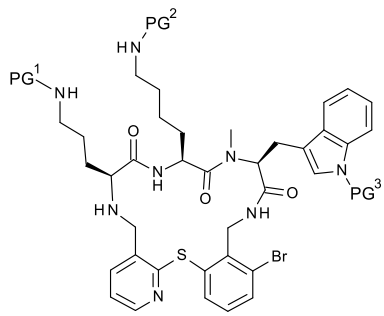
WO2019206853 discloses a laboratory scale synthesis of the compound of formula (Ia), which relies on a solid phase synthesis of a particular tripeptide. However, it has been found that said solid-phase synthesis is not suitable for industrial scale manufacturing of the compound of formula (Ia) due to various issues, such as low yields, long reaction times and epimerization of certain stereocentres.

Accordingly, there is a high unmet need for a new process for manufacturing the compound of formula (Ia).

Summary

The present disclosure provides a solution phase process for manufacturing compounds of formula (I), which overcomes the problems outlined above. The present disclosure also provides certain intermediates that are useful in the new process. Finally, the present disclosure provides a new method for Fmoc deprotection of Fmoc protected amines.

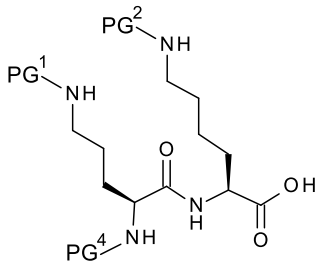
In one aspect, the present disclosure provides a process for manufacturing a compound of formula (I), or a salt thereof,



(I)

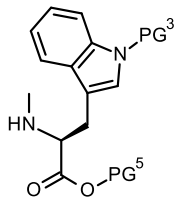
comprising:

(a) reacting a carboxylic acid of formula (II)



(II)

with a secondary amine of formula (III)



(III)

using reagents selected from:

(i) HOAt and DIC;

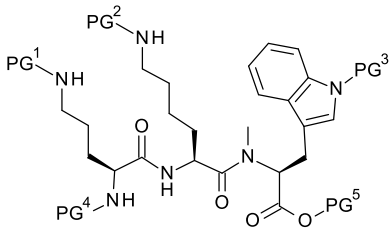
(ii) HODhat and DIC;

(iii) HOPO and DIC;

(iv) HOPO and DCC; and

(v) HOPO and EDC;

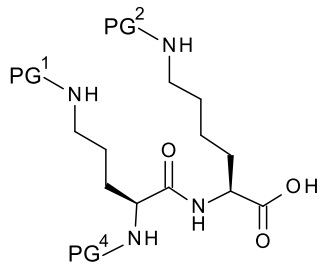
to form a compound of formula (IV)



(IV)

wherein PG^1, PG^2, PG^3 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

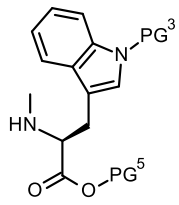
In another aspect, the present disclosure provides a compound of formula (II),



(II)

or a salt thereof, wherein PG^1, PG^2 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

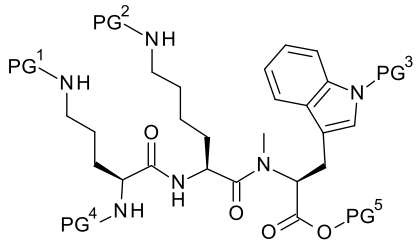
In another aspect, the present disclosure provides a compound of formula (III),



(III)

or a salt thereof, wherein PG^3 is an amino protective group selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

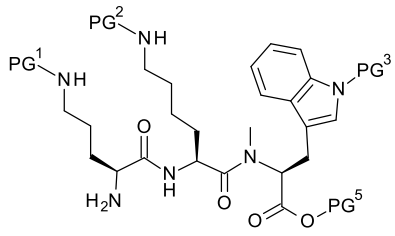
In another aspect, the present disclosure provides a compound of formula (IV),



(IV)

or a salt thereof, wherein PG^1, PG^2, PG^3 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

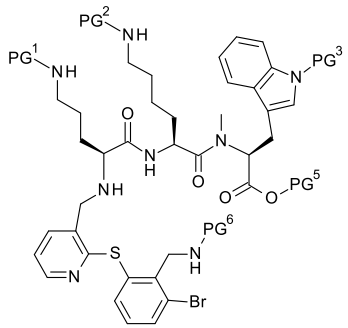
In another aspect, the present disclosure provides a compound of formula (V),



(V)

or a salt thereof, wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

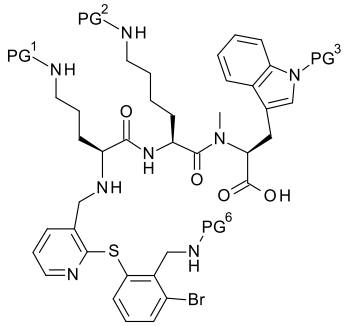
In another aspect, the present disclosure provides a compound of formula (VII),



(VII)

or a salt thereof, wherein PG^1, PG^2, PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

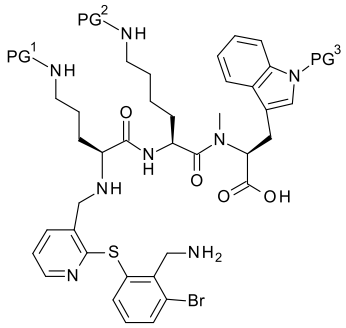
In another aspect, the present disclosure provides a compound of formula (VIII),



(VIII)

or a salt thereof, wherein PG^1, PG^2 and PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

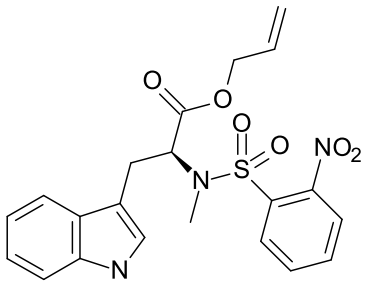
In another aspect, the present disclosure provides a compound of formula (IX),



(IX)

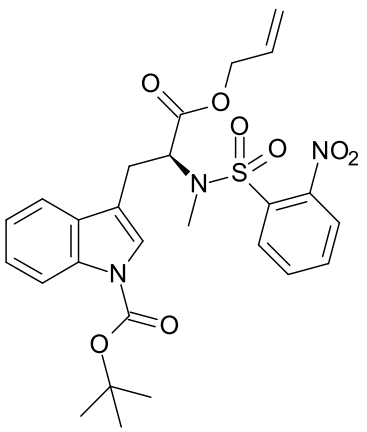
or a salt thereof, wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

In another aspect, the present disclosure provides a compound, which is N-NBS-N-Me-Trp-OAll



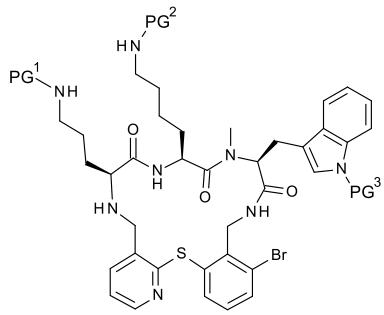
or a salt thereof.

In another aspect, the present disclosure provides a compound, which is N-NBS-N-Me-Trp(Boc)-OAll



or a salt thereof.

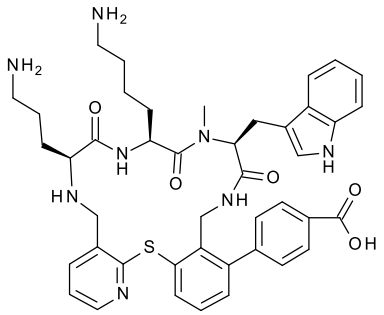
In another aspect, the present disclosure provides a compound of formula (I), or a salt thereof,



(I)

wherein PG^1, PG^2 and PG^3 are amino protective groups, when manufactured according to the process as described herein.

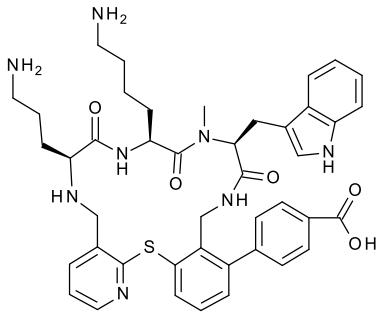
In another aspect, the present disclosure provides a process for manufacturing a compound of formula (1), or a salt thereof,



(1)

comprising a process as described herein.

In another aspect, the present disclosure provides use of the process as described herein in the manufacture of the compound of formula (1)



(1)

or a salt thereof.

Detailed Description of the Invention

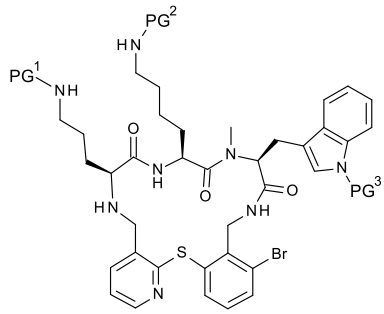
Definitions

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims and the abstract), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims and the abstract), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

The term “protective group” (PG) denotes a group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Protective groups can be removed at the appropriate point. Exemplary amino protective groups are Boc (tert-butoxycarbonyl), benzyl, 4-methoxybenzyl,

CLAIMS

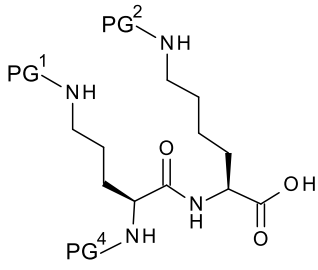
1. A process for manufacturing a compound of formula (I), or a salt thereof,



(I)

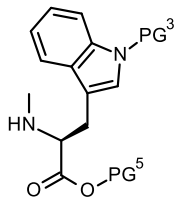
comprising:

(a) reacting a carboxylic acid of formula (II)



(II)

with a secondary amine of formula (III)



(III)

using reagents selected from:

(i) HOAt and DIC;

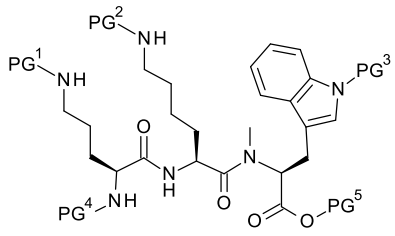
(ii) HODhat and DIC;

(iii) HOPO and DIC;

(iv) HOPO and DCC; and

(v) HOPO and EDC;

to form a compound of formula (IV)



(IV)

wherein PG^1, PG^2, PG^3 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

2. The process according to claim 1, wherein the process is performed in a solvent selected from:

(i) a mixture of *tert*-butyl methyl ether, *n*-heptane and dimethylacetamide;

(ii) isopropylacetate with or without 1,3-dimethyl-2-imidazolidinone;

(iii) *tert*-butyl methyl ether with or without 1,3-dimethyl-2-imidazolidinone;

(iv) dichloromethane with or without 1,3-dimethyl-2-imidazolidinone;

(v) THF with or without 1,3-dimethyl-2-imidazolidinone;

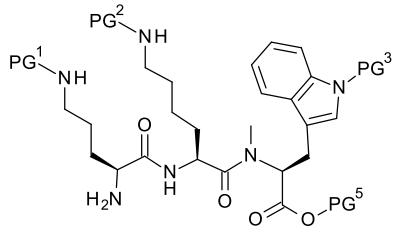
(vi) 2-methyl-THF with or without 1,3-dimethyl-2-imidazolidinone;

(vii) toluene with or without 1,3-dimethyl-2-imidazolidinone; and

(viii) acetonitrile.

3. The process according to any one of claims 1 or 2, further comprising:

(b1) reacting said compound of formula (IV), wherein PG^4 is Fmoc, with N-acetylcysteine and $tAmNH_2$ or $tBuNH_2$, to form a compound of formula (V):



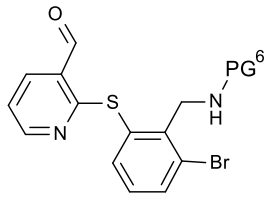
(V);

wherein PG^1, PG^2, and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl; and

(b2) washing the reaction mixture obtained in (b1) with a basic aqueous solution.

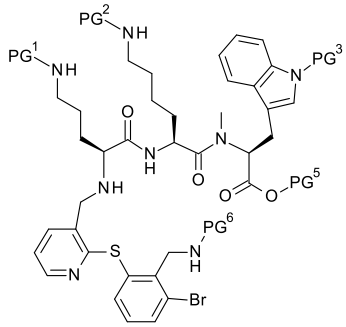
4. The process according to claim 3, further comprising:

(c) reacting said compound of formula (V), with a compound of formula (VI):



(VI);

wherein PG^6 is an amino protective group selected from BOC, Adoc, Moz, and Fmoc; in the presence of (i) a reducing agent selected from $NaBH_3CN$ and $NaBH(OAc)_3$; and (ii) a carboxylic acid selected from acetic acid and propionic acid; to form a compound of formula (VII):

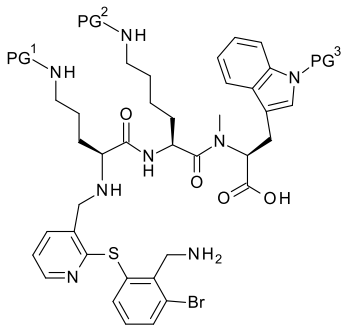


(VII)

wherein PG^1, PG^2, PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

5. The process according to claim 4, further comprising:

(d) reacting said compound of formula (VII), wherein PG^5 is an allyl group, with a transition metal catalyst in the presence of a secondary amine, to form a compound of formula (IX):



(IX)

wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

6. The process according to claim 5, wherein the secondary amine is Et_2NH and the transition metal catalyst is $(PPh_3)_4Pd$.

7. The process according to claim 5 or 6, wherein step (d) is performed in acetonitrile and further comprises working up the reaction mixture obtained from step (d) by:

(d2) adding N-acetylcysteine to said reaction mixture obtained from step (d);

(d3) adding Cy_2NH to the reaction mixture obtained from step (d2);

(d4) distilling off the secondary amine from step (d); and

(d5) filtering the reaction mixture obtained from step (d4).

8. The process according to any one of claims 5 to 7, further comprising:

(e) reacting said compound of formula (IX) with:

(i) a mixture of HOBt and EDCI;

(ii) a mixture of DIC and oxyma;

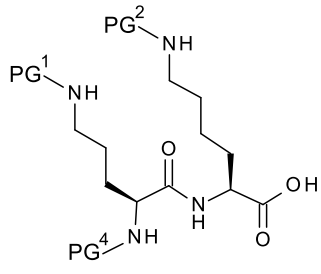
(iii) COMU;

(iv) 2,4,6-trichloro-1,3,5-triazine (TCT); or

(v) 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM);

to form a compound of formula (I).

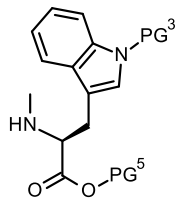
9. A compound of formula (II),



(II)

or a salt thereof, wherein PG^1, PG^2 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

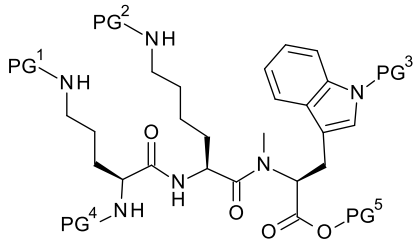
10. A compound of formula (III),



(III)

or a salt thereof, wherein PG^3 is an amino protective group selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

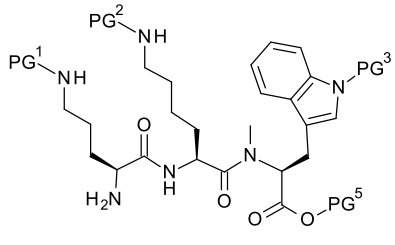
11. A compound of formula (IV),



(IV)

or a salt thereof, wherein PG^1, PG^2, PG^3 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

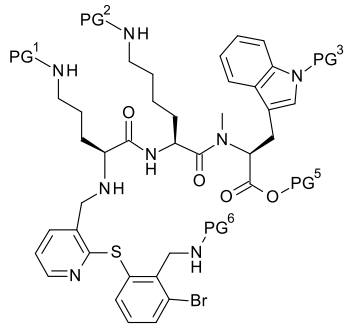
12. A compound of formula (V),



(V)

or a salt thereof, wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

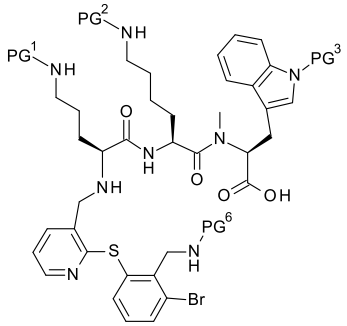
13. A compound of formula (VII),



(VII)

or a salt thereof, wherein PG^1, PG^2, PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

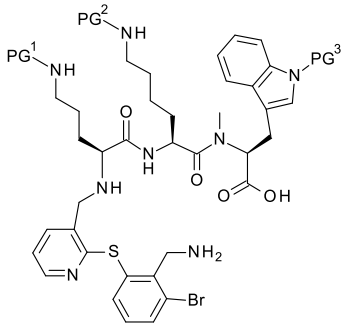
14. A compound of formula (VIII),



(VIII)

or a salt thereof, wherein PG^1, PG^2 and PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

15. A compound of formula (IX),



(IX)

or a salt thereof, wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

16. The process according to claim 1 or the compound of formula (IV) according to claim 11, wherein PG^1, PG^2 and PG^3 are BOC; PG^4 is Fmoc; and PG^5 is allyl.

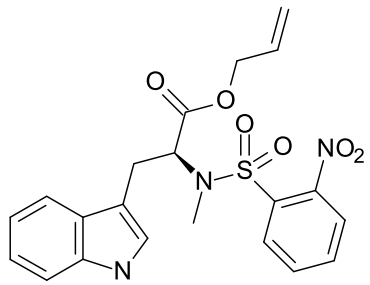
17. The process according to claim 3 or the compound of formula (V) according to claim 12, wherein PG^1, PG^2 and PG^3 are BOC; and PG^5 is allyl.

18. The process according to claim 4 or the compound of formula (VII) according to claim 13, wherein PG^1, PG^2 and PG^3 are BOC; PG^5 is allyl; and PG^6 is Fmoc.

19. The process according to claim 6 or the compound of formula (VIII) according to claim 14, wherein PG^1, PG^2 and PG^3 are BOC; and PG^6 is Fmoc.

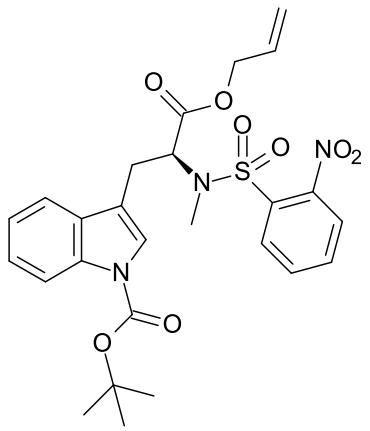
20. The process according to claim 7 or the compound of formula (IX) according to claim 15, wherein PG^1, PG^2 and PG^3 are BOC.

21. A compound, which is N-NBS-N-Me-Trp-OAll



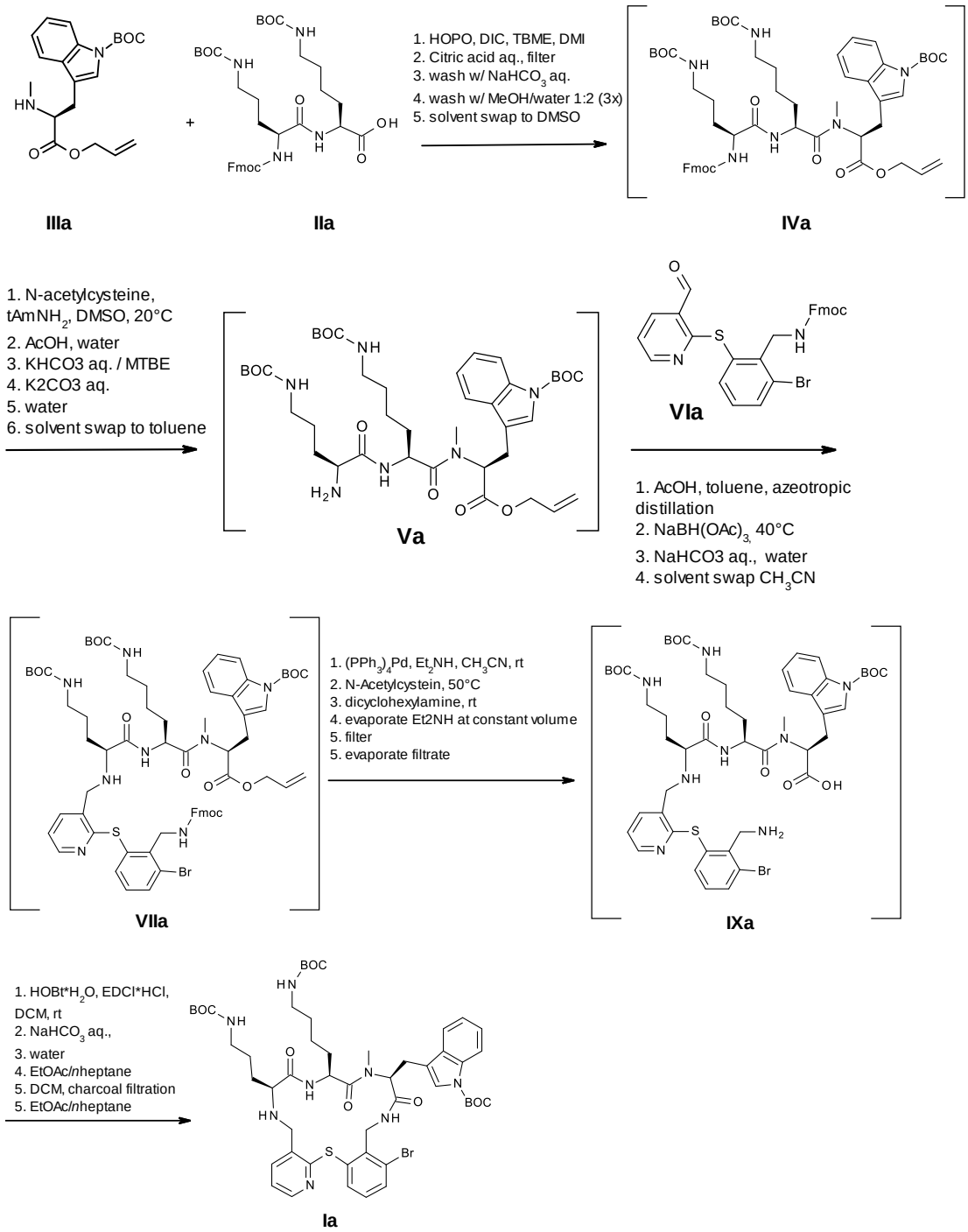
or a salt thereof.

22. A compound, which is N-NBS-N-Me-Trp(Boc)-OAll

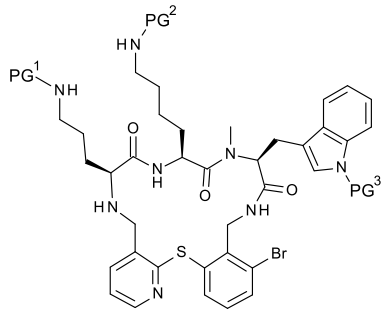


or a salt thereof.

23. The process according to any one of claims 1 to 8, and 16 to 20, which is:



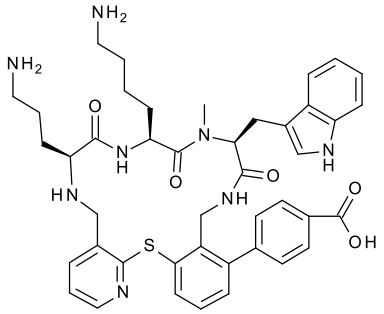
24. A compound of formula (I), or a salt thereof,



(I)

wherein PG^1, PG^2 and PG^3 are amino protective groups, when manufactured according to the process of any one of claims 1 to 8 or 16 to 21.

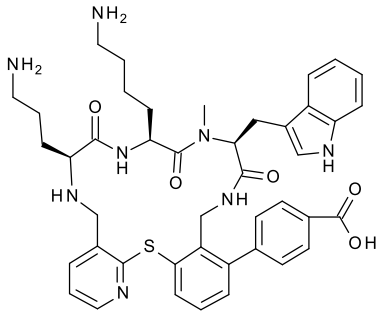
25. A process for manufacturing a compound of formula (1), or a salt thereof,



(1)

comprising a process according to any one of claims 1 to 8 or 16 to 21.

26. Use of the process according to any one of claims 1 to 8 or 16 or 21 in the manufacture of the compound of formula (1)



(1)

or a salt thereof.