formula (5).

37. The production method according to claim 36, wherein the acid is 1-hydroxybenzotriazole.

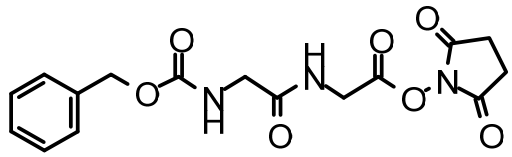
38. The production method according to any one of claims 28 to 37, further comprising producing the compound represented by the formula (6) by a method comprising the steps of:

condensing the compound represented by formula (23):



(23)

with N-hydroxysuccinimide to convert it into the compound represented by formula (24):

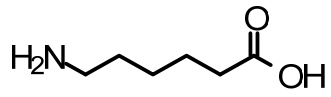


(24) ; and then

condensing the compound represented by the formula (24) with L-phenylalanine to convert it into the compound represented by the formula (6).

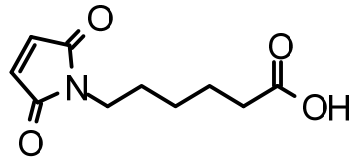
39. The production method according to any one of claims 28 to 38, further comprising producing the compound represented by the formula (9) by a method comprising the steps of:

reacting the compound represented by formula (17):



(17)

with maleic anhydride to convert it into the compound represented by formula (18):



(18) ; and then

adding thionyl chloride to the compound represented by the formula (18) and a mixed solution containing N-

hydroxysuccinimide and 2,6-lutidine to convert it into the compound represented by the formula (9).

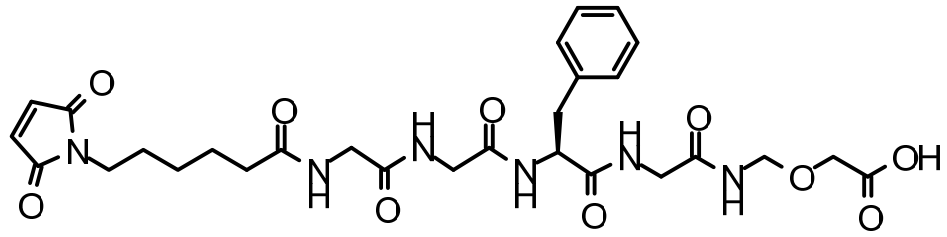
40. The production method according to any one of claims 28 to 39, wherein the compound represented by the formula (11) is in the form of a methanesulfonic acid salt.

41. The production method according to any one of claims 28 to 39, wherein the compound represented by the formula (11) is in the form of a methanesulfonic acid salt m-hydrate, wherein m is in the range of 0 to 3.

42. The production method according to any one of claims 28 to 39, wherein the compound represented by the formula (11) is in the form of a methanesulfonic acid salt dihydrate.

43. The production method according to any one of claims 2 to 42, wherein no chromatography is used.

44. Crystals of a 1,2-dimethoxyethane adduct of the compound represented by formula (10):

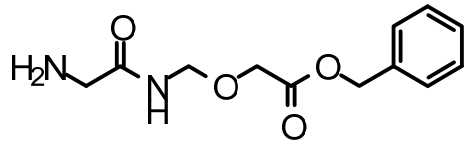


(10)

.

45. The crystals according to claim 44, wherein the crystals show main peaks at diffraction angles (2θ) of 19.0 ± 0.2° and 25.0 ± 0.2° in powder X-ray diffraction obtained by irradiation with a copper Kα radiation.

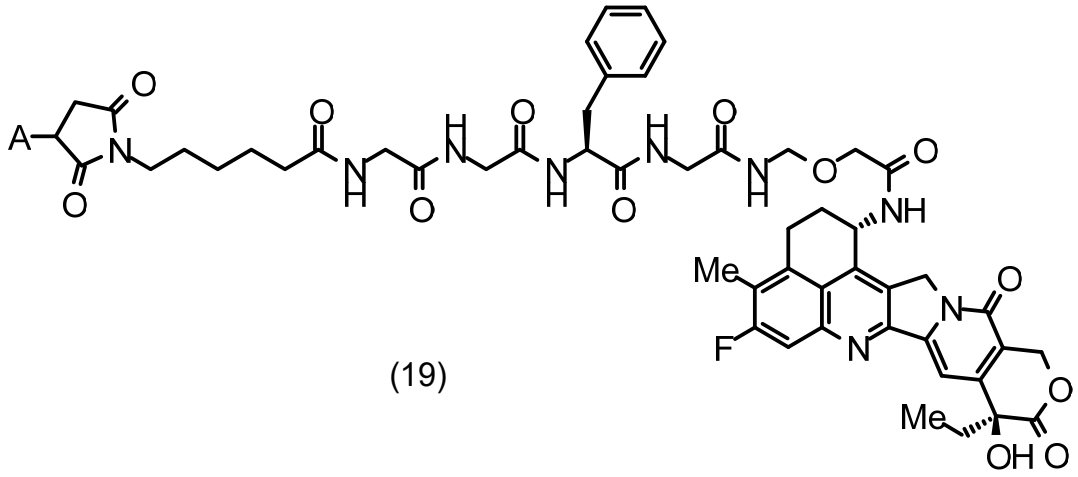
46. A salt of the compound represented by formula (5):



(5)

and an acid, wherein the acid is 1-hydroxybenzotriazole.

47. A method for producing an antibody-drug conjugate, in which a drug-linker represented by formula (19):

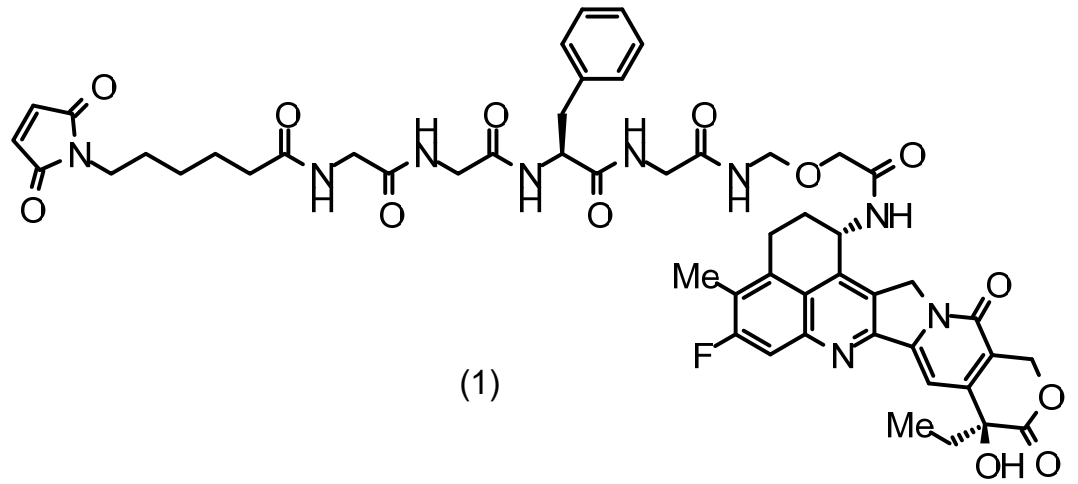


(19)

wherein A represents the connecting position to an antibody,

is conjugated to the antibody via a thioether bond,

wherein crystals of the compound represented by formula (1):



(1)

according to claim 1 are used as a starting material, and the method comprises the steps of:

i) reducing an antibody; and then

ii) adding a solution in which the crystals of the compound represented by the formula (1) are dissolved, to react the solution with the reduced antibody.

48. The production method according to claim 47, wherein the antibody is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, or an anti-GPR20 antibody.