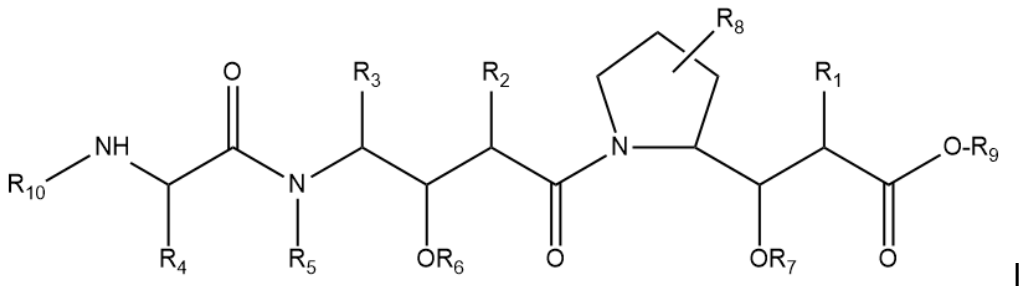
CLAIMS

1. A method for making a dolastatin, auristatin or related compounds comprising the steps of:

providing a compound of Formula I, or salt thereof,



I

wherein

R_1, R_2, R_3, R_4 R_5 and R_8 are each individually selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 substituted alkyl, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11} and halo,

R_{11} and R_{12} are individually selected from the group consisting of H, C_1-C_6 alkyl,

R_6 and R_7 are each individually H or C_1-C_4 alkyl,

R_9 is H or an acid protecting group, and

R_{10} is H or an amino protecting group;

if R_9 is an acid protecting group, deprotecting the C-terminal carboxylic acid group,

reacting the C-terminal carboxylic acid group with an amine (A) to form an amide bond;

if R_{10} is an amino protecting group, deprotecting the N-terminal amine,

reacting the N-terminal amine with a carboxylic acid (CA) to form an amide bond,

provided that when R_1, R_5, R_6 and R_7 are methyl, R_2, R_8 and R_9 are H, R_3 is sec-butyl, R_4 is isopropyl, and R_{10} is a tert-butoxycarbonyl (Boc) protecting group; then carboxylic acid (CA) is not amine-protected N-methyl-valine when amine (A) is a salt of phenylalanine.

2. The method of claim 1 wherein the steps of

if R_9 is an acid protecting group, deprotecting the C-terminal carboxylic acid group,

reacting the C-terminal carboxylic acid group with an amine (A) to form an amide bond;

are performed before the steps of

if R_{10} is an amino protecting group, deprotecting the N-terminal amine,

reacting the N-terminal amine with a carboxylic acid (CA) to form an amide bond.

3. The method according to any of claims 1 or 2 wherein the amine (A) is selected from the group consisting of alkylamines, alkanolamines, arylalkanolamines, amino acids, amino acid derivatives, peptides and peptide derivatives,

wherein the amine (A) may have one or more substituents, and

wherein the amine (A) may have a protecting group.

4. The method according to any of claims 1-3 wherein the amine (A) is selected from the group consisting of phenylalanine, phenylalanine derivatives, substituted phenylalanine, substituted phenylalanine derivatives, tryptophan, tryptophan derivatives, substituted tryptophan, substituted tryptophan derivatives, phenylpropanolamine, protected phenylpropanolamine, substituted phenylpropanolamine, protected substituted phenylpropanolamine, dolaphenine and protected dolaphenine, substituted dolaphenine, protected substituted dolaphenine, dolaphenine derivatives, protected

dolaphenine derivatives, substituted dolaphenine derivatives, protected dolaphenine derivatives.

5. The method according to any of claims 1 to 4 wherein the carboxylic acid (CA) is selected from the group consisting of amino acids, amino acid derivatives, peptides and peptide derivatives,

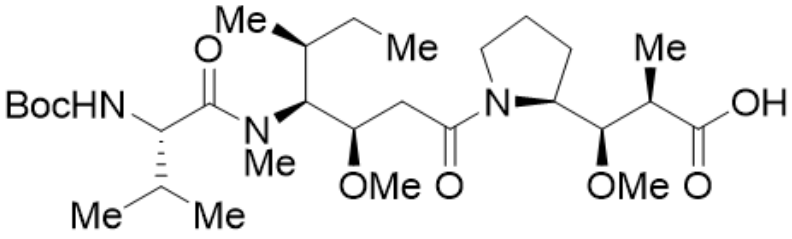
wherein the carboxylic acid (CA) may have one or more substituents, and

wherein the carboxylic acid (CA) may have a protecting group.

6. The method according to any of claims 1 to 5 wherein the carboxylic acid (CA) is selected from the group consisting of valine, protected valine, substituted valine, protected substituted valine, valine derivatives, protected valine derivatives, substituted valine derivatives, protected substituted valine derivatives, alanine, protected alanine, substituted alanine, protected substituted alanine, alanine derivatives, protected alanine derivatives, substituted alanine derivatives and protected substituted alanine derivatives.

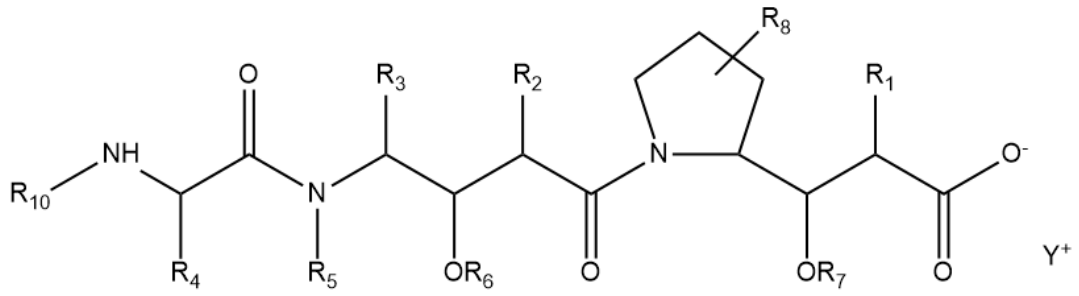
7. The method according to any of claims 1 to 6 wherein the carboxylic acid (CA) comprises one or more of a spacer, a linker and an attachment group.

8. The method according to any of claims 1-7 wherein the compound of Formula I is



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9. An isolated salt of Formula II:



II

wherein

R_1, R_2, R_3, R_4 R_5 and R_8 are each individually selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 substituted alkyl, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11} and halo,

R_{11} and R_{12} are individually selected from the group consisting of H and C_1-C_6 alkyl,

R_6 and R_7 are each individually H or C_1-C_4 alkyl,

R_{10} is H or an amino protecting group; and

Y^+ is counterion.

10. The isolated salt of claim 9, wherein

R_1, R_2, R_3, R_4 R_5 and R_8 are each individually selected from the group consisting of H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, and iso-butyl;

R_6 and R_7 are each individually H or methyl,

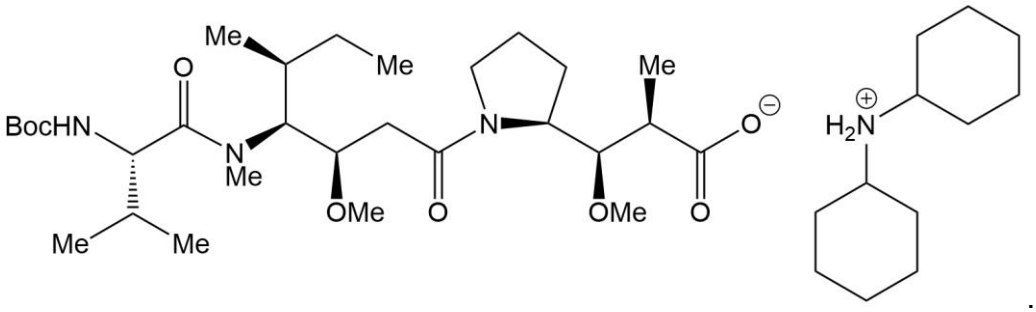
R_{10} is H or tert-butoxycarbonyl (Boc), and

Y^+ is an ammonium ion of the formula $N^+HR_{13}R_{14}R_{15}$ wherein R_{13} is selected from the group consisting of optionally substituted C_1-C_8 alkyl and optionally substituted C_3-C_8 cycloalkyl; R_{14} and R_{15} are independently selected from the group consisting of H, optionally substituted C_1-C_8 alkyl and optionally substituted C_3-C_8 cycloalkyl; wherein

each optional substituent, if present, is selected from the group consisting of alkyl and aryl.

11. The isolated salt according to either of claims 9 or 10 wherein Y^+ is selected from the group consisting diethylammonium ion, dibutylammonium ion, dicyclohexylammonium ion, methylcyclohexylammonium ion and methylbenzylammonium ion.

12. The isolated salt according to any of claims 9 to 11, wherein the salt is



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13. The method according to any of claims 1-8, with the proviso that when R_1, R_5, R_6 and R_7 are methyl, R_2, R_8 and R_9 are H, R_3 is *sec*-butyl, R_4 is isopropyl, R_{10} is a *tert*-butoxycarbonyl (Boc) protecting group, and amine (A) is a salt of phenylalanine, then carboxylic acid (CA) is not protected substituted valine.

14. The method according to any of claims 1-8, with the proviso that when R_1, R_5, R_6 and R_7 are methyl, R_2, R_8 and R_9 are H, R_3 is *sec*-butyl, R_4 is isopropyl, R_{10} is a *tert*-butoxycarbonyl (Boc) protecting group and carboxylic acid (CA) is protected substituted valine, then amine (A) is not a salt of phenylalanine.