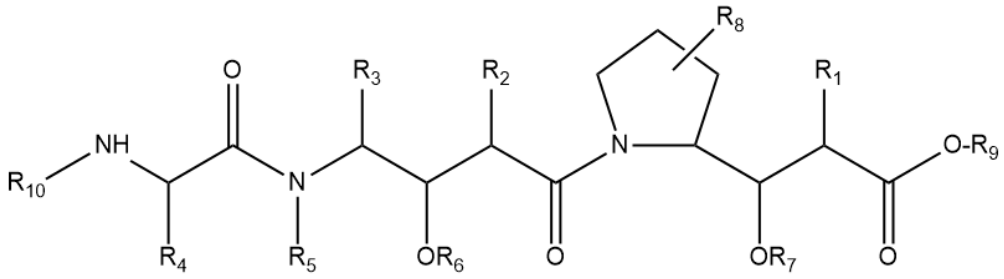
Claims

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.

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 of claim 1 wherein 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

are performed before 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.

4. The method according to any of claims 1 to 3 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.

5. The method according to any of claims 1 to 4 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.

6. The method according to any of claims 1 to 5 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

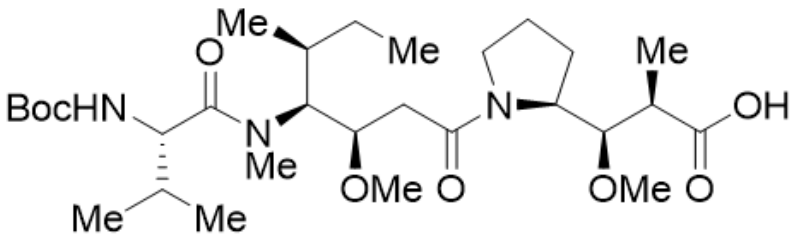
wherein the carboxylic acid (CA) may have a protecting group.

7. The method according to any of claims 1 to 6 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.

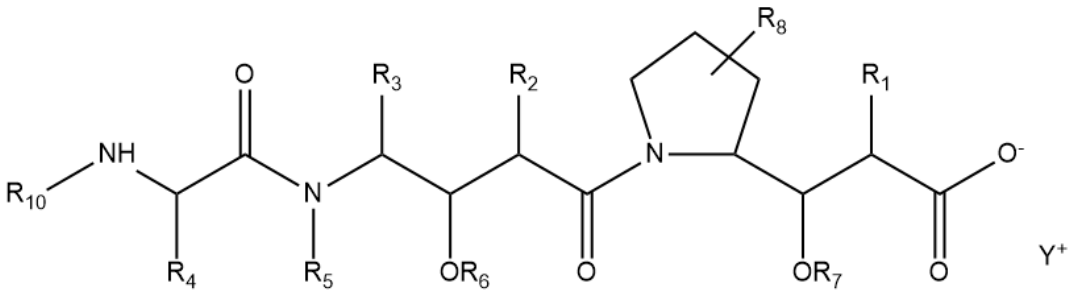
8. The method according to any of claims 1 to 7 wherein the carboxylic acid (CA) comprises one or more of a spacer, a linker and an attachment group.

9. The method according to any of claims 1, 2 or 4 to 8 wherein the compound of Formula I is




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10. 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.

11. The isolated salt of claim 10, 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;

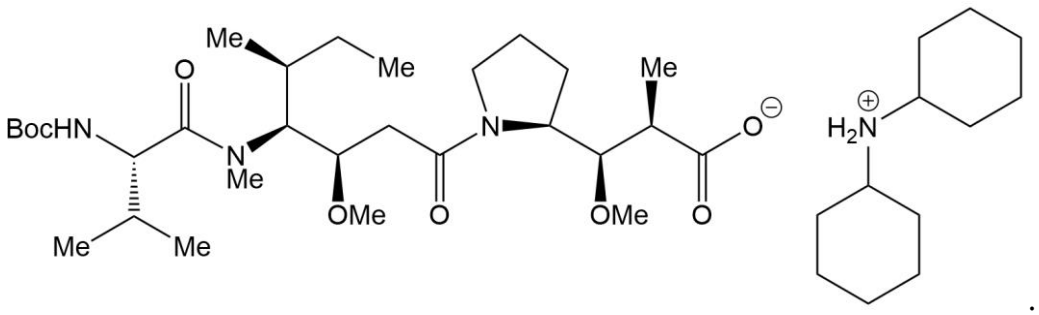
$R_6$ and $R_7$ are each individually H or methyl,

$R_{10}$ 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.

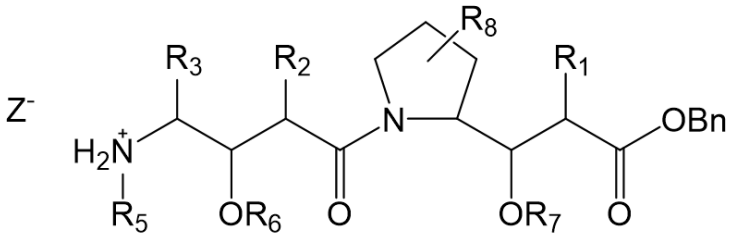
12. The isolated salt according to either of claims 10 or 11 wherein $Y^+$ is selected from the group consisting diethylammonium ion, dibutylammonium ion, dicyclohexylammonium ion, methylcyclohexylammonium ion and methylbenzylammonium ion.

13. The isolated salt according to any of claims 10 to 12, wherein the salt is




.

14. A compound of Formula III:




III

wherein

$R_1$, $R_2$, $R_3$, $R_5$ 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 selected from the group consisting of H or $C_1$-$C_4$ alkyl, and

$Z^-$ is a counterion.

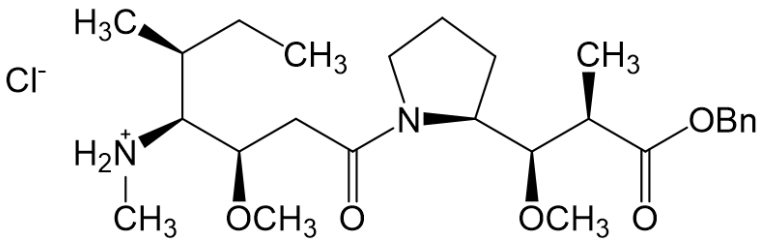
15. The compound of claim 14, wherein

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

$R_6$ and $R_7$ are each individually selected from the group consisting of H and methyl, and

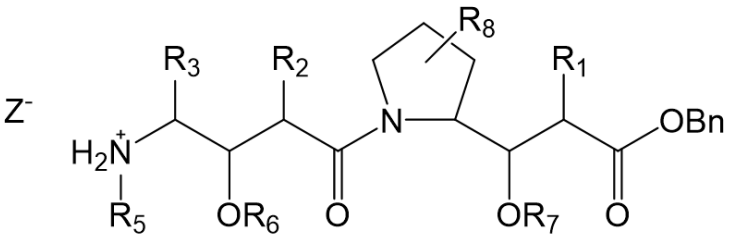
$Z^-$ is selected from the group consisting of halide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, mesylate, tosylate, benzene sulfonate, ethylsulfonate, nitrate, formate, acetate, trifluoroacetate, oxalate, and citrate.

16. The compound of according to either of claims 14 or 15, wherein the compound is:




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17. A method of coupling an amino acid to a compound of Formula III




III

wherein

$R_1$, $R_2$, $R_3$, $R_5$ 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,

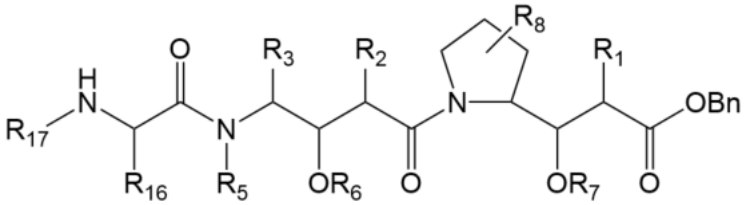
$R_6$ and $R_7$ are each individually selected from the group consisting of H or $C_1$-$C_4$ alkyl, and

$Z^-$ is a counterion

comprising the steps of

contacting the compound of Formula III with an aqueous base to remove the counterion, and

contacting the compound of Formula III with an N-protected amino acid N-carboxyanhydride to yield a compound of Formula IV:




IV

wherein

$R_1$, $R_2$, $R_3$, $R_5$, $R_6$, $R_7$ and $R_8$ are defined as above,

$R_{16}$ is an amino acid side chain, and

$R_{17}$ is a protecting group.

18. The method of claim 17 wherein

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

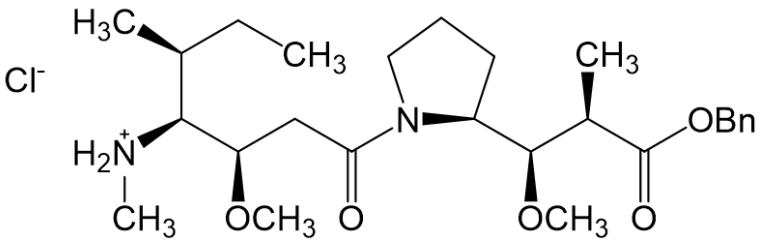
$R_6$ and $R_7$ are each individually selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, and tert-butyl,

$Z^-$ is selected from the group consisting of halide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, mesylate, tosylate, benzene sulfonate, ethylsulfonate, nitrate, formate, acetate, trifluoroacetate, oxalate, and citrate;

the aqueous base is selected from the group consisting of $Na_2CO_3$, $NaHCO_3$, NaOH, $Na_2HPO_4$, and $Na_3PO_4$,

the N-protected amino acid N-carboxyanhydride is a Boc- protected amino acid N-carboxyanhydride.

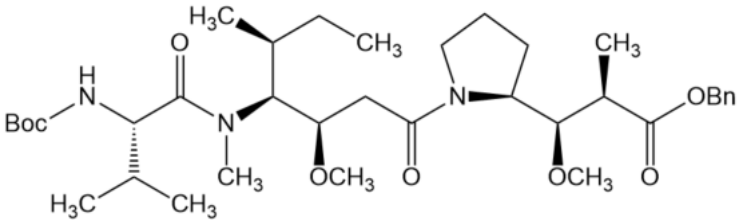
19. The method according to either of claims 17 or 18 wherein the compound of Formula III is



the aqueous base is $Na_2CO_3$,

the N-protected amino acid N-carboxyanhydride is Boc-Val-NCA, and

the compound of Formula IV is:



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20. The method according to any of claims 1-9, 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.

21. The method according to any of claims 1-9, 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.