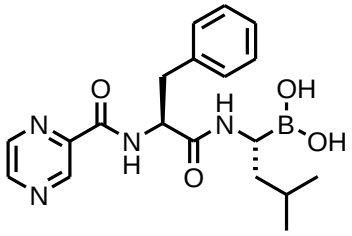
CLAIMS

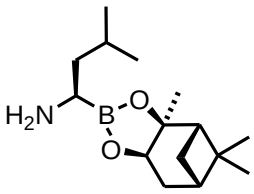
1. A process for forming a compound of formula (***XIV***):



(***XIV***)

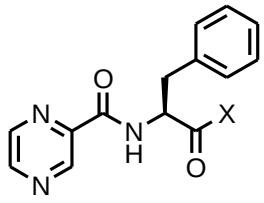
or a boronic acid anhydride thereof, comprising the steps:

(e') coupling of a compound of formula (***XVIII***), or an acid addition salt thereof:



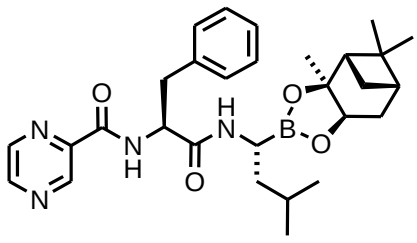
(***XVIII***)

with a compound of formula (***XIXa***):



(***XIXa***)

wherein the moiety –C(O)X is an activated ester generated *in situ* by contacting N-(2-pyrazinecarbonyl)-L-phenylalanine with a peptide coupling reagent, to form a compound of formula (***XXIII***):



(***XXIII***); and

(f') deprotecting the boronic acid moiety to form the compound of formula (***XIV***) or a boronic acid anhydride thereof.

2. The process of claim 1, wherein in the compound of formula (***XIXa***) the moiety C(O)-X is an O-(N-hydroxysuccinimide) ester.

3. The process of claim 2, wherein the compound of formula (***XIXa***) is generated *in situ* by contacting N-(2-pyrazinecarbonyl)-L-phenylalanine with a carbodiimide peptide coupling reagent and N-hydroxysuccinimide.

4. The process of claim 3, wherein the carbodiimide peptide coupling reagent is dicyclohexylcarbodiimide.

5. The process of claim 2, 3 or 4, wherein the coupling step (e') comprises the steps:

(i) coupling an acid addition salt of a compound of formula (***XVIII***) with a compound of formula (***XIXa***), in the presence of N-methylmorpholine in DMF;

(ii) filtering the reaction mixture; and

(iii) concentrating the filtrate.

6. The process of any preceding claim, wherein the boronic acid deprotecting step (f') comprises the steps:

(i) providing a biphasic mixture comprising the compound of formula (***XXIII***), an organic boronic acid acceptor, a lower alkanol, a C_{5-8} hydrocarbon solvent, and aqueous mineral acid;

(ii) stirring the biphasic mixture to afford the compound of formula (***XIV***);

(iii) separating the solvent layers; and

(iv) extracting the compound of formula (***XIV***), or a boronic acid anhydride thereof, into an organic solvent.

7. The process of claim 6, wherein step (f')(iii) comprises the steps:

(1) separating the solvent layers;

(2) adjusting the aqueous layer to basic pH;

(3) washing the aqueous layer with an organic solvent; and

(4) adjusting the aqueous layer to a pH less than 8.

8. The process of claim 7, wherein in step (f')(iii)(4), the aqueous layer is adjusted to a pH less than 6.

9. The process of claim 6, wherein in step (f')(iv), the compound of formula (***XIV***), or a boronic acid anhydride thereof, is extracted into ethyl acetate, and the compound of formula (***XIV***), or a boronic acid anhydride thereof, is crystallized by addition of hexane or heptane.

10. The process of claim 1, wherein the process is for producing N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride,

wherein step (e') comprises coupling an acid addition salt of a compound of formula (***XVIII***) with a compound of formula (***XIXa***) and involves:

(i) providing a solution of (1*R*)-(*S*)-pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate and N-hydroxysuccinimide in DMF, followed by addition of dicyclohexylcarbodiimide to form a suspension;

(ii) providing a solution of N-(2-pyrazinecarbonyl)-L-phenylalanine in DMF and adding N-methylmorpholine thereto;

(iii) adding the solution resulting from step (ii) to the suspension resulting from step (i) and adjusting the resulting suspension to pH7 by adding N-methylmorpholine, filtering the suspension, washing the filtrate with *tert*-butylmethyl ether and concentrating the filtrate;

and wherein the boronic acid deprotecting step (f') comprises the steps of:

(i) providing a biphasic mixture comprising the compound of formula (***XXIII***), methanol, hexane and hydrochloric acid and adding 2-methylpropane boronic acid thereto;

(ii) stirring the biphasic mixture;

(iii) separating the solvent layers; and

(iv) extracting N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride into ethyl acetate, followed by crystallization by the addition of *tert*-butylmethyl ether.