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(54) Title: GROUP-ASSISTANT-PURIFICATION (GAP) SYNTHESIS OF VELCADE, DIMERIC ANALOGS, AND AMINO COMPOUNDS

(57) Abstract:



WO 2014/093723 A2

**GROUP-ASSISTANT-PURIFICATION (GAP) SYNTHESIS OF VELCADE,
DIMERIC ANALOGS, AND AMINO COMPOUNDS**

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. provisional patent application No. 61/736,357 filed on December 12, 2012 and entitled "GROUP-ASSISTANT-PURIFICATION (GAP) SYNTHESIS OF PROTECTED AMINO ACID AND PEPTIDE DERIVATIVES," and U.S. provisional patent application No. 61/761,131 filed on February 5, 2013 and entitled "GAP SYNTHESIS OF VELCADE, DIMERIC ANALOGS, AND AMINO COMPOUNDS;" each of which is hereby incorporated by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR
DEVELOPMENT

[0002] This invention was made with government support under R21DA031860-01 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD

[0003] Provided herein are methods to synthesize polypeptides with GAP (Group-Assistant-Purification) approach. The GAP approach allows the reactions to be purified without chromatography or recrystallization and can avoid the disadvantage of solid phase synthesis to ease the scale-up of reactions. Also provided herein are novel phosphonyl halide, phosphonyl amide, and phosphonyl amino acid compounds, including biphalin and phosphinyl protected amino acids. The phosphonyl and phosphinyl halide compounds are useful as protecting groups for amino acid sequencing. The phosphonyl and phosphinyl amide compounds are useful in GAP synthesis methods. The phosphonyl and phosphinyl halide compounds simplify purification methods and can be utilized to synthesize biologically active peptides and proteins. The phosphonyl and phosphinyl halide compounds are particularly useful to protect amino acid esters and synthesize peptides using environmentally friendly purification methods. Also provided herein are methods for the synthesis of the phosphonyl halide compounds, phosphonyl and phosphinyl amide compounds, synthesis of protected amino acid esters and poly peptides.

[0004] Provided herein are novel methods of GAP synthesis of Velcade, Velcade analogs and amino compounds. The methods involve organic syntheses with chiral auxiliaries

which allow pure products, often pure isomers, to be obtained simply by washing crude products with organic solvents. In some embodiments, the crude products themselves are pure or optically pure enough due to excellent reactivity, chemoselectivity, and asymmetric induction of GAP methods. In preferred embodiments, chiral auxiliaries can be recycled easily after deprotection, in some cases without racemization of the chiral auxiliaries. The “Group” in GAP methods can be, but is not limited to, phosphonyl or phosphinyl auxiliaries. The phosphonyl and phosphinyl auxiliaries can provide efficient asymmetric induction and control in organic transformations. Additionally, corresponding chiral products, mostly solidified, can be utilized to synthesize Velcade, Velcade analogs and amino compounds. Also provided herein are novel dimeric Velcade analogs and methods of synthesis thereof, which have potential use as alternatives to Velcade monomer cancer therapeutics.

BACKGROUND

[0005] Chemical synthesis of proteins is a powerful tool for the investigation of biomedical activity of peptides and protection of amino acids is an initial step in the peptide synthesis process. Isidro-Llobet, A.; Alvarez, M.; Albericio, F. *Chem. Rev.* **2009**, *109*, 2455. Development of new protecting groups has been deeply tied to peptide chemistry. Protecting group development is based on three general criterions: (1) it is readily introduced into the functional groups and accessible to be removed safely when required; (2) it is tolerable to a wide range of reaction conditions; (3) two or more independent types of protecting groups can be removed by distinct mechanisms. Isidro-Llobet, A.; Alvarez, M.; Albericio, F. *Chem. Rev.* **2009**, *109*, 2455; Bergmann, M.; Zervas, L. *Ber. Deut. Chem. Ges.* **1932**, *65B*, 1192; Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363; Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, *107*, 4936.

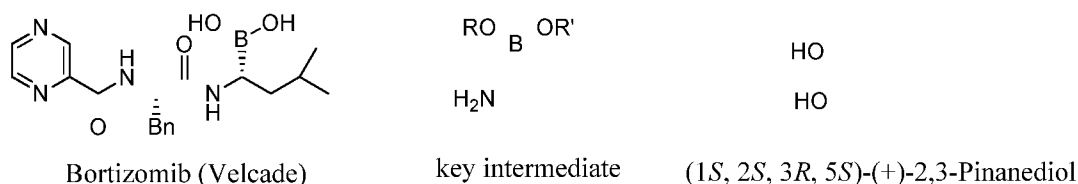
[0006] Most of the modern protecting groups are developed from aforementioned consideration of group reactivity. Isidro-Llobet, A.; Alvarez, M.; Albericio, F. *Chem. Rev.* **2009**, *109*, 2455; Shinohara, Y.; Kudo, F.; Eguchit, T. *J. Am. Chem. Soc.* **2011**, *133*, 18134; Yamamoto, N.; Tanabe, Y.; Okamoto, R.; Dawson, P. E.; Kajihara, Y. *J. Am. Chem. Soc.* **2008**, *130*, 501. From an experimental manipulation perspective, protecting groups with convenience of purification and with economic and environmentally friendly methodology have not generally been developed in amino acid protection and peptide synthesis. Schreiber, S. L. *Science*. **2000**, *287*, 1964; Frederic, L. -M.; Thierry, C.; Jean, R. *J. Am. Chem. Soc.* **2005**, *127*, 17176; Trost, B. M. *Science* **1991**, *254*, 1471; Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 2836; Snyder, S. A.;

Breazzano, S. P.; Lin, R. Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753; Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581; Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13197.

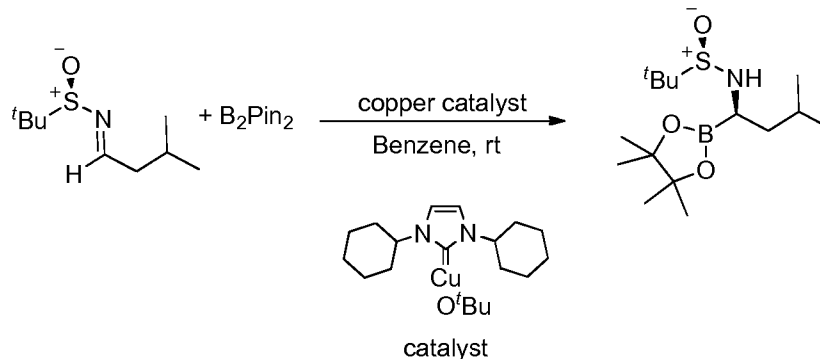
[0007] Recently, chiral *N*-phosphonyl imines were developed and utilized in several asymmetric nucleophilic addition reactions such as aza-Henry, aza-Darzen, *etc.* to achieve excellent diastereoselectivities. A. Kattuboina, P. Kaur, T. Ai, G. Li, *Chem. Biol. & Drug Design*, **2008**, *71*, 216; A. Kattuboina, G. Li, *Tetrahedron Lett.* **2008**, *49*, 1573. Later research focused on further simplifying the imine chemistry by means of easy purification methods. In this process, a concept named Group Assistant Purification (GAP) was developed in which the addition reaction products are purified by simple washing with minimum amounts of solvents such as pentane, hexanes, heptane, ethyl acetate, *etc.* or a mixture of solvents, depending on the solubility nature of the impurities and side products. Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem.* **2009**, 912; Han, J.; Ai, T.; Li, G. *Synthesis* **2008**, *16*, 2519; Han, J.; Chen, Z. -X.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2009**, *73*, 203; Chen, Z. -X.; Ai, T.; Kaur, P.; Li, G. *Tetrahedron Lett.* **2009**, *50*, 1079; Ai, T.; Li, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3967; Kaur, P.; Shakya, G.; Sun, H.; Pan, Y.; Li, G. *Org. Biomol. Chem.* **2010**, *8*, 1091; Ai, T.; Han, J.; Chen, Z. X.; Li, G. *Chem. Biol. Drug. Des.* **2009**, *73*, 203; Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216; Ai, T.; Pindi, S.; Kattamuri, P. V.; Li, G. *Sci. China Series B: Chem.* **2010**, *53*, 125; Pindi, S.; Kaur, P.; Shakya, G.; Li, G. *Chem. Biol. Drug Design*, **2011**, *75*, 20; Kattamuri, P. V.; Ai, T.; Pindi, S.; Sun, Y.; Gu, P.; Shi, M.; Li, G. *J. Org. Chem.* **2011**, *76*, 2792. However, almost all the phosphonyl imines developed were aromatic imines until development of a phosphinyl auxiliary (Pindi, et al., *Chem. Biol. Drug Design*, **2011**, *75*, 20), which made available aliphatic imines. Nevertheless, the sulfinyl auxiliary, developed by Davis (*see*, Davis, et al., *J. Org. Chem.* **1997**, *62*, 2555) and Ellman (*see*, Liu, et al., *J. Am. Chem. Soc.* **1997**, *119*, 9913.; and Robak, et al., *Chem. Rev.* **2010**, *110*, 3600), could achieve good to excellent asymmetric induction. Usually, column chromatography was necessary to purify the products, which is disfavored in the pharmaceutical industry.

[0008] Velcade (bortezomib) is used to treat people with multiple myeloma or mantle cell lymphoma. Velcade is in a class of medications called antineoplastic agents which kill cancer cells. While the structure of Velcade is not complicated, there are only a few methods to synthesize this compound. The key step in these synthetic methods is to produce a chiral amino boric ester center. An example of asymmetric catalysis is disclosed in PCT

international application publication no. WO 2010/146176 A2. However, other synthesis require at least one chiral auxiliary, usually (1*S*, 2*S*, 3*R*, 5*S*)- (+)-2,3-Pinanediol. *See*, U.S. patent no. 6,617,317 B1; U.S. patent application publication no. 2005/107307 A1; and Zhu, et al., *J. Med. Chem.* **2009**, 52, 4192. However, the auxiliary was expensive and not able to be recycled.



[0009] In 2008, Ellman and et al. reported a new methodology to produce the chiral amino boric ester intermediate (see, Beenen, et al., *J. Am. Chem. Soc.* **2008**, 130, 6910–6911) with a copper-catalyzed borylation reaction and a chiral sulfinyl auxiliary. Ellman reported good diastereoselectivity (dr > 98:2), however the auxiliary is not recyclable due to racemization on the auxiliary. The product separation reported by Ellman was also difficult (dual column chromatography on deactivated silica gel was used, which is costly and not suitable for industrial production). This is likely due to the high polarity of the product.



[00010] Additionally, traditional organic synthesis, such as drug synthesis, generally involves purification processes including chromatography and/or recrystallization. Chromatography makes use of the interaction between the synthesis product and the chromatography medium, which interaction can sometimes cause damages to the product, for example, epimerization of the chiral center so as to cause a reduction of stereoselectivity to the product since the chromatography medium such as silica gel is acidic and acts as a Lewis acid which can facilitate many organic reactions such as epimerization. Recrystallization is a product purification process that notoriously known for its laborious nature as well as inefficiency, not to mention the solvent wastes caused by recrystallization. To illustrate the

inefficiency nature of recrystallization, a 90% yield of recrystallization step, which is generally regarded as a high yield rate, would cause the synthesis product to lose 10% yield. Two or more recrystallization steps (n steps), which are often required to achieve satisfactory purity of the synthesis product, would cause a loss of $(1-0.9^n)$ portion of the synthesis product (if $n = 3$, the product loss equals 0.271 of the total synthesis product). Additionally, solvent wastes, which are often toxic and environmentally damaging, can cause substantial environment damages.

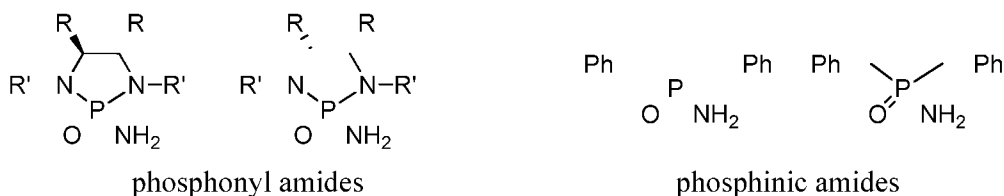
SUMMARY

[00011] The embodiments disclosed below address the above identified issues and needs and illustrate the unique advantages and utilities of the present invention over prior art.

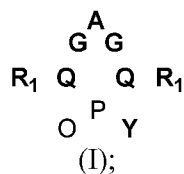
[00012] In some embodiments, new *N*-protection groups have been developed to avoid traditional column chromatography and assist the GAP technique, which is more economic and environmental friendly. As part of this discovery, a novel methodology of synthesis of *N*-protected amino acid esters and peptides via GAP chemistry was developed. Therefore, provided herein are novel phosphonyl and phosphinyl halides, for example phosphonyl and phosphinyl chlorides and bromides, and methods of synthesizing the same, which can be utilized to protect amino acid esters and to synthesize peptides. Also provided herein are methods to synthesize phosphonyl and phosphinyl amides, which are widely used in GAP imine chemistry, from phosphonyl and phosphinyl bromides, where the former method requires sodium azide, an explosive chemical compound.

[00013] For example, to avoid the above disadvantages in the asymmetric borylation reaction, provided herein is a new methodology using a chiral phosphinic auxiliary in the GAP concept, in which no column chromatography is required and the auxiliary can be recycled after deprotection. Also provided herein are novel analogs of Velcade and synthetic routes to the analogs.

[00014] To further expand the scope of substrates and assist the GAP technique, which is more economic and environmental friendly, novel phosphinic amides and their imines were designed and synthesized. Several are provided below, more are provided in U.S. provisional patent application number 61/736,357 filed 12 December 2012 entitled "Group-Assistant-Purification (Gap) Synthesis of Protected Amino Acid and Peptide Derivatives," which is hereby incorporated by reference as if fully set forth herein.

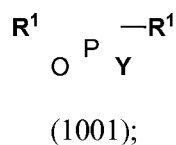


[00015] In certain embodiments, provided herein are compounds according to Formula I:



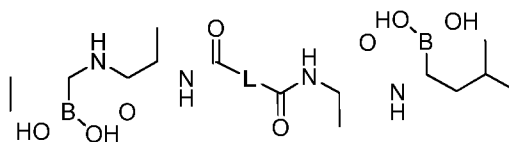
wherein: each **R₁** is independently hydrogen, alkyl, aryl or arylalkyl; ring **A** is a carbocyclic ring or absent; each **Q** is nitrogen, carbon, or oxygen; each **G** is carbon; or when ring **A** is absent and **Q** is oxygen, then **G** is absent; and **Y** is hydroxyl, halogen, amide, imine, an amino acid sequence or an amino acid, or ester thereof.

[00016] The in certain embodiments, provided herein are compounds according to Formula 1001:



wherein: each **R¹** is independently aryl or arylalkyl; and **Y** is hydroxyl, halogen, amine, or imine.

[00017] In certain embodiments, provided herein are compounds according to Formula 1010:



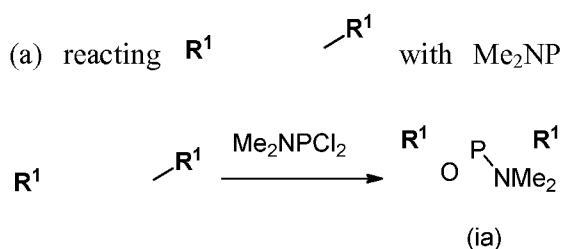
(1010);

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomeric form, tautomeric form

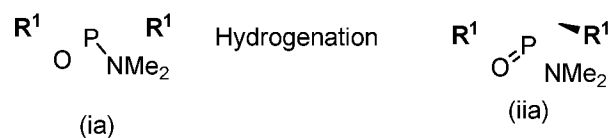
or polymorphic form thereof; wherein: L is $\begin{array}{c} \text{N} \\ | \\ \text{N} \end{array}$ or $\begin{array}{c} \text{N} \\ | \\ \text{N} \end{array}$ or $\begin{array}{c} \text{N} \\ | \\ \text{N} \end{array}$; J is $-(\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CHO})_n-$, $-(\text{CH}_2-\text{CH}-\text{NH})_n-$, $-\text{O}-(\text{CH}_2-\text{CHO})_n-$, $-\text{NH}-(\text{CH}_2-\text{CH}-\text{NH})_n-$, $-\text{NH}-(\text{CH}_2-\text{CHO})_n-$, $-\text{O}-(\text{CH}_2-\text{CH}-\text{NH})_n-$ or $-(\text{amino acid residue})_n-$; and each n is independently a positive integer.

[00018] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1002 comprising:

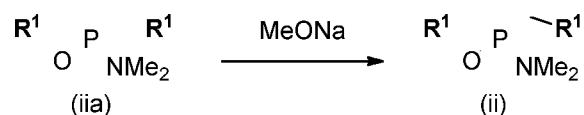
(a) reacting R^1 with Me_2NPCl_2 to form a compound of Formula (ia):



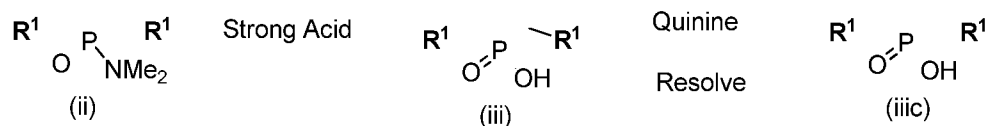
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



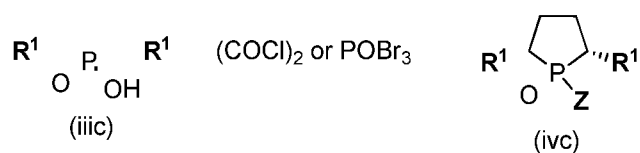
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



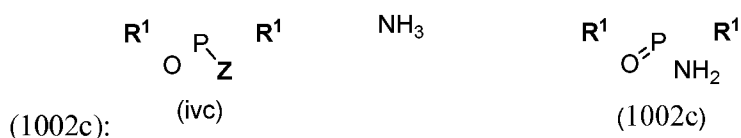
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiic):



(e) reacting the compound of Formula (iiic) with $(\text{COCl})_2$ or POBr_3 to form a compound of Formula (ivc):



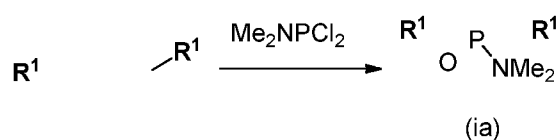
(f) reacting the compound of Formula (ivc) with NH_3 to form a compound of Formula



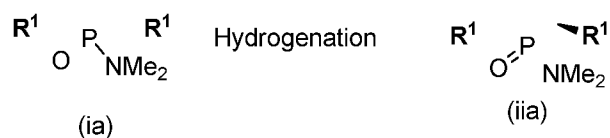
wherein: **Z** is chloro or bromo; and each **R**¹ is independently aryl or arylalkyl.

[00019] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1002 comprising:

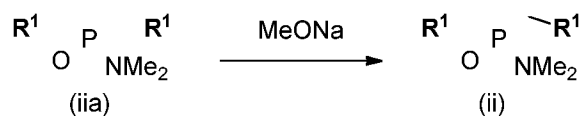
(a) reacting **R**¹ with Me_2NPCl_2 to form a compound of Formula (ia):



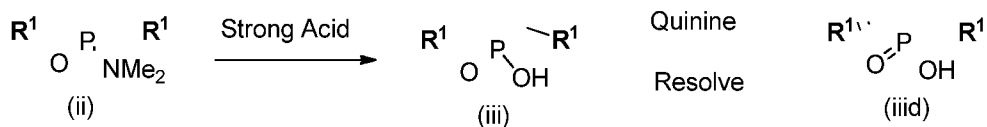
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



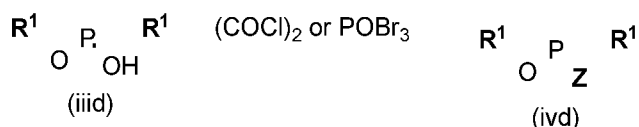
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



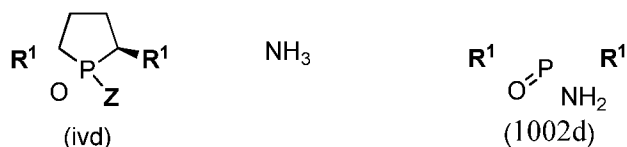
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiid):



(e) reacting the compound of Formula (iiid) with $(\text{COCl})_2$ or POBr_3 to form a compound of Formula (ivd):

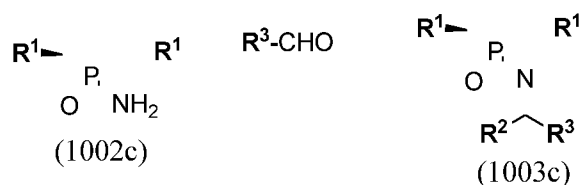


(f) reacting the compound of Formula (ivd) with NH_3 to form a compound of Formula (1002d):



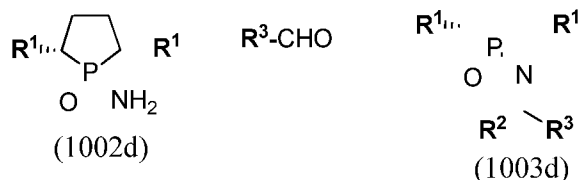
wherein: **Z** is chloro or bromo; and each **R**¹ is independently aryl or arylalkyl.

[00020] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1003c comprising reacting a compound of Formula 1002c with **R**³-CHO to form a compound of Formula 1003c:



wherein: each **R**¹ is independently aryl or arylalkyl; **R**² is hydrogen; and **R**³ is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, or C₆-C₁₂ aryl.

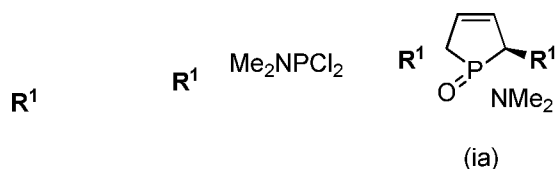
[00021] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1003d comprising reacting a compound of Formula 1002d with **R**³-CHO to form a compound of Formula 1003d:



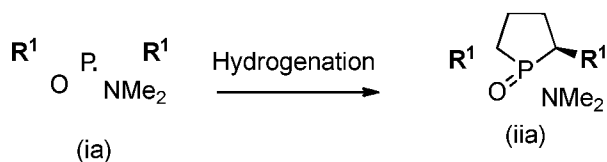
wherein: each R^1 is independently aryl or arylalkyl; R^2 is hydrogen; and R^3 is $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, or $\text{C}_6\text{-C}_{12}$ aryl.

[00022] In certain embodiments provided herein is a method of synthesizing Velcade comprising:

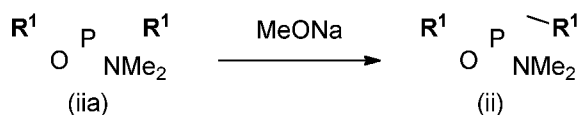
(a) reacting R^1 with Me_2NPCl_2 to form a compound of Formula (ia):



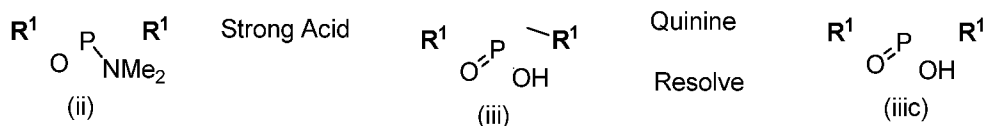
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



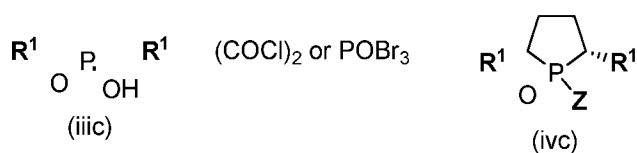
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



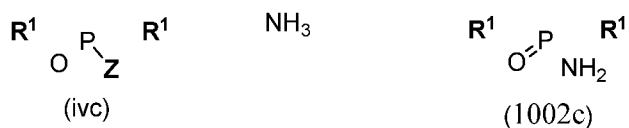
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiic):



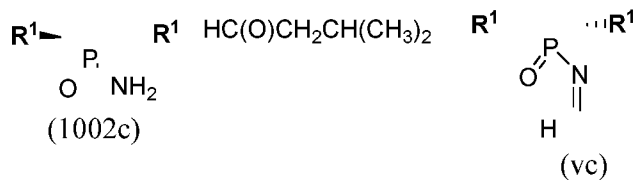
(e) reacting the compound of Formula (iiic) with $(\text{COCl})_2$ or POBr_3 to form a compound of Formula (ivc):



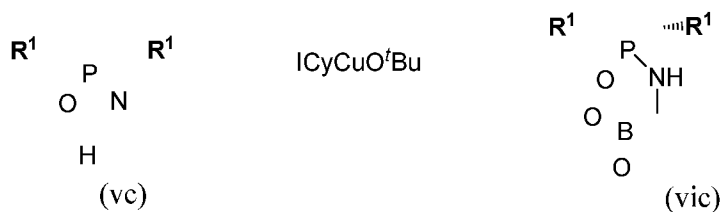
(f) reacting the compound of Formula (ivc) with NH_3 to form a compound of Formula (1002c):



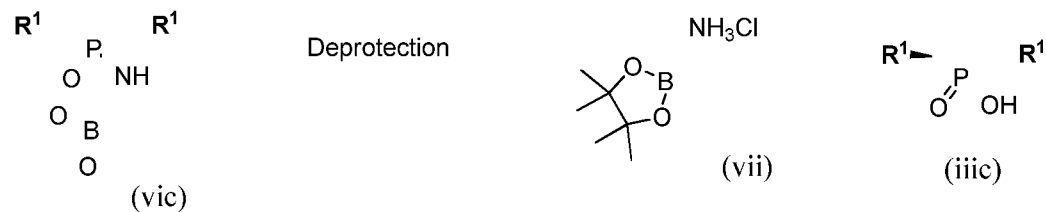
(g) reacting the compound of Formula 1002c with $\text{HC(O)CH}_2\text{CH(CH}_3)_2$ to form a compound of Formula vc:



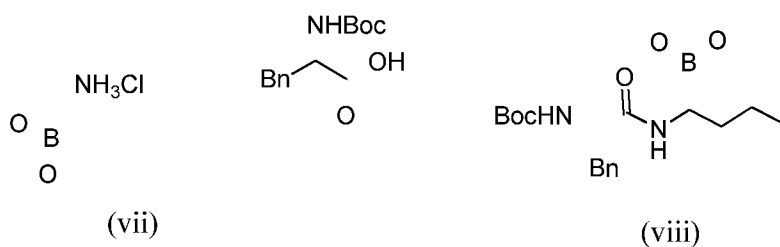
(h) reacting a compound of Formula (vc) with ICyCu^tBu to form a compound of Formula (vic):



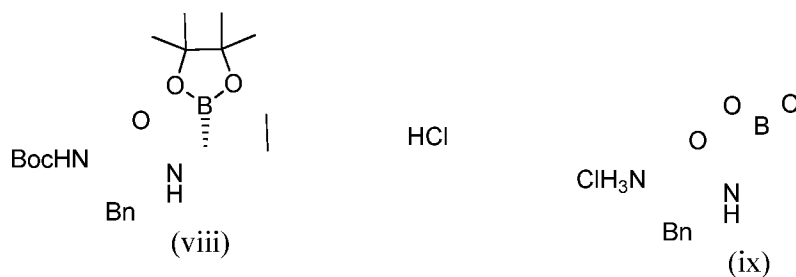
(i) deprotecting the compound of Formula (vic) to form a compound of Formula (vii) and a compound of Formula (iiic):

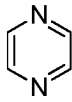


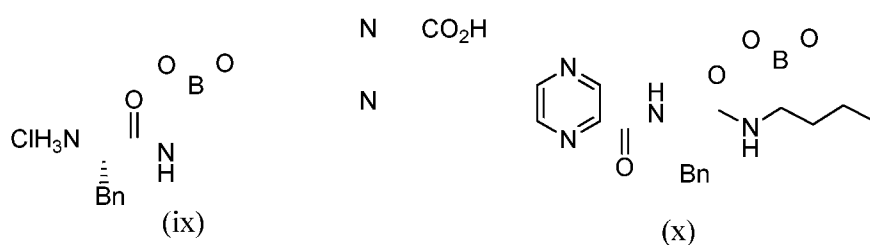
(j) reacting the compound of Formula (vii) with BnCH(NHBoc)C(O)OH to form a compound of Formula (viii):



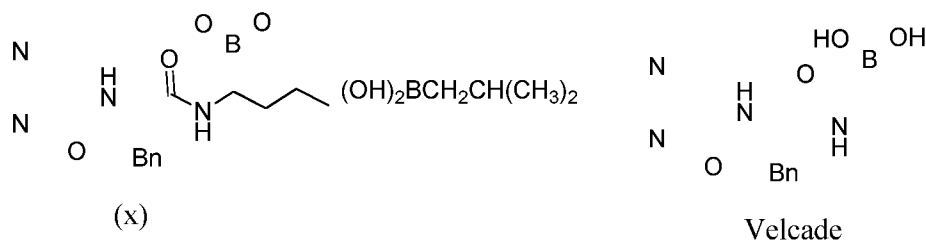
(k) reacting the compound of Formula (viii) with HCl to form a compound of Formula (ix):



(l) reacting the compound of Formula (ix) with  to form a compound of Formula (x):



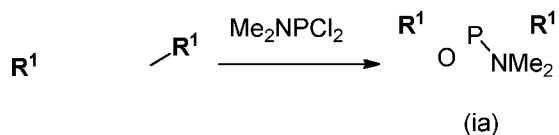
(m) reacting the compound of Formula (x) with $(\text{OH})_2\text{BCH}_2\text{CH}(\text{CH}_3)_2$ to form Velcade:



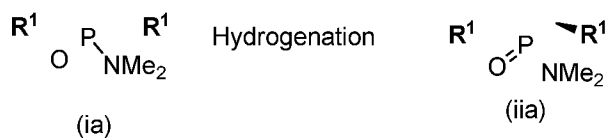
wherein: **Z** is chloro or bromo; and each **R¹** is independently aryl or arylalkyl.

[00023] In certain embodiments, provided herein is a method of synthesizing Velcade comprising:

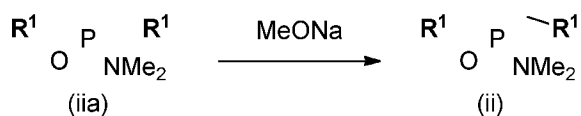
(a) reacting R^1  with Me_2NPCl_2 to form a compound of Formula (ia):



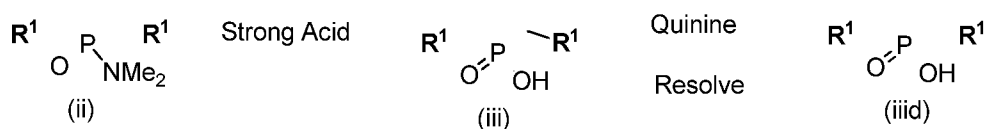
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



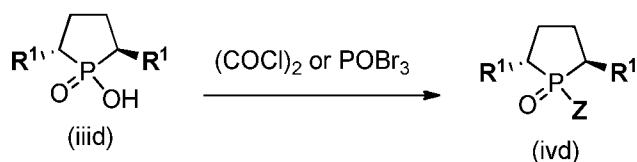
(c) reacting the compound of Formula (iia) with $MeONa$ to form a compound of Formula (ii):



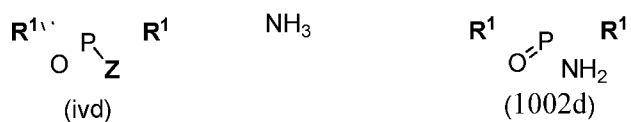
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiid):



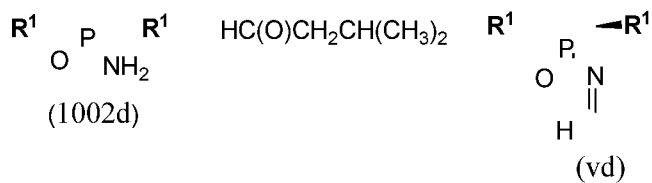
(e) reacting the compound of Formula (iiid) with $(COCl)_2$ or $POBr_3$ to form a compound of Formula (ivd):



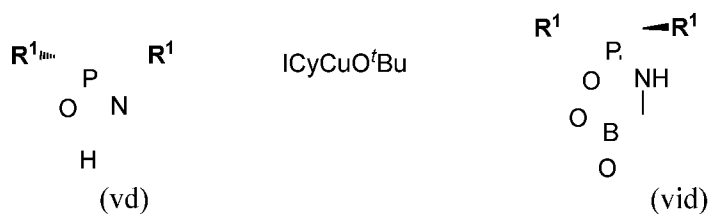
(f) reacting the compound of Formula (ivd) with NH_3 to form a compound of Formula (1002d):



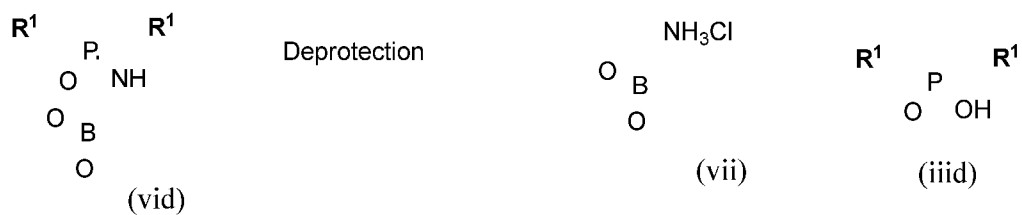
(g) reacting the compound of Formula 1002d with $\text{HC(O)CH}_2\text{CH(CH}_3)_2$ to form a compound of Formula vd:



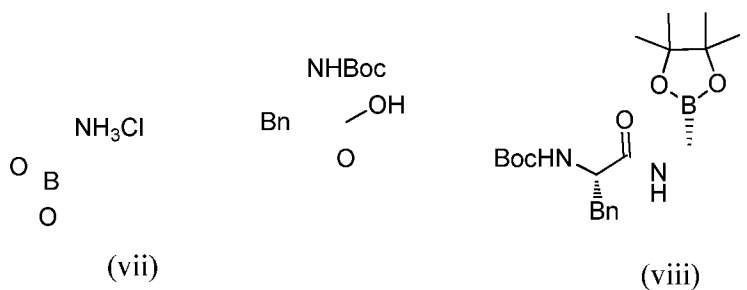
(h) reacting a compound of Formula (vd) with ICyCu^tBu to form a compound of Formula (vid):



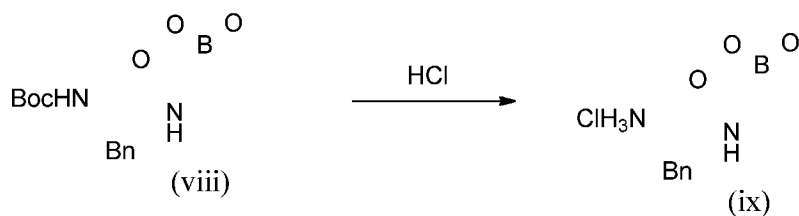
(i) deprotecting the compound of Formula (vid) to form a compound of Formula (vii) and a compound of Formula (iiid):

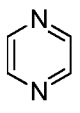


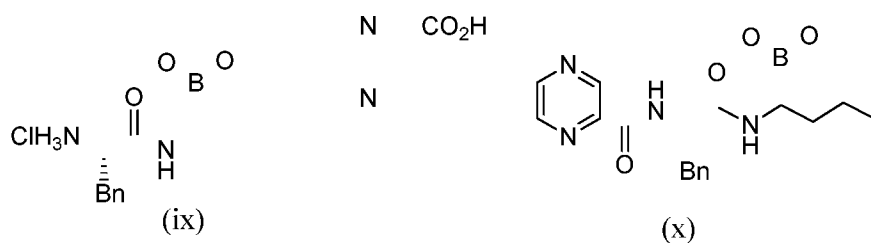
(j) reacting the compound of Formula (vii) with BnCH(NHBoc)C(O)OH to form a compound of Formula (viii):



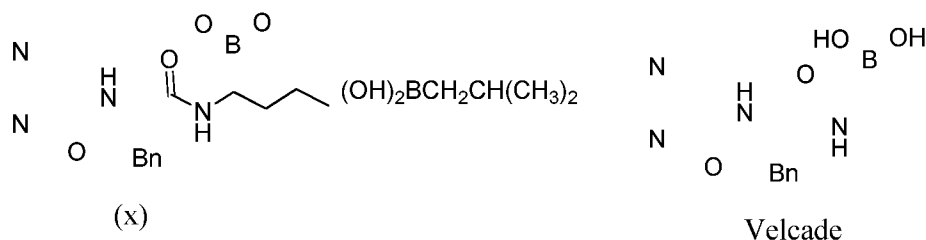
(k) reacting the compound of Formula (viii) with HCl to form a compound of Formula (ix):



(l) reacting the compound of Formula (ix) with  to form a compound of Formula (x):

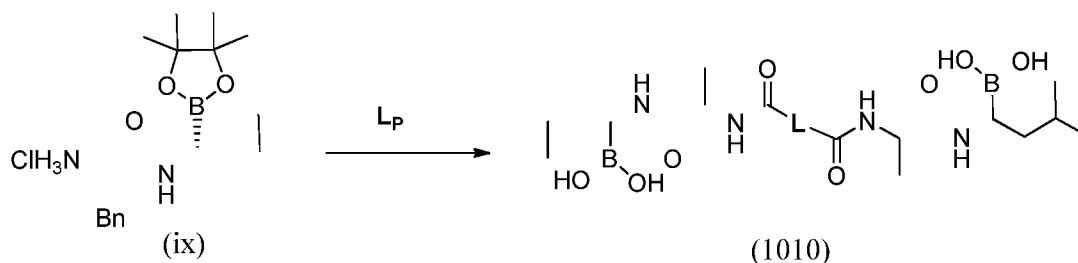


(m) reacting the compound of Formula (x) with $(\text{OH})_2\text{BCH}_2\text{CH}(\text{CH}_3)_2$ to form Velcade:



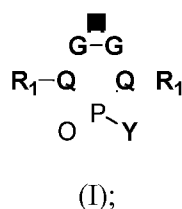
wherein: **Z** is chloro or bromo; and each **R¹** is independently aryl or arylalkyl.

[00024] In certain embodiments, provided herein is a method of synthesizing a compound of Formula 1010 comprising reacting a compound of Formula (ix) with **L_p**:



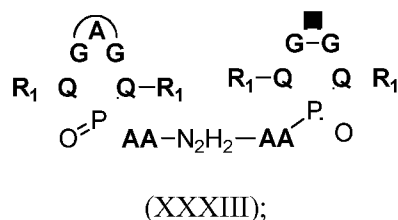
wherein: L is N or N — J —; L_p is O_2C-N or CO_2-N or ; J is $-(CH_2)_n-$, $-(CH_2-CHO)_n-$, $-(CH_2-CH-NH)_n-$, $-O-(CH_2-CHO)_n-$, $-NH-(CH_2-CH-NH)_n-$, $-NH-(CH_2-CHO)_n-$, $-O-(CH_2-CH-NH)_n-$ or $-(\text{amino acid residue})_n-$; and each n is independently a positive integer.

[00025] In certain embodiments, provided herein is a compound according to Formula I:



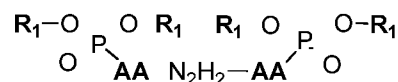
wherein: each **R**₁ is independently hydrogen, alkyl, aryl or aryl alkyl; ring **A** is a carbocyclic ring or absent; each **Q** is nitrogen, carbon, or oxygen; each **G** is carbon; or when ring **A** is absent and **Q** is oxygen, then **G** is absent; and **Y** is halogen, amide, an amino acid sequence or an amino acid, or ester thereof.

[00026] In certain embodiments, provided herein is a protected amino acid sequence of Formula XXXIII:



wherein: each **R₁** is independently hydrogen, alkyl, aryl or aryl alkyl; and each **AA** is an amino acid sequence, or ester thereof.

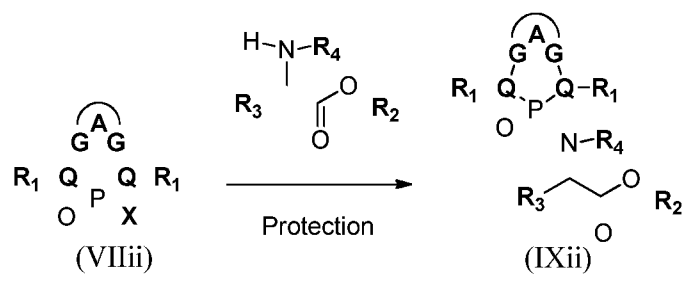
[00027] In certain embodiments, provided herein is a compound according to Formula XXXIV:



(XXXIV):

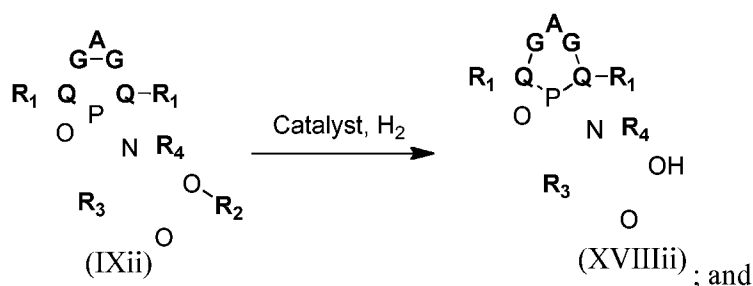
wherein: each **R₁** is independently hydrogen, alkyl, aryl or aryl alkyl; and each **AA** is an amino acid sequence, or ester thereof.

[00028] In certain embodiments, provided herein is a method of protecting an amino acid comprising reacting an amino acid with a compound of formula VIIIi to form a protected amino acid of formula IXii:

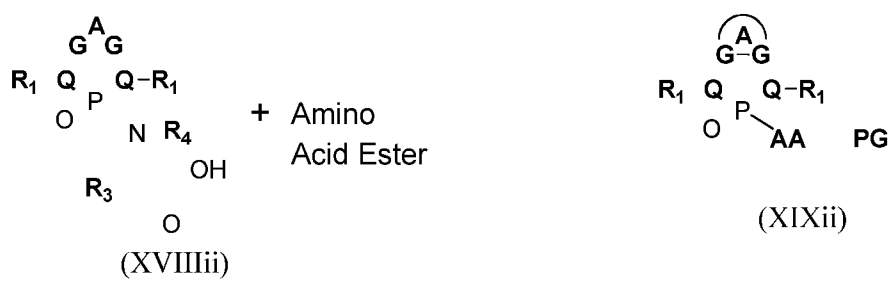


wherein: **X** is halogen; ring **A** is a carbocyclic ring or absent; each **Q** is nitrogen or carbon, or oxygen; each **G** is carbon; or when ring **A** is absent and **Q** is oxygen, then **G** is absent; each **R₁** is independently hydrogen, alkyl, aryl or aryl alkyl; **R₂** is hydrogen or alkyl; **R₃** is a side chain of a natural or unnatural amino acid; and **R₄** is hydrogen; or, in the alternative, **R₃** and **R₄** combine to form a 5-membered ring.

[00029] In certain embodiments, provided herein is a method of producing a protected amino acid sequence, comprising: (a) hydrogenating a compound of Formula IXii in the presence of a hydrogenation catalyst to form a compound of Formula XVIIIii:

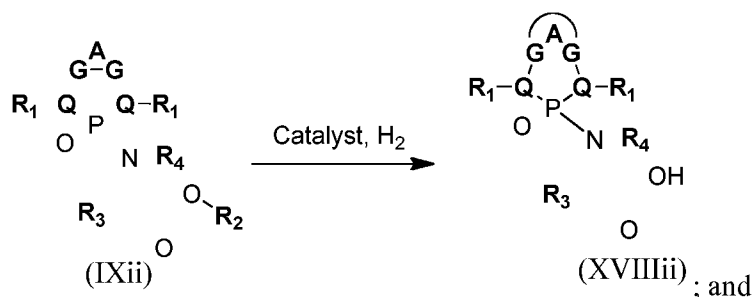


(b) reacting the compound of Formula XVIIIii with an amino acid ester to form a protected amino acid sequence of Formula XIXii:

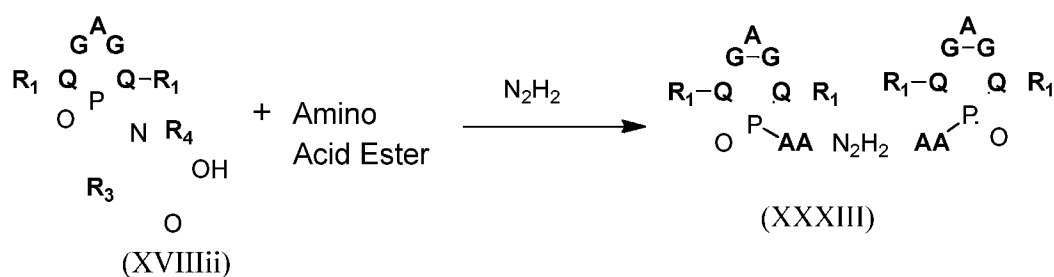


wherein: each **Q** is nitrogen, carbon, or oxygen; each **G** is carbon; or when ring **A** is absent and **Q** is oxygen, then **G** is absent; **AA** is an amino acid sequence; **PG** is protecting group attached to the carboxyl terminal of **AA**; ring **A** is a carbocyclic ring or absent each **R**₁ is independently hydrogen, alkyl, aryl or aryl alkyl; **R**₂ is alkyl; **R**₃ is a side chain of a natural or unnatural amino acid; and **R**₄ is hydrogen; or, in the alternative, **R**₃ and **R**₄ combine to form a 5-membered ring.

[00030] In certain embodiments, provided herein is a method of producing a protected amino acid sequence, comprising: (a) hydrogenating a compound of Formula IXii in the presence of a hydrogenation catalyst to form a compound of Formula XVIIIii:

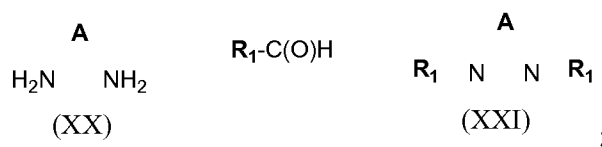


(b) reacting the compound of Formula XVIIIii with an amino acid ester to form a protected amino acid sequence of Formula XXXIII:

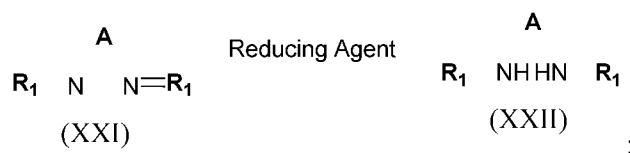


wherein: each **Q** is nitrogen, carbon, or oxygen; each **G** is carbon; or when ring **A** is absent and **Q** is oxygen, then **G** is absent; **AA** is an amino acid sequence; **PG** is protecting group attached to the carboxyl terminal of **AA**; ring **A** is a carbocyclic ring or absent each **R**₁ is independently hydrogen, alkyl, aryl or aryl alkyl; **R**₂ is alkyl; **R**₃ is a side chain of a natural or unnatural amino acid; and **R**₄ is hydrogen; or, in the alternative, **R**₃ and **R**₄ combine to form a 5-membered ring.

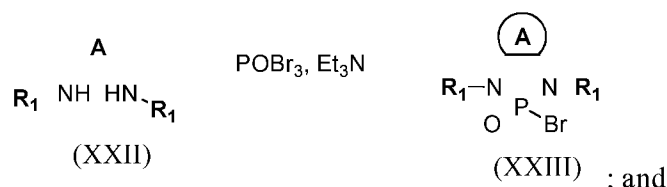
[00031] In certain embodiments, provided herein is a method of synthesizing a compound of Formula VIIIi, comprising: (a) reacting a compound of Formula XXi with **R**₁-C(O)H to form a compound of Formula XXII:



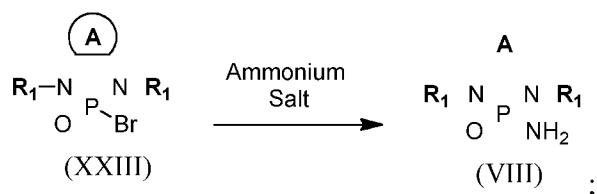
(b) reducing the compound of Formula XXI to form a compound of Formula XXII:



(c) reacting the compound of formula XXII with POBr₃ to form a compound of Formula XXIII:

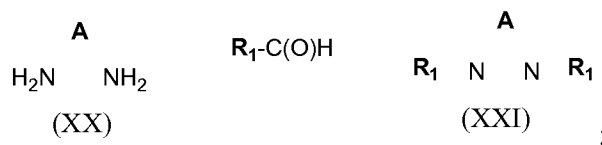


(d) reacting the compound of Formula XXIII with an ammonium salt to form a compound of Formula VIII:

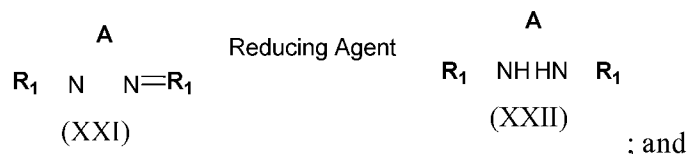


wherein: each R_1 is independently hydrogen, alkyl, aryl or aryl alkyl; and ring **A** is a carbocyclic ring or absent. In an embodiment, the ammonium salt is NH_4Cl or $(\text{NH}_4)_2\text{SO}_4$. In an embodiment, the ammonium salt is NH_4Cl . In an embodiment, the ammonium salt is $(\text{NH}_4)_2\text{SO}_4$.

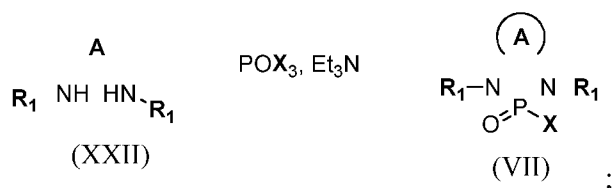
[00032] In certain embodiments, provided herein is a method of synthesizing a compound of Formula VII, comprising: (a) reacting a compound of Formula XX with $\text{R}_1\text{-C(O)H}$ to form a compound of Formula XXI:



(b) reducing the compound of Formula XXI to form a compound of Formula XXII:

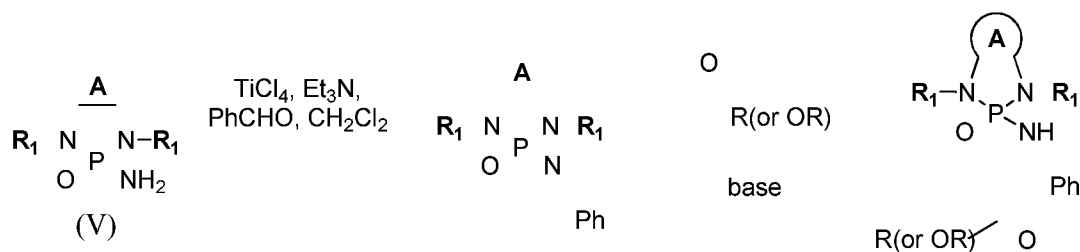


(c) reacting the compound of formula XXII with POX_3 to form a compound of Formula VII:



wherein: **X** is halogen; each R_1 is independently hydrogen, alkyl, aryl or aryl alkyl; and ring **A** is a carbocyclic ring or absent.

[00033] The phosphonyl amines described herein are useful, for example, in GAP imine chemistry. The phosphonyl amides can be used to synthesis phosphonyl imines which can be converted to β -amino-ketone or β -amino-acid esters. An example is provided in the scheme below:



DESCRIPTION OF EXEMPLARY EMBODIMENTS

[00034] Provided herein are novel phosphonyl halide and phosphonyl amide compounds. Also provided herein are methods of synthesizing the novel phosphonyl halide and phosphonyl amide compounds. The novel phosphonyl halide compounds are useful, for example, as protecting groups in the synthesis of amino acid sequences, peptides, and proteins. The phosphonyl amide compounds are useful, for example in GAP imine chemistry.

[00035] Provided herein are novel methods of GAP synthesis of Velcade, Velcade analogs and amino compounds. GAP, the abbreviation of Group-Assisted Purification, refers to synthesis methods which avoid or minimize the use of traditional purification methods such as chromatography and recrystallization. The methods involve organic syntheses with chiral auxiliaries which allow pure products, often pure isomers, to be obtained simply by washing crude products with organic solvents. In some embodiments, the crude products themselves are pure or optically pure enough due to excellent reactivity, chemoselectivity, and asymmetric induction of GAP methods. In preferred embodiments, chiral auxiliaries can be recycled easily after deprotection, in some cases without racemization of the chiral auxiliaries. The “Group” in GAP methods can be, but is not limited to, phosphonyl or phosphinyl auxiliaries. The phosphonyl and phosphinyl auxiliaries can provide efficient asymmetric induction and control in organic transformations. Additionally, corresponding chiral products, mostly solidified, can be utilized to synthesize Velcade, Velcade analogs and amino compounds. Also provided herein are novel dimeric Velcade analogs and methods of synthesis thereof, which have potential use as alternatives to Velcade monomer cancer therapeutics.

Definitions

[00036] When referring to the compounds provided herein, the following terms have the following meanings unless indicated otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of

ordinary skill in the art. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[00037] The term “alkyl”, as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In certain embodiments, the alkyl group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkyl group includes one to ten carbon atoms, i.e., C₁ to C₁₀ alkyl. In certain embodiments, the alkyl group is selected from the group consisting of methyl, CF₃, CCl₃, CFCI₂, CF₂Cl, ethyl, CH₂CF₃, CF₂CF₃, propyl, isopropyl, butyl, isobutyl, secbutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups, including halogenated alkyl groups. In certain embodiments, the alkyl group is a fluorinated alkyl group. Non-limiting examples of moieties with which the alkyl group can be substituted are selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

[00038] The term “lower alkyl”, as used herein, and unless otherwise specified, refers to a saturated straight or branched hydrocarbon having one to six carbon atoms, i.e., C₁ to C₆ alkyl. In certain embodiments, the lower alkyl group is a primary, secondary, or tertiary hydrocarbon. The term includes both substituted and unsubstituted moieties.

[00039] The terms “cycloalkyl” and “carbocyclic”, as used herein, unless otherwise specified, refers to a saturated cyclic hydrocarbon. In certain embodiments, the cycloalkyl group may be a saturated, and/or bridged, and/or non-bridged, and/or a fused bicyclic group. In certain embodiments, the cycloalkyl group includes three to ten carbon atoms, i.e., C₃ to C₁₀ cycloalkyl. In some embodiments, the cycloalkyl has from 3 to 15 (C₃₋₁₅), from 3 to 10 (C₃₋₁₀), or from 3 to 7 (C₃₋₇) carbon atoms. In certain embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, cycloheptyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, decalinyl, or adamantyl.

[00040] The term “cycloalkenyl”, as used herein, unless otherwise specified, refers to an unsaturated cyclic hydrocarbon. In certain embodiments, cycloalkenyl refers to mono- or multicyclic ring systems that include at least one double bond. In certain embodiments, the

cycloalkenyl group may be a bridged, non-bridged, and/or a fused bicyclic group. In certain embodiments, the cycloalkyl group includes three to ten carbon atoms, i.e., C₃ to C₁₀ cycloalkyl. In some embodiments, the cycloalkenyl has from 3 to 7 (C₃₋₁₀), or from 4 to 7 (C₃₋₇) carbon atoms.

[00041] “Alkylene” refers to divalent saturated aliphatic hydrocarbon groups particularly having from one to eleven carbon atoms which can be straight-chained or branched. In certain embodiments, the alkylene group contains 1 to 10 carbon atoms. The term includes both substituted and unsubstituted moieties. This term is exemplified by groups such as methylene (–CH₂–), ethylene (–CH₂CH₂–), the propylene isomers (e.g., –CH₂CH₂CH₂– and –CH(CH₃)CH₂–) and the like.

[00042] “Alkenyl” refers to monovalent olefinically unsaturated hydrocarbon groups, in certain embodiment, having up to about 11 carbon atoms, from 2 to 8 carbon atoms, or from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 or from 1 to 2 sites of olefinic unsaturation. The term includes both substituted and unsubstituted moieties. Exemplary alkenyl groups include ethenyl (i.e., vinyl, or –CH=CH₂), n-propenyl (–CH₂CH=CH₂), isopropenyl (–C(CH₃)=CH₂), and the like.

[00043] “Alkenylene” refers to divalent olefinically unsaturated hydrocarbon groups, in certain embodiments, having up to about 11 carbon atoms or from 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 or from 1 to 2 sites of olefinic unsaturation. This term is exemplified by groups such as ethenylene (–CH=CH–), the propenylene isomers (e.g., –CH=CHCH₂– and –C(CH₃)=CH– and –CH=C(CH₃)–) and the like.

[00044] “Alkynyl” refers to acetylenically unsaturated hydrocarbon groups, in certain embodiments, having up to about 11 carbon atoms or from 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 or from 1 to 2 sites of alkynyl unsaturation. Non-limiting examples of alkynyl groups include acetylenic, ethynyl (–C≡CH), propargyl (–CH₂C≡CH), and the like.

[00045] The term “aryl”, as used herein, and unless otherwise specified, refers to a cyclic aromatic hydrocarbon. In certain embodiments, aryl is furanyl, pyridinyl, phenyl, biphenyl, or naphthyl. The term includes both substituted and unsubstituted moieties. An aryl group can be substituted with any described moiety, including, but not limited to, one or more moieties selected from the group consisting of halogen (fluoro, chloro, bromo or iodo),

alkyl, haloalkyl, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Second Edition, 1991.

[00046] “Alkoxy” refers to the group $-OR'$ where R' is alkyl or cycloalkyl. Alkoxy groups include, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

[00047] “Alkoxy carbonyl” refers to a radical $-C(O)$ -alkoxy where alkoxy is as defined herein.

[00048] “Amino” refers to the radical $-NH_2$.

[00049] “Carboxyl” or “carboxy” refers to the radical $-C(O)OH$.

[00050] The term “alkylamino” or “arylamino” refers to an amino group that has one or two alkyl or aryl substituents, respectively. In certain embodiments, the alkyl substituent is lower alkyl. In another embodiment, the alkyl or lower alkyl is unsubstituted.

[00051] “Halogen” or “halo” refers to chloro, bromo, fluoro or iodo.

[00052] “Monoalkylamino” refers to the group $alkyl-NR'$ —, wherein R' is selected from hydrogen and alkyl or cycloalkyl.

[00053] “Thioalkoxy” refers to the group $-SR'$ where R' is alkyl or cycloalkyl.

[00054] The term “heterocyclyl” or “heterocyclic” refers to a monovalent monocyclic non-aromatic ring system and/or multicyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms independently selected from O, S, or N; and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclyl or heterocyclic group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. Heterocyclyl groups are bonded to the rest of the molecule through the non-aromatic ring. In certain embodiments, the heterocyclyl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include a fused or bridged ring system, and in which the nitrogen or sulfur atoms may be optionally oxidized, the nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclyl may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic radicals include, but are not limited to, azepinyl,

benzodioxanyl, benzodioxolyl, benzofuranonyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiopyranyl, benzoxazinyl, β -carbolinyl, chromanyl, chromonyl, cinnoliny, coumarinyl, decahydroisoquinoliny, dihydrobenzothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, imidazoliny, indoliny, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, isoindoliny, isothiazolidinyl, isoxazolidinyl, morpholiny, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazoliny, pyrrolidinyl, pyrroliny, quinuclidiny, tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydropyranyl, tetrahydrothienyl, thiamorpholiny, thiazolidinyl, tetrahydroquinoliny, and 1,3,5-trithianyl. In certain embodiments, heterocyclic may also be optionally substituted as described herein.

[00055] The term “heteroaryl” refers to refers to a monovalent monocyclic aromatic group and/or multicyclic aromatic group that contain at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, S, and N in the ring. Heteroaryl groups are bonded to the rest of the molecule through the aromatic ring. Each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, and/or one to four N atoms, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, and triazolyl. Examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indoliziny, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinoliny, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinoliny, quinoxaliny, quinazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Examples of tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthroliny,

phenanthridinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and xanthenyl. In certain embodiments, heteroaryl may also be optionally substituted as described herein.

[00056] The term “alkylaryl” refers to an aryl group with an alkyl substituent. The term “aralkyl” or “arylalkyl” includes an alkyl group with an aryl substituent.

[00057] The term “alkylheterocyclyl” refers to a heterocyclyl group with an alkyl substituent. The term alkylheterocyclyl includes an alkyl group with a heterocyclyl substituent.

[00058] The term “alkylheteroaryl” refers to a heteroaryl group with an alkyl substituent. The term alkylheteroaryl includes an alkyl group with a heteroaryl substituent.

[00059] The term “protecting group” as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis.

[00060] The term “amino acid” refers to naturally occurring and non-naturally occurring amino acids, as well as amino acids such as proline, amino acid analogs and amino acid mimetics that function in a manner similar to naturally occurring amino acids. The term refers to naturally occurring and synthetic α , β , γ or δ amino acids. The term includes, but is not limited to, amino acids found in proteins, i.e. glycine (Gly), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), methionine (Met), phenylalanine (Phe), tryptophan (Trp), proline (Pro), serine, threonine (Thr), cysteine (Cys), tyrosine (Tyr), asparagine (Asn), glutamine (Gln), aspartate (Asp), glutamate (Glu), lysine (Lys), arginine (Arg) and histidine (His). In certain embodiments, the amino acid is in the L-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleuccinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β -alanyl, β -valinyl, β -leucinyl, β -isoleuccinyl, β -prolinyl, β -phenylalaninyl, β -tryptophanyl, β -methioninyl, β -glycyl, β -serinyl, β -threoninyl, β -cysteinyl, β -tyrosinyl, β -asparaginyl, β -glutaminyl, β -aspartoyl, β -glutaroyl, β -lysinyl, β -argininyl or β -histidinyl.

[00061] Naturally encoded amino acids are the proteinogenic amino acids known to those of skill in the art. They include the 20 common amino acids (alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine,

leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine) and the less common pyrrolysine and selenocysteine. Naturally encoded amino acids include post-translational variants of the 22 naturally occurring amino acids such as prenylated amino acids, isoprenylated amino acids, myrisoylated amino acids, palmitoylated amino acids, N-linked glycosylated amino acids, O-linked glycosylated amino acids, phosphorylated amino acids and acylated amino acids.

[00062] The term “modified amino acid” refers to an amino acid that is not a proteinogenic amino acid, or a post-translationally modified variant thereof. In particular, the term refers to an amino acid that is not one of the 20 common amino acids or pyrrolysine or selenocysteine, or post-translationally modified variants thereof.

[00063] The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues. That is, a description directed to a polypeptide applies equally to a description of a peptide and a description of a protein, and vice versa. The terms apply to naturally occurring amino acid polymers as well as amino acid polymers in which one or more amino acid residues is a modified amino acid. Additionally, such “polypeptides,” “peptides” and “proteins” include amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds.

[00064] The term “acyl” or “O-linked ester” refers to a group of the formula $C(O)R'$, wherein R' is alkyl or cycloalkyl (including lower alkyl), carboxylate residue of amino acid, aryl including phenyl, alkaryl, arylalkyl including benzyl, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl; or substituted alkyl (including lower alkyl), aryl including phenyl optionally substituted with chloro, bromo, fluoro, iodo, C1 to C4 alkyl or C1 to C4 alkoxy, sulfonate esters such as alkyl or arylalkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxy-trityl, substituted benzyl, alkaryl, arylalkyl including benzyl, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl. Aryl groups in the esters optimally comprise a phenyl group. In particular, acyl groups include acetyl, trifluoroacetyl, methylacetyl, cyclopropylacetyl, propionyl, butyryl, hexanoyl, heptanoyl, octanoyl, neo-heptanoyl, phenylacetyl, 2-acetoxy-2-phenylacetyl, diphenylacetyl, α -methoxy- α -trifluoromethyl-phenylacetyl, bromoacetyl, 2-nitro-benzeneacetyl, 4-chloro-benzeneacetyl, 2-chloro-2,2-diphenylacetyl, 2-chloro-2-phenylacetyl, trimethylacetyl, chlorodifluoroacetyl, perfluoroacetyl, fluoroacetyl, bromodifluoroacetyl, methoxyacetyl, 2-thiopheneacetyl,

chlorosulfonylacetyl, 3-methoxyphenylacetyl, phenoxyacetyl, tert-butylacetyl, trichloroacetyl, monochloro-acetyl, dichloroacetyl, 7H-dodecafluoro-heptanoyl, perfluoro-heptanoyl, 7H-dodeca-fluoroheptanoyl, 7-chlorododecafluoro-heptanoyl, 7-chloro-dodecafluoro-heptanoyl, 7H-dodecafluoroheptanoyl, 7H-dodeca-fluoroheptanoyl, nona-fluoro-3,6-dioxa-heptanoyl, nonafluoro-3,6-dioxaheptanoyl, perfluoroheptanoyl, methoxybenzoyl, methyl 3-amino-5-phenylthiophene-2-carboxyl, 3,6-dichloro-2-methoxy-benzoyl, 4-(1,1,2,2-tetrafluoro-ethoxy)-benzoyl, 2-bromo-propionyl, omega-aminocapryl, decanoyl, n-pentadecanoyl, stearyl, 3-cyclopentyl-propionyl, 1-benzene-carboxyl, O-acetylmandelyl, pivaloyl acetyl, 1-adamantane-carboxyl, cyclohexane-carboxyl, 2,6-pyridinedicarboxyl, cyclopropane-carboxyl, cyclobutane-carboxyl, perfluorocyclohexyl carboxyl, 4-methylbenzoyl, chloromethyl isoxazolyl carbonyl, perfluorocyclohexyl carboxyl, crotonyl, 1-methyl-1H-indazole-3-carbonyl, 2-propenyl, isovaleryl, 1-pyrrolidinecarbonyl, 4-phenylbenzoyl.

[00065] The term “substantially free of” or “substantially in the absence of” with respect to a composition refers to a composition that includes at least 85% or 90% by weight, in certain embodiments 95%, 98%, 99% or 100% by weight, of a designated enantiomer of a compound. In certain embodiments, in the methods and compounds provided herein, the compounds are substantially free of enantiomers.

[00066] Similarly, the term “isolated” with respect to a composition refers to a composition that includes at least 85%, 90%, 95%, 98%, 99% or 100% by weight, of a compound, the remainder comprising other chemical species or enantiomers.

[00067] Similarly, the term “diastereomerically pure” with respect to a compound refers to a compound that includes at least 85% or 90% by weight, in certain embodiments 95%, 98%, 99% or 100% by weight of the designated diastereomer.

[00068] “Isotopic composition” refers to the amount of each isotope present for a given atom, and “natural isotopic composition” refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as “non-enriched” atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural isotopic composition.

[00069] "Isotopic enrichment" refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic abundance. For example, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[00070] "Isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom.

[00071] As used herein, "alkyl," "cycloalkyl," "alkenyl," "cycloalkenyl," "alkynyl," "aryl," "alkoxy," "alkoxycarbonyl," "amino," "carboxyl," "alkylamino," "arylamino," "thioalkoxy," "heterocyclyl," "heteroaryl," "alkylheterocyclyl," "alkylheteroaryl," "acyl," "aralkyl," "alkaryl," "purine," "pyrimidine," "carboxyl" and "amino acid" groups optionally comprise deuterium at one or more positions where hydrogen atoms are present, and wherein the deuterium composition of the atom or atoms is other than the natural isotopic composition.

[00072] Also as used herein, "alkyl," "cycloalkyl," "alkenyl," "cycloalkenyl," "alkynyl," "aryl," "alkoxy," "alkoxycarbonyl," "carboxyl," "alkylamino," "arylamino," "thioalkoxy," "heterocyclyl," "heteroaryl," "alkylheterocyclyl," "alkylheteroaryl," "acyl," "aralkyl," "alkaryl," "purine," "pyrimidine," "carboxyl" and "amino acid" groups optionally comprise carbon-13 at an amount other than the natural isotopic composition.

[00073] The term "protected", as used herein and unless specified otherwise, refers to a group that is added to an oxygen, nitrogen or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen, nitrogen and phosphorus protecting groups are known to those skilled in the art of organic synthesis.

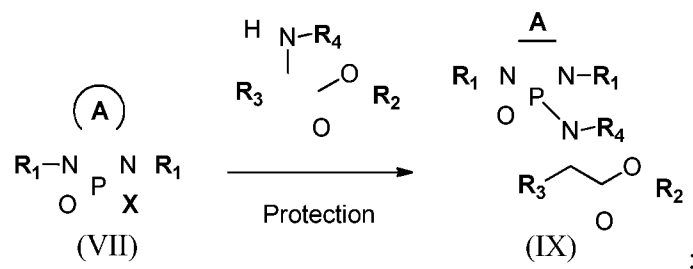
[00074] Examples of suitable protecting groups include, but not limited to, benzoyl; substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted silyl groups; substituted or unsubstituted aromatic or aliphatic esters, such as,

for example, aromatic groups like benzoyl, toluoyls (e.g. p-toluoyl), nitrobenzoyl, chlorobenzoyl; ether groups such as, for example, -C-O-aralkyl, -C-O-alkyl, or -C-O-aryl; and aliphatic groups like acyl or acetyl groups, including any substituted or unsubstituted aromatic or aliphatic acyl, -(C=O)-aralkyl, -(C=O)-alkyl, or -(C=O)-aryl; wherein the aromatic or aliphatic moiety of the acyl group can be straight-chained or branched; all of which may be further optionally substituted by groups not affected by the reactions comprising the improved synthesis (see Greene et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, 2nd Edition, 1991). For example, in one embodiment of the invention, the protecting groups are substituted by groups not affected by the reducing agent of choice, such as Red-Al. For the use of ethers as protective groups, attention is directed to U.S. Pat. No. 6,229,008 to Saischek et al., herein incorporated by reference, wherein it is reported that the use of an ether as a protective group may offer significant advantages for stability toward reagents and process conditions. This affords an ultimate advantage for separation, isolation, and purification of the desired product and thus, on the product's percent yield.

[00075] "Derivative," "analog," "chemical derivative," "derivatizing," and similar terms are given their ordinary meanings as well-known in the fields of chemistry, biochemistry, and/or biology. A derivative may be any chemical substance structurally related to another chemical substance and at least theoretically derivable from it. An analog may be a chemical or biological species that is similar enough to a parent species that it may substitute for the parent species in at least one set of chemical or biochemical interactions.

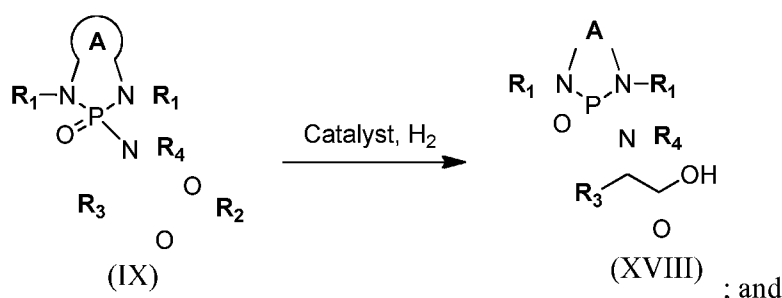
Synthetic Methods

[00076] In certain embodiments, provided herein is a method of protecting an amino acid comprising reacting an amino acid with a compound of formula VII to form a protected amino acid of formula IX:

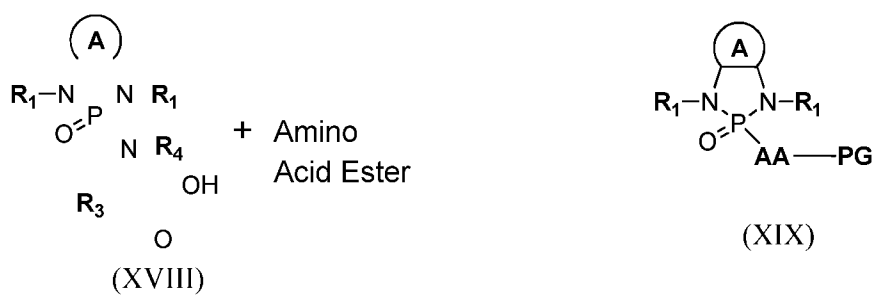


wherein: **X** is halogen; ring **A** is a carbocyclic ring or absent; each **R₁** is independently hydrogen, alkyl, aryl or aryl alkyl; **R₂** is hydrogen or alkyl; **R₃** is a side chain of a natural or unnatural amino acid; and **R₄** is hydrogen; or, in the alternative, **R₃** and **R₄** combine to form a 5-membered ring.

[00077] In certain embodiments, provided herein is a method of producing a protected amino acid sequence, comprising: (a) hydrogenating a compound of Formula IX in the presence of a hydrogenation catalyst to form a compound of Formula XVIII:



(b) reacting the compound of Formula XVIII with an amino acid ester to form a protected amino acid sequence of Formula XIX:



wherein: **AA** is an amino acid sequence; **PG** is protecting group attached to the carboxyl terminal of **AA**; ring **A** is a carbocyclic ring or absent each **R₁** is independently hydrogen, alkyl, aryl or aryl alkyl; **R₂** is alkyl; **R₃** is a side chain of a natural or unnatural amino acid; and **R₄** is hydrogen; or, in the alternative, **R₃** and **R₄** combine to form a 5-membered ring.

[00078] In certain embodiments, the hydrogenation catalyst comprises palladium.

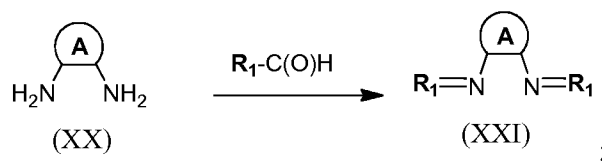
[00079] In certain embodiments, the method further comprises repeating steps (a) and (b) starting from a compound of Formula XIX. In an embodiment, the steps are repeated to synthesize an amino acid sequence. In an embodiment, the steps are repeated to synthesize a peptide. In an embodiment, the steps are repeated to synthesize a protein.

[00080] In certain embodiments, of the methods, $\mathbf{R}_2$ is methyl or benzyl; $\mathbf{R}_3$ is

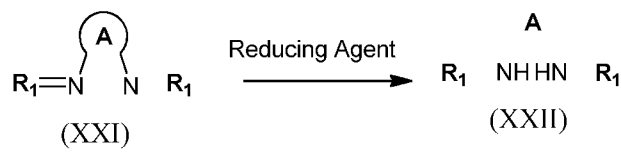
hydrogen, $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, , or -OH; and R_4 is

hydrogen; or, in the alternative, **R**₃ and **R**₄ combine to form

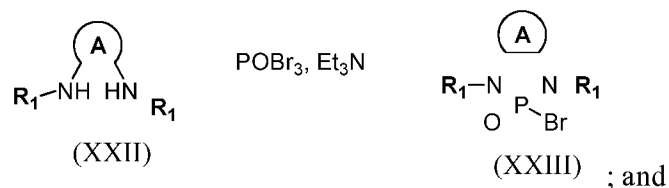
[00081] In certain embodiments, provided herein is a method of synthesizing a compound of Formula VIII, comprising: (a) reacting a compound of Formula XX with **R**₁-C(O)H to form a compound of Formula XXI:



(b) reducing the compound of Formula XXI to form a compound of Formula XXII:



(c) reacting the compound of formula XXII with POBr₃ to form a compound of Formula XXIII;



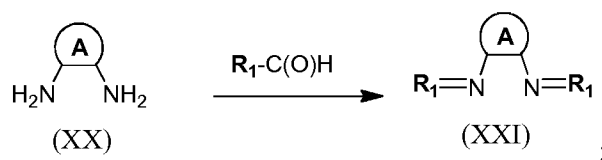
(d) reacting the compound of Formula XXIII with an ammonium salt to form a compound of Formula VIII;



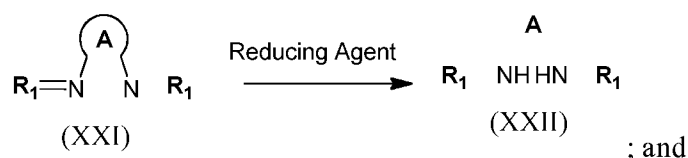
wherein: each **R**₁ is independently hydrogen, alkyl, aryl or aryl alkyl; and ring **A** is a carbocyclic ring or absent. In an embodiment, the ammonium salt is NH₄Cl or (NH₄)₂SO₄. In

an embodiment, the ammonium salt is NH_4Cl . In an embodiment, the ammonium salt is $(\text{NH}_4)_2\text{SO}_4$.

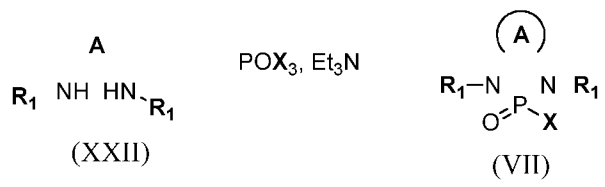
[00082] In certain embodiments, provided herein is a method of synthesizing a compound of Formula VII, comprising: (a) reacting a compound of Formula XX with $\text{R}_1\text{-C(O)H}$ to form a compound of Formula XXI:



(b) reducing the compound of Formula XXI to form a compound of Formula XXII:



(c) reacting the compound of formula XXII with POX_3 to form a compound of Formula VII:

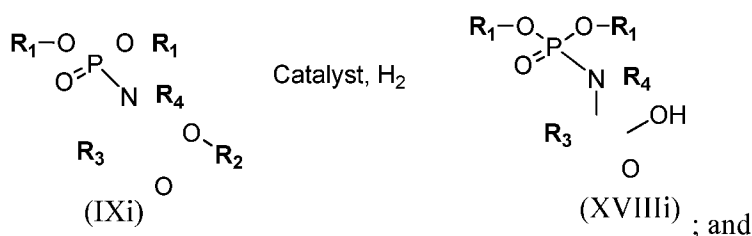


wherein: **X** is halogen; each R_1 is independently hydrogen, alkyl, aryl or aryl alkyl; and ring **A** is a carbocyclic ring or absent.

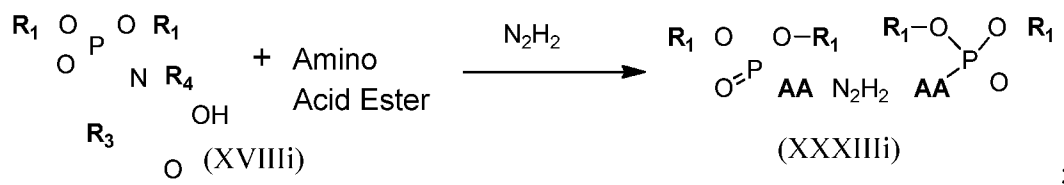
[00083] In certain embodiments of the methods, the Reducing Agent is NaBH_4 .

[00084] In certain embodiments of the methods, **X** is chloro or bromo. In certain embodiments, **X** is chloro. In certain embodiments, **X** is bromo.

[00085] In certain embodiments, provided herein is a method of producing a protected amino acid sequence, comprising: (a) hydrogenating a compound of Formula IXi in the presence of a hydrogenation catalyst to form a compound of Formula XVIIIi:



(b) reacting the compound of Formula XVIIIi with an amino acid ester to form a protected amino acid sequence of Formula XXXIIIi:



wherein: **AA** is an amino acid sequence; each **R₁** is independently hydrogen, alkyl, aryl or aryl alkyl; **R₂** is alkyl; **R₃** is a side chain of a natural or unnatural amino acid; and **R₄** is hydrogen; or, in the alternative, **R₃** and **R₄** combine to form a 5-membered ring.

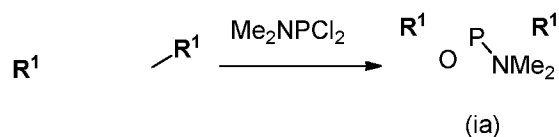
[00086] In certain embodiments of the methods described herein, each **R₁** is the same and selected from alkyl, aryl and aryl alkyl. In certain embodiments of the methods described herein, each **R₁** is the same and is alkyl. In certain embodiments of the methods described herein, each **R₁** is the same and is aryl alkyl. In certain embodiments of the methods described herein, each **R₁** is the same and is aryl. In certain embodiments of the methods described herein, each **R₁** is the same and is isopropyl. In certain embodiments of the methods described herein, each **R₁** is the same and is naphthyl. In certain embodiments of the methods described herein, each **R₁** is the same and is phenyl. In certain embodiments of the methods described herein, each **R₁** is the same and is hydrogen.

[00087] In certain embodiments of the methods described herein, each **Y** is independently chloro or bromo. In certain embodiments of the methods described herein, each **Y** is chloro. In certain embodiments of the methods described herein, each **Y** is bromo. In certain embodiments of the methods described herein, each **X** is independently chloro or bromo. In certain embodiments of the methods described herein, each **X** is chloro. In certain embodiments of the methods described herein, each **X** is bromo.

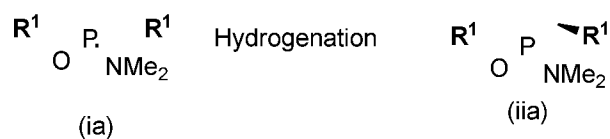
[00088] In certain embodiments of the methods described herein, ring **A** is a carbocyclic ring. In certain embodiments of the methods described herein, ring **A** is a six-membered carbocyclic ring. In certain embodiments of the methods described herein, ring **A** is a cyclohexane ring. In certain embodiments of the methods described herein, ring **A** is absent.

[00089] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1002 comprising:

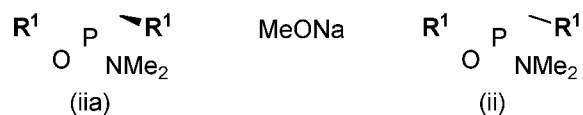
(a) reacting R^1  with Me_2NPCl_2 to form a compound of Formula (ia):



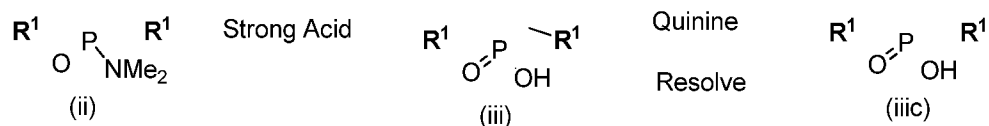
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



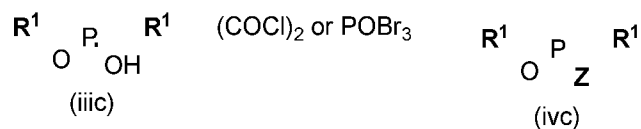
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



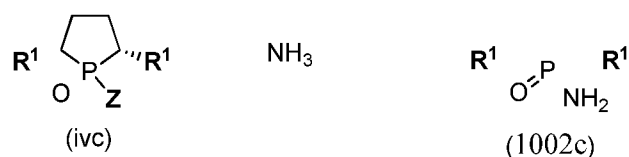
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiic):



(e) reacting the compound of Formula (iiic) with $(\text{COCl})_2$ or POBr_3 to form a compound of Formula (ivc):



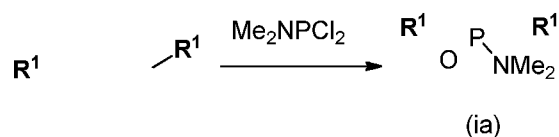
(f) reacting the compound of Formula (ivc) with NH_3 to form a compound of Formula (1002c):



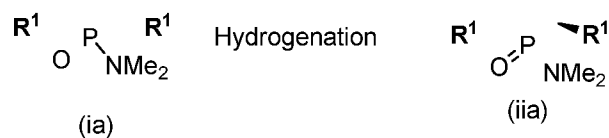
wherein: **Z** is chloro or bromo; and each **R**¹ is independently aryl or arylalkyl.

[00090] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1002 comprising:

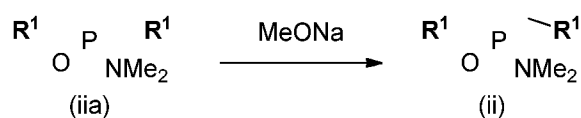
(a) reacting **R**¹  with Me₂NPCl₂ to form a compound of Formula (ia):



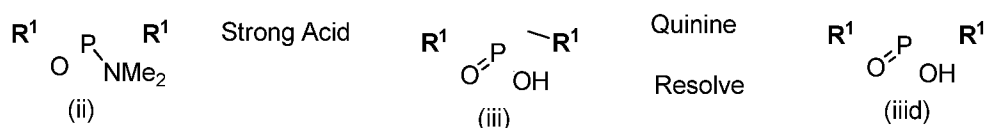
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



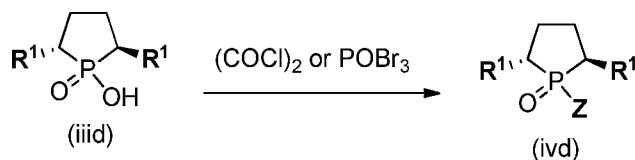
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



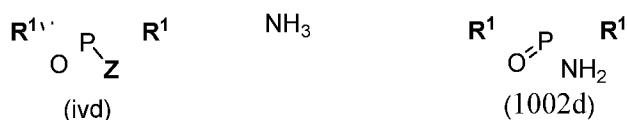
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiid):



(e) reacting the compound of Formula (iiid) with (COCl)₂ or POBr₃ to form a compound of Formula (ivd):

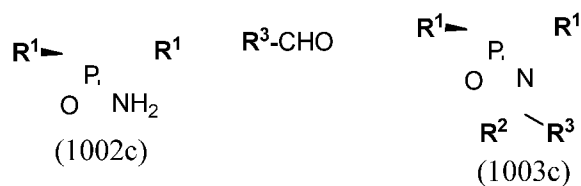


(f) reacting the compound of Formula (ivd) with NH₃ to form a compound of Formula (1002d):



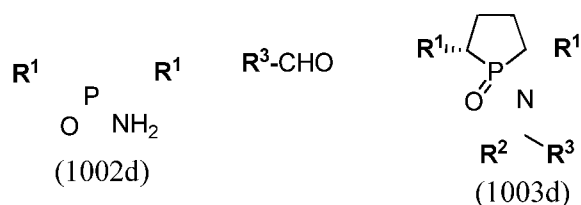
wherein: **Z** is chloro or bromo; and each **R**¹ is independently aryl or arylalkyl.

[00091] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1003c comprising reacting a compound of Formula 1002c with **R**³-CHO to form a compound of Formula 1003c:



wherein: each **R**¹ is independently aryl or arylalkyl; **R**² is hydrogen; and **R**³ is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, or C₆-C₁₂ aryl.

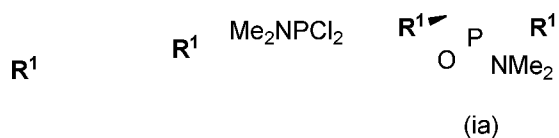
[00092] In certain embodiments provided herein is a method of synthesizing a compound of Formula 1003d comprising reacting a compound of Formula 1002d with **R**³-CHO to form a compound of Formula 1003d:



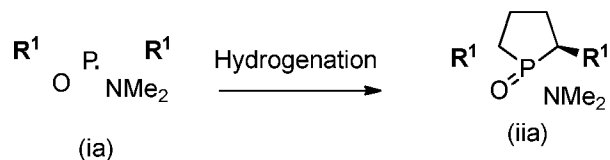
wherein: each **R**¹ is independently aryl or arylalkyl; **R**² is hydrogen; and **R**³ is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, or C₆-C₁₂ aryl.

[00093] In certain embodiments provided herein is a method of synthesizing Velcade comprising:

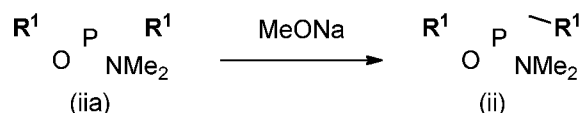
(a) reacting **R**¹ with Me₂NPCl₂ to form a compound of Formula (ia):



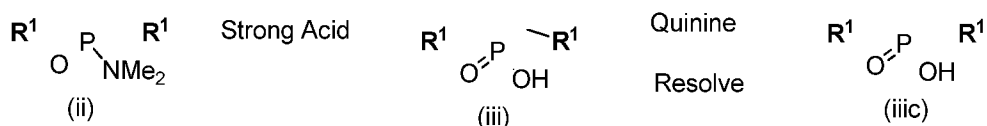
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



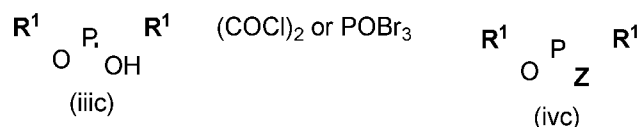
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



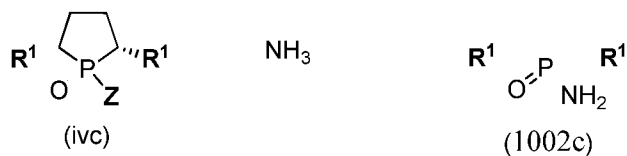
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiic):



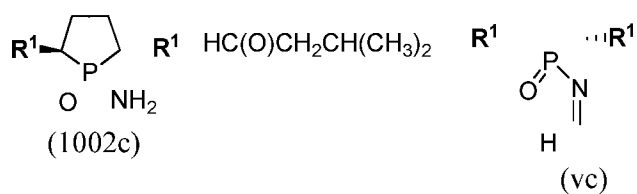
(e) reacting the compound of Formula (iiic) with (COCl)₂ or POBr₃ to form a compound of Formula (ivc):



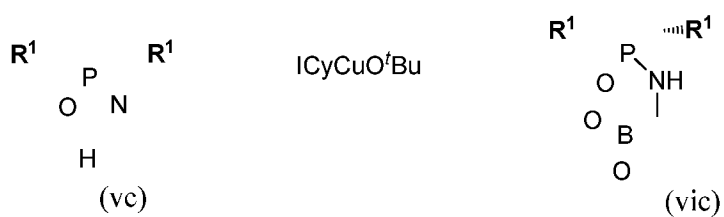
(f) reacting the compound of Formula (ivc) with NH₃ to form a compound of Formula (1002c):



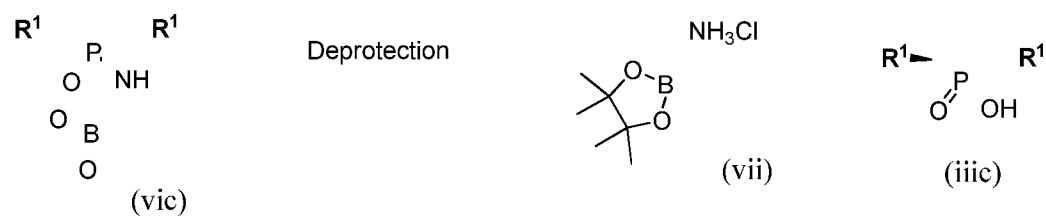
(g) reacting the compound of Formula 1002c with HC(O)CH₂CH(CH₃)₂ to form a compound of Formula vc:



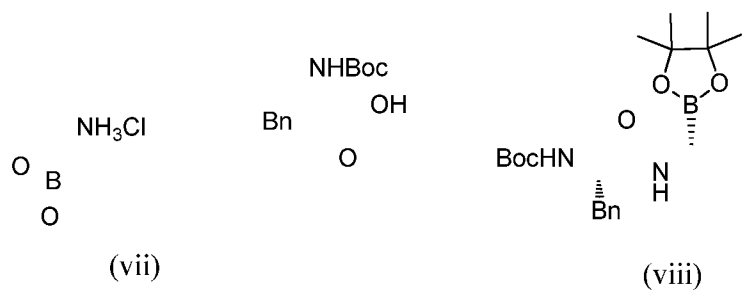
(h) reacting a compound of Formula (vc) with ICyCu^tBu to form a compound of Formula (vic):



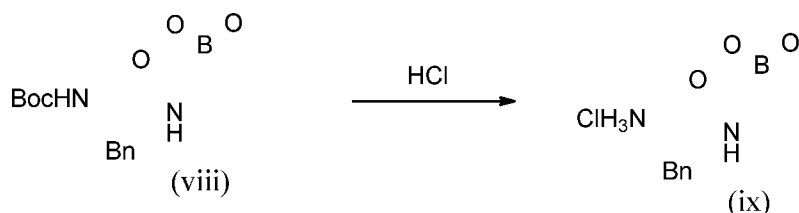
(i) deprotecting the compound of Formula (vic) to form a compound of Formula (vii) and a compound of Formula (iiic):



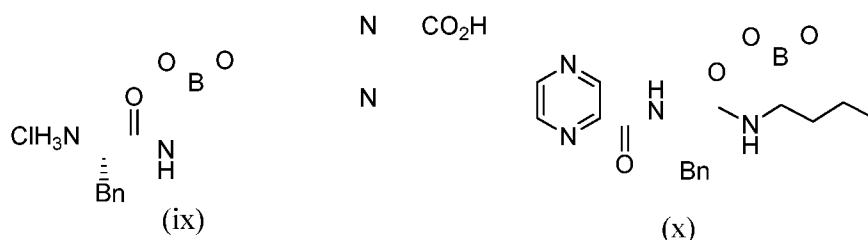
(j) reacting the compound of Formula (vii) with BnCH(NHBoc)C(O)OH to form a compound of Formula (viii):



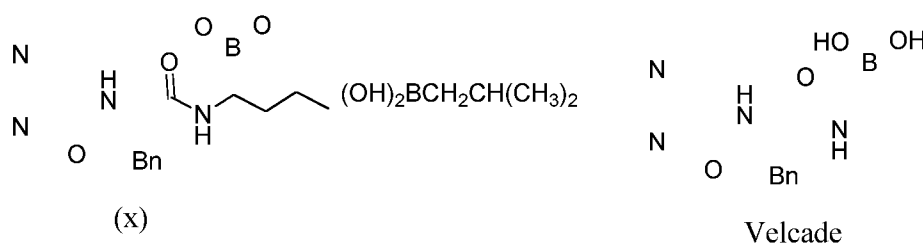
(k) reacting the compound of Formula (viii) with HCl to form a compound of Formula (ix):



(l) reacting the compound of Formula (ix) with CO_2H to form a compound of Formula (x):



(m) reacting the compound of Formula (x) with $(\text{OH})_2\text{BCH}_2\text{CH}(\text{CH}_3)_2$ to form Velcade:

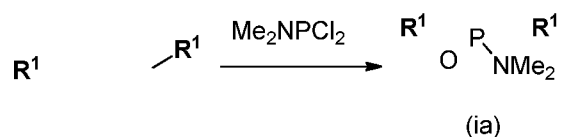


wherein: **Z** is chloro or bromo; and each **R**¹ is independently aryl or arylalkyl.

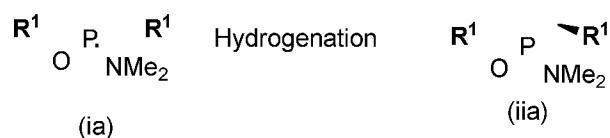
[00094] In certain embodiments, the method of synthesizing Velcade further comprises recycling the chiral auxiliary by using the compound of Formula (iiic) produced in step (i) in step (e).

In certain embodiments, provided herein is a method of synthesizing Velcade comprising:

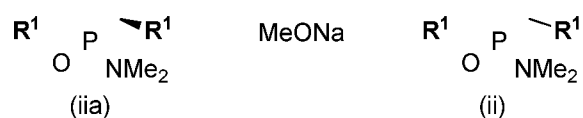
(a) reacting $\text{R}^1\text{-CH=CH-CH=CH-R}^1$ with Me_2NPCl_2 to form a compound of Formula (ia):



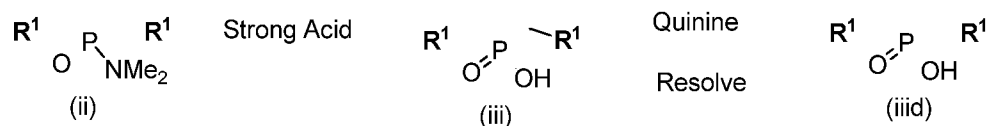
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



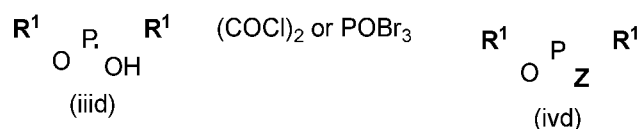
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



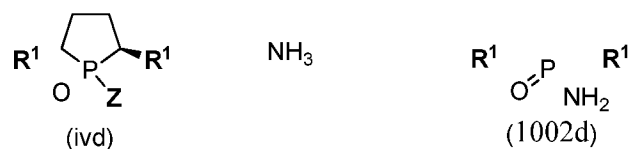
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiid):



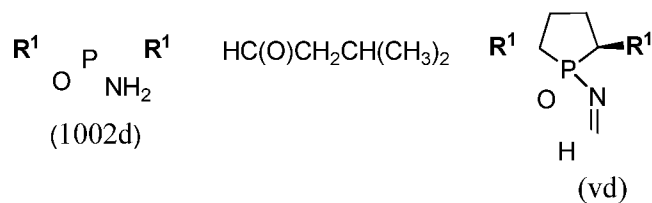
(e) reacting the compound of Formula (iiid) with (COCl)₂ or POBr₃ to form a compound of Formula (ivd):



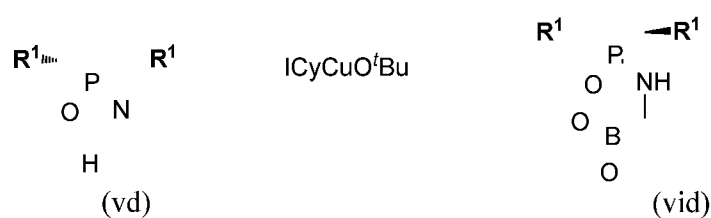
(f) reacting the compound of Formula (ivd) with NH₃ to form a compound of Formula (1002d):



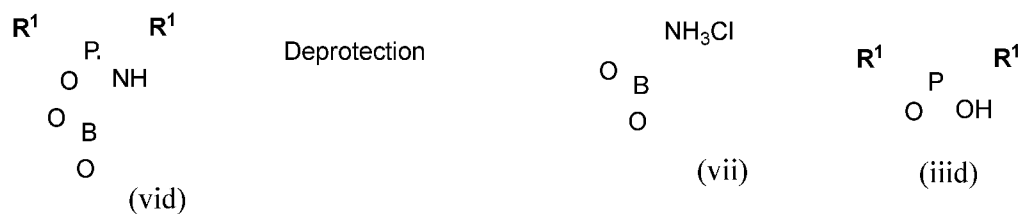
(g) reacting the compound of Formula 1002d with $\text{HC(O)CH}_2\text{CH(CH}_3)_2$ to form a compound of Formula vd:



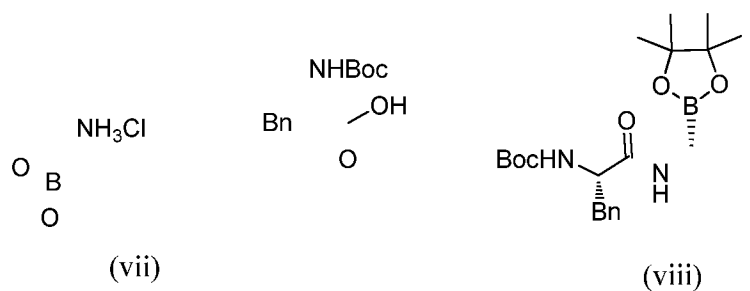
(h) reacting a compound of Formula (vd) with ICyCuO^tBu to form a compound of Formula (vid):



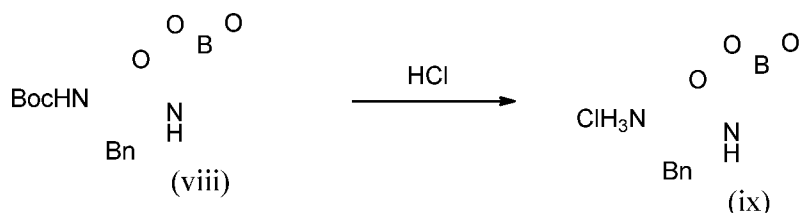
(i) deprotecting the compound of Formula (vid) to form a compound of Formula (vii) and a compound of Formula (iiid):

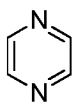


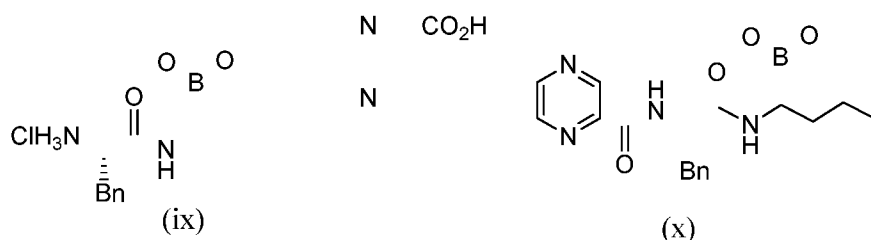
(j) reacting the compound of Formula (vii) with BnCH(NHBoc)C(O)OH to form a compound of Formula (viii):



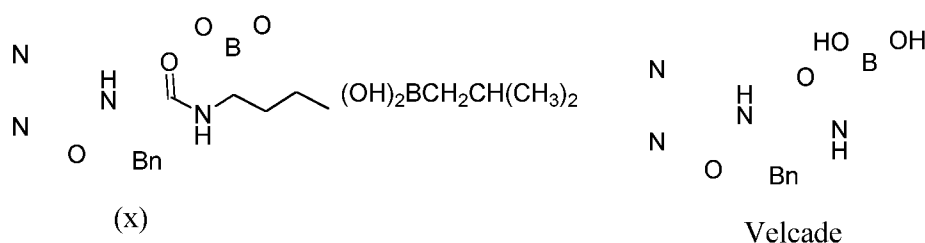
(k) reacting the compound of Formula (viii) with HCl to form a compound of Formula (ix):



(l) reacting the compound of Formula (ix) with  to form a compound of Formula (x):



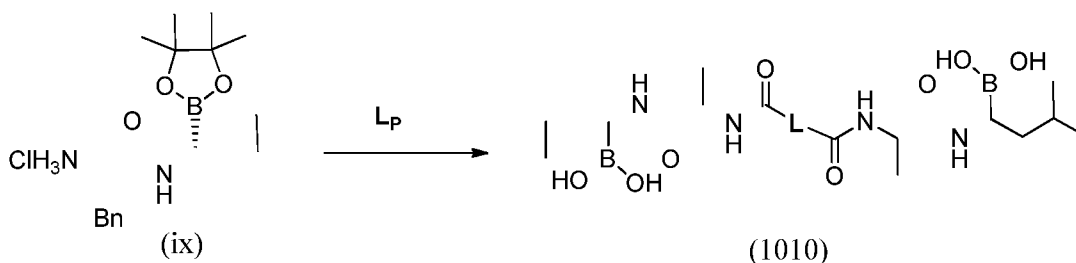
(m) reacting the compound of Formula (x) with $(\text{OH})_2\text{BCH}_2\text{CH}(\text{CH}_3)_2$ to form Velcade:



wherein: **Z** is chloro or bromo; and each **R**¹ is independently aryl or arylalkyl.

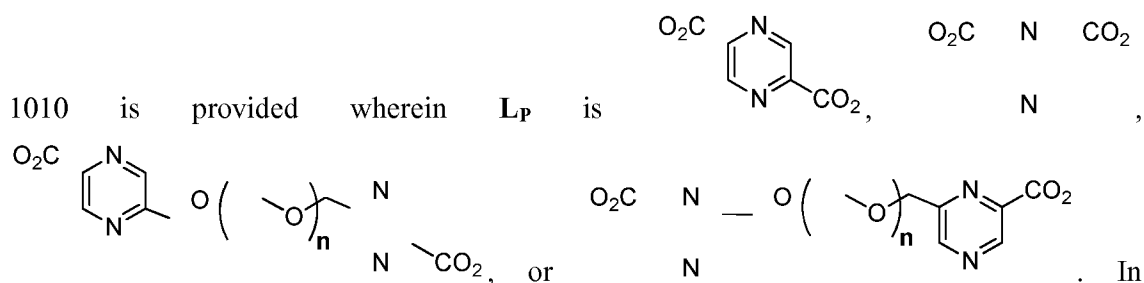
[00095] In certain embodiments, the method of synthesizing Velcade further comprises recycling the chiral auxiliary by using the compound of Formula (iiid) produced in step (i) in step (e).

[00096] In certain embodiments, provided herein is a method of synthesizing a compound of Formula 1010 comprising reacting a compound of Formula (ix) with **Lp**:

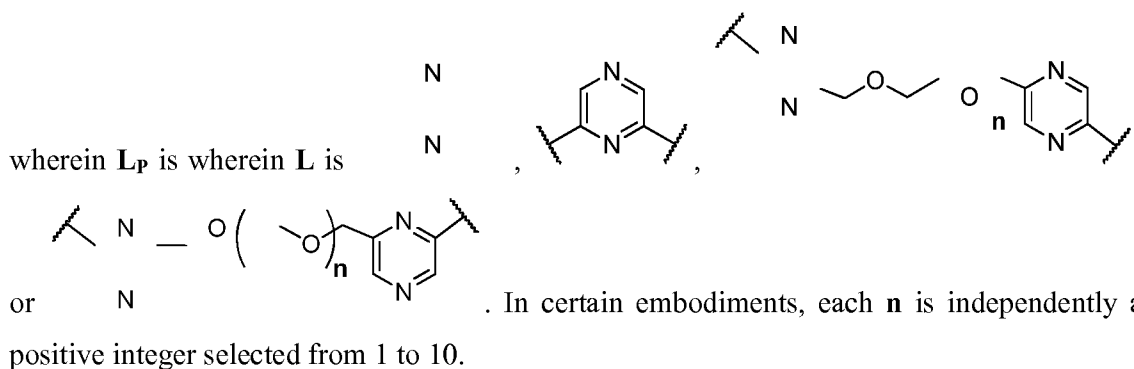


wherein: L is $\begin{array}{c} \text{N} \\ | \\ \text{N} \end{array}$ or $\begin{array}{c} \text{N} \\ | \\ \text{N} \end{array} - \text{J} - \begin{array}{c} \text{N} \\ | \\ \text{N} \end{array}$; L_P is $\begin{array}{c} \text{O}_2\text{C} - \text{N} \\ | \quad \quad | \\ \text{N} \quad \quad \text{CO}_2 \end{array}$ or $\begin{array}{c} \text{O}_2\text{C} \\ | \\ \text{N} \end{array} \quad \text{J} \quad \begin{array}{c} \text{N} \\ | \\ \text{CO}_2 \end{array}$; J is $-(\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CHO})_n-$, $-(\text{CH}_2-\text{CH}-\text{NH})_n-$, $-\text{O}-(\text{CH}_2-\text{CHO})_n-$, $-\text{NH}-(\text{CH}_2-\text{CH}-\text{NH})_n-$, $-\text{NH}-(\text{CH}_2-\text{CHO})_n-$, $-\text{O}-(\text{CH}_2-\text{CH}-\text{NH})_n-$ or $-(\text{amino acid residue})_n-$; and each n is independently a positive integer.

[00097] In certain embodiments, a method of synthesizing a compound of Formula

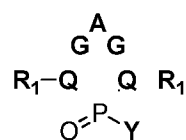


certain embodiments, a method of synthesizing a compound of Formula 1010 is provided



Compounds

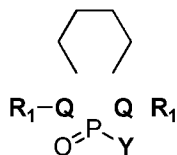
[00098] In certain embodiments, provided herein is a compound according to Formula I:



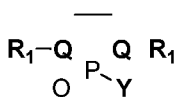
(I);

wherein: each R_1 is independently hydrogen, alkyl, aryl or aryl alkyl; ring A is a carbocyclic ring or absent; each Q is nitrogen, carbon, or oxygen; each G is carbon; or when ring A is absent and Q is oxygen, then G is absent; and Y is halogen, amide, an amino acid sequence or an amino acid, or ester thereof. In certain embodiments, ring A is a six-membered carbocyclic ring. In certain embodiments, ring A is a cyclohexane ring.

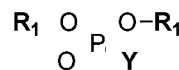
[00099] In certain embodiments, a compound is provided according to Formula II, III, or IV:



(II)



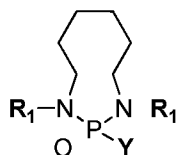
(III)



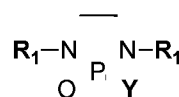
(IV);

wherein Q , R_1 and Y are as described in the context of Formula I.

[000100] In certain embodiments, a compound is provided according to Formula V or VI:



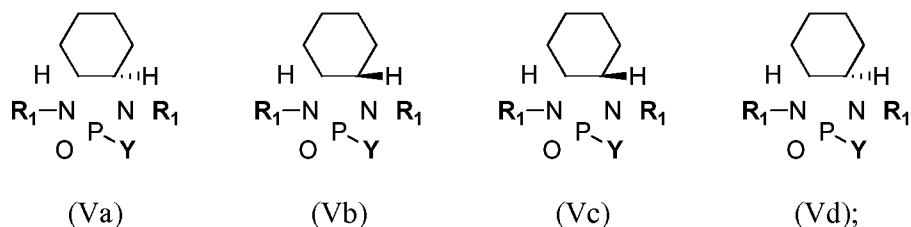
(V)



(VI);

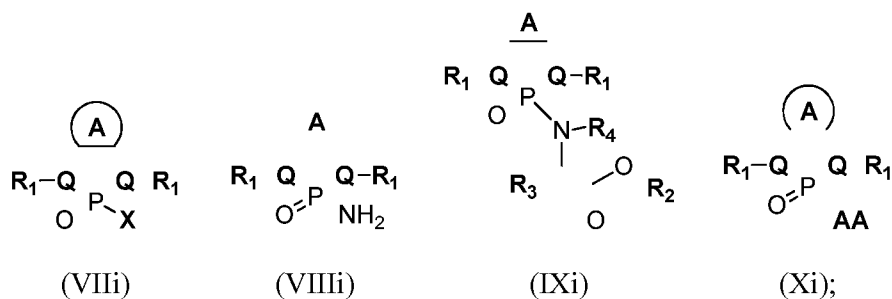
wherein R_1 and Y are as described in the context of Formula I.

[000101] In certain embodiments, a compound is provided according to any of Formulas Va-Vd:



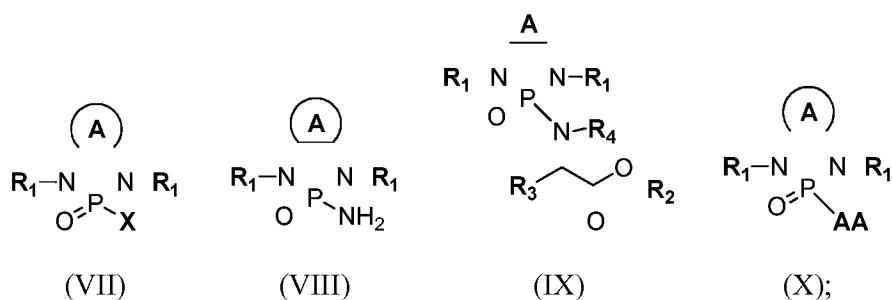
wherein **R**₁ and **Y** are as described in the context of Formula I. In an embodiment, a compound according to Formula Va is provided.

[000102] In certain embodiments, a compound is provided according to Formula VIII, VIIIi, IXi, or Xi:



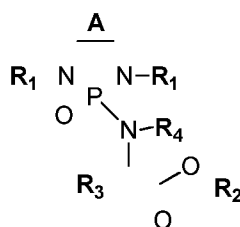
wherein: **Q**, **R**₁ and ring **A** are as described in the context of Formula I, **X** is halogen; **R**₂ is hydrogen or alkyl; **R**₃ is a side chain of a natural or unnatural amino acid; and **R**₄ is hydrogen; or, in the alternative, **R**₃ and **R**₄ combine to form a 5-membered ring.

[000103] In certain embodiments, a compound is provided according to Formula VII, VIII, IX, or X:



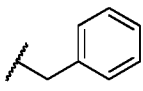
wherein: **R**₁ and ring **A** are as described in the context of Formula I, **X** is halogen; **R**₂ is hydrogen or alkyl; **R**₃ is a side chain of a natural or unnatural amino acid; and **R**₄ is hydrogen; or, in the alternative, **R**₃ and **R**₄ combine to form a 5-membered ring.

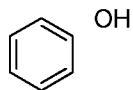
[000104] In certain embodiments, a compound is provided according to Formula IX:



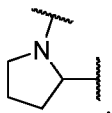
(IX);

wherein: **R**₁ and ring **A** are as described in the context of Formula I, **R**₂ is hydrogen, methyl

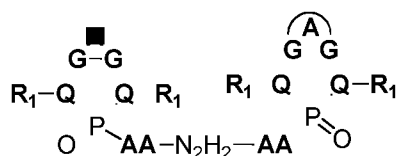
or benzyl; **R**₃ is hydrogen, -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, , or



; and **R**₄ is hydrogen; or, in the alternative, **R**₃ and **R**₄ combine to form



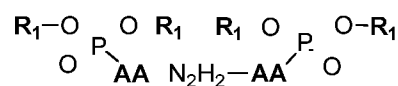
[000105] In certain embodiments, provided herein is a compound according to Formula XXXIII:



(XXXIII);

wherein: each **R**₁ is independently hydrogen, alkyl, aryl or aryl alkyl; ring **A** is a carbocyclic ring or absent; each **Q** is nitrogen, carbon, or oxygen; each **G** is carbon; or when ring **A** is absent and **Q** is oxygen, then **G** is absent; and each **AA** is independently an amino acid, an amino acid sequence, or ester thereof. In some embodiments, a compound of Formula XXXIII is provided wherein each **R**₁ is aryl. In some embodiments, a compound of Formula XXXIII is provided wherein each **R**₁ is phenyl. In some embodiments, a compound of Formula XXXIII is provided wherein each **Q** is nitrogen. In some embodiments, a compound of Formula XXXIII is provided wherein each ring **A** is absent.

[000106] In certain embodiments, provided herein is a protected amino acid sequence of Formula XXXIV:

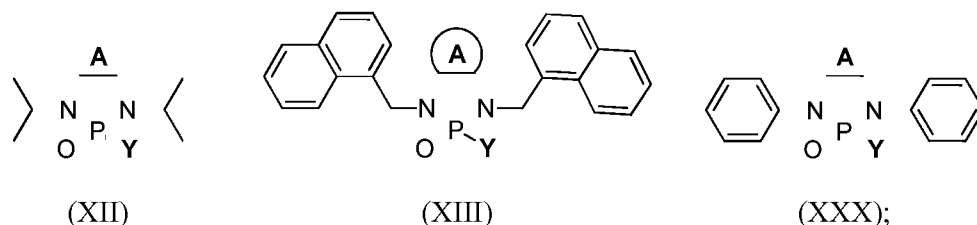


(XXXIV);

wherein: **R**₁ and **AA** are as described in the context of Formula XXXIII.

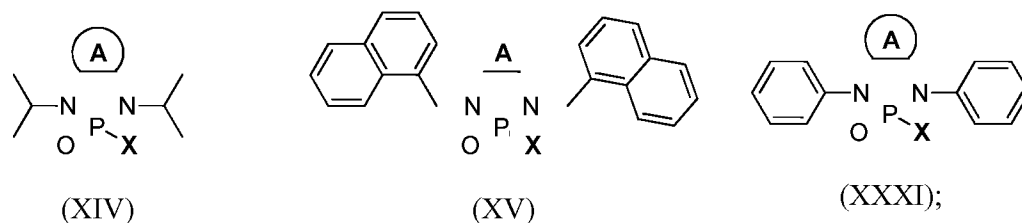
[000107] In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, VIIi-Xi, VII-XI or XXXIII-XXXIV is provided wherein each **R**₁ is the same and selected from alkyl, aryl and aryl alkyl. In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, VIIi-Xi, VII-XI or XXXIII-XXXIV is provided wherein each **R**₁ is the same and is alkyl. In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, VIIi-Xi, VII-XI or XXXIII-XXXIV is provided wherein each **R**₁ is the same and is aryl alkyl. In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, VIIi-Xi, VII-XI or XXXIII-XXXIV is provided wherein each **R**₁ is the same and is aryl. In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, VIIi-Xi, VII-XI or XXXIII-XXXIV is provided wherein each **R**₁ is the same and is hydrogen.

[000108] In certain embodiments, a compound is provided according to Formula XII, XIII, or XXX:



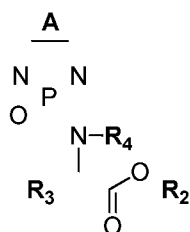
wherein **Y** and ring **A** are as described in the context of Formula I.

[000109] In certain embodiments, a compound is provided according to Formula XIV, XV or XXXI:

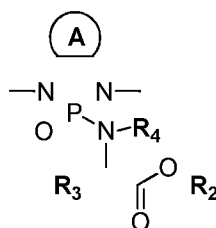


wherein **X** is as described in the context of Formula VII and ring **A** is as described in the context of Formula I.

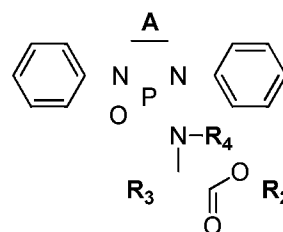
[000110] In certain embodiments, a compound is provided according to Formula XVI, XVII or XXXII:



(XVI)



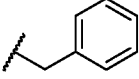
(XVII)

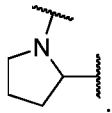


(XXXII);

wherein **R**₂, **R**₃ and **R**₄ are as described in the context of Formula XI and ring **A** is as described in the context of Formula I.

[000111] In certain embodiments, a compound of Formula IX or IXi is provided, wherein: **R**₂ is hydrogen, methyl or benzyl; **R**₃ is hydrogen, -CH₃, -CH(CH₃)₂, -

CH₂CH(CH₃)₂, , or  OH; and **R**₄ is hydrogen; or, in the alternative,

R₃ and **R**₄ combine to form .

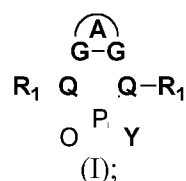
[000112] In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, XII, XIII, or XXX is provided, wherein each **Y** is independently chloro or bromo. In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, XII, XIII, or XXX is provided, wherein each **Y** is chloro. In certain embodiments, a compound of any of Formulas I-VI, Va-Vd, XII, XIII, or XXX is provided, wherein each **Y** is bromo. In certain embodiments, a compound of any of Formulas VII, VIIi, XIV, XV, or XXXI is provided, wherein each **X** is independently chloro or bromo. In certain embodiments, a compound of any of Formulas VII, VIIi, XIV, XV, or XXXI is provided, wherein each **X** is chloro. In certain embodiments, a compound of any of Formulas VII, VIIi, XIV, XV, or XXXI is provided, wherein each **X** is bromo.

[000113] In an embodiment, a compound according to any of Formulas I, VIIi-Xi, VII-X, XII-XVII or XXX-XXXIII is provided wherein ring **A** is a carbocyclic ring. In an embodiment, a compound according to any of Formulas I, VIIi-Xi, VII-X, XII-XVII or XXX-XXXIII is provided wherein ring **A** is a six-membered carbocyclic ring. In an

embodiment, a compound according to any of Formulas I, VIIi-Xi, VII-X, XII-XVII or XXX-XXXIII is provided wherein ring **A** is a cyclohexane ring.

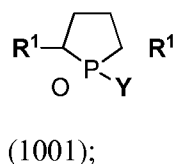
[000114] In some embodiments, provided herein is a process for the preparation of a compound as described herein, *e.g.*, of any of Formula I-XXXIII, Va-Vd, or VIIi-Xi as described in more detail elsewhere herein.

[000115] In certain embodiments, provided herein are compounds according to Formula I:



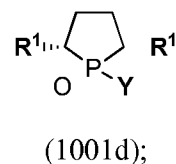
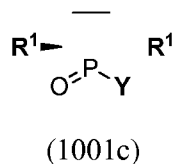
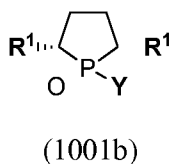
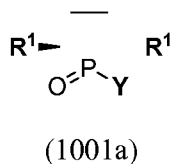
wherein: each **R**₁ is independently hydrogen, alkyl, aryl or arylalkyl; ring **A** is a carbocyclic ring or absent; each **Q** is nitrogen, carbon, or oxygen; each **G** is carbon; or when ring **A** is absent and **Q** is oxygen, then **G** is absent; and **Y** is hydroxyl, halogen, amide, imine, an amino acid sequence or an amino acid, or ester thereof.

[000116] The in certain embodiments, provided herein are compounds according to Formula 1001:



wherein: each **R**¹ is independently aryl or arylalkyl; and **Y** is hydroxyl, halogen, amine, or imine.

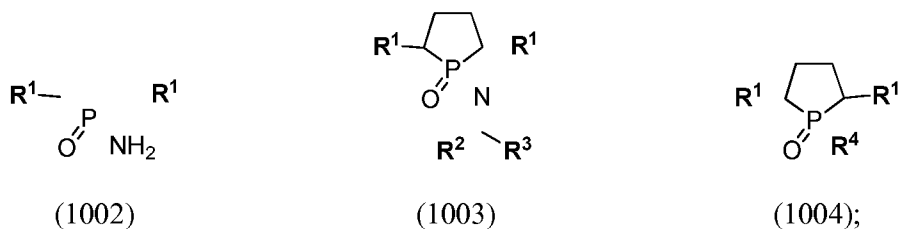
[000117] In certain embodiments, provided herein are compounds according to any of Formulas 1001a, 1001b, 1001c or 1001d:



wherein **R**¹ and **Y** are as described in the context of Formula 1001.

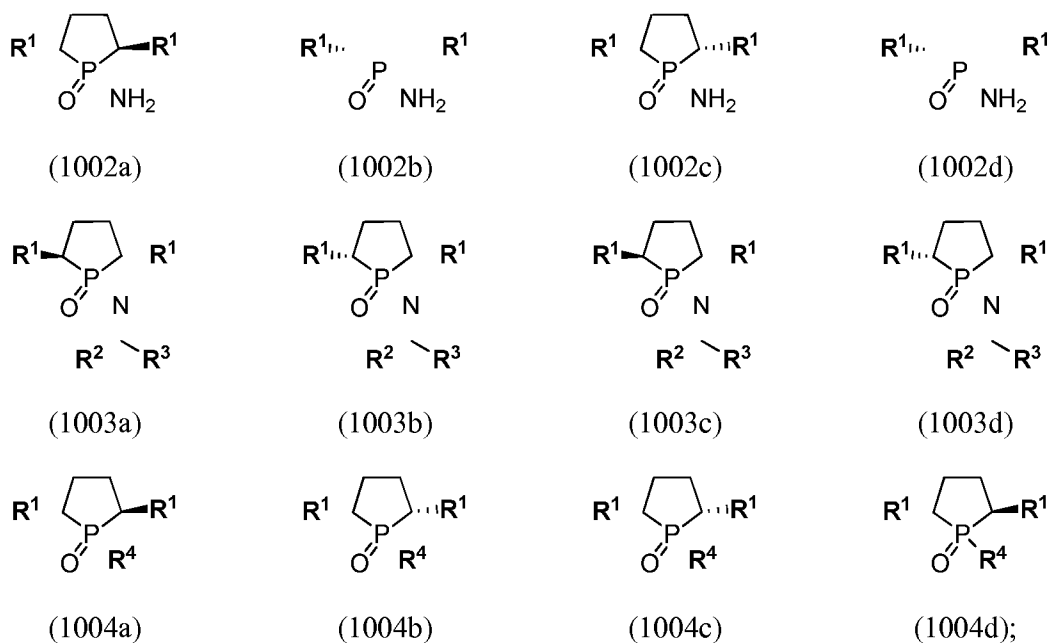
[000118] In certain embodiments, provided herein are compounds according to any of Formulas 1001-1001d, wherein: each **Y** is independently hydroxyl, chloro, bromo, $-\text{NH}_2$ or $-\text{N}=\text{CH}-\text{R}^3$; and **R**³ is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, or C₆-C₁₂ aryl.

[000119] In certain embodiments, provided herein are compounds according to any of Formulas 1002, 1003, or 1004:



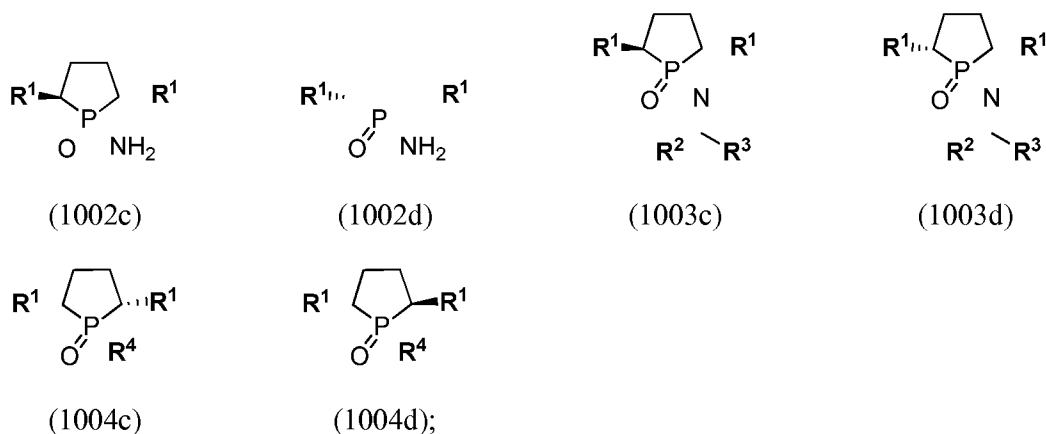
wherein: **R**² is hydrogen or C₁-C₈ alkyl; **R**³ is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, or C₆-C₁₂ aryl; and **R**⁴ is hydroxyl or halogen; where **R**¹ is as described in the context of Formula 1001.

[000120] In certain embodiments, provided herein are compounds according to any of Formulas 1002a-1004d:



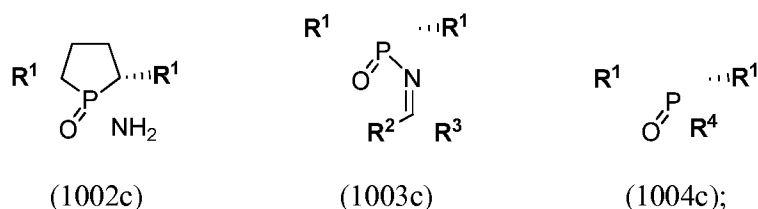
where **R**¹ is as described in the context of Formula 1001 and **R**², **R**³ and **R**⁴ are as described in the context of Formulas 1002-1004.

[000121] In certain embodiments, provided herein are compounds according to any of Formulas 1002c-1004d:



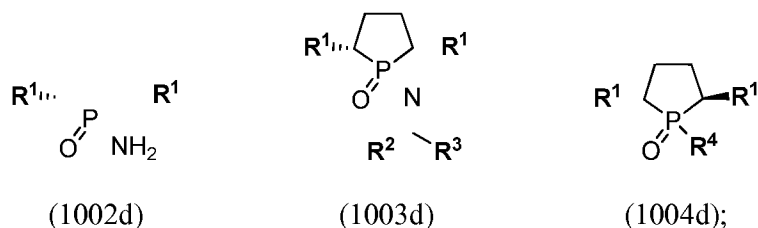
where **R**¹ is as described in the context of Formula 1001 and **R**², **R**³ and **R**⁴ are as described in the context of Formulas 1002-1004.

[000122] In an embodiment, provided herein are compounds according to any of Formulas 1002c-1004c:



where **R**¹ is as described in the context of Formula 1001 and **R**², **R**³ and **R**⁴ are as described in the context of Formulas 1002-1004.

[000123] In certain embodiments, provided herein are compounds according to any of Formulas 1002d-1004d:



where **R**¹ is as described in the context of Formula 1001 and **R**², **R**³ and **R**⁴ are as described in the context of Formulas 1002-1004.

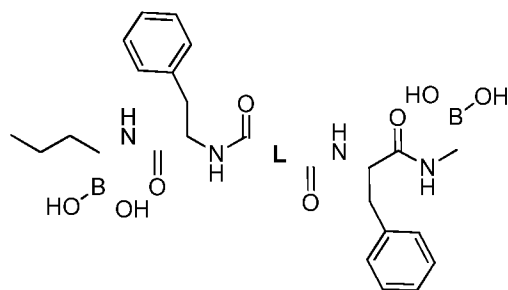
[000124] In certain embodiments provided herein are compounds according to any of Formulas 1001 and 1001-1004d, wherein each **R**¹ is independently phenyl, 1'-naphthyl,

5',6',7',8'-tetrahydronaphthalen-1-yl, 2',4',6'-trimethylphenyl, 4'-biphenyl, or 2',6'-di-tert-butyl-phenyl.

[000125] In certain embodiments provided herein are compounds according to any of Formulas 1004-1004d, wherein R^4 is hydroxyl, chloro, or bromo.

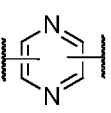
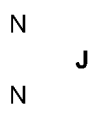
[000126] In certain embodiments provided herein are compounds according to any of Formulas 1003-1003d, wherein each R^3 is independently C_1 - C_8 alkyl. In certain embodiments provided herein are compounds according to any of Formulas 1003-1003d, wherein each R^3 is $-\text{CH}_2\text{CH}(\text{CH}_3)_2$. In certain embodiments provided herein are compounds according to any of Formulas 1003-1003d, wherein R^2 is hydrogen and R^3 is C_1 - C_8 alkyl.

[000127] In certain embodiments, provided herein are compounds according to Formula 1010:

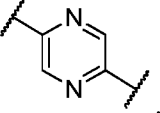
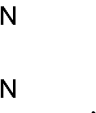
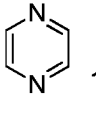
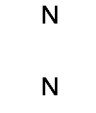
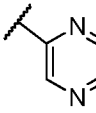
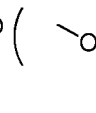
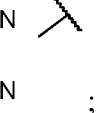


(1010);

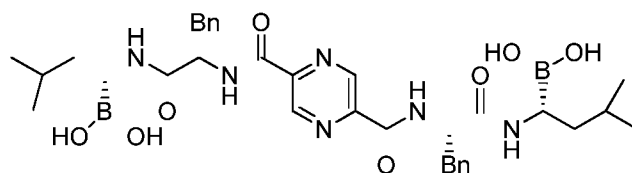
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomeric form, tautomeric form

or polymorphic form thereof; wherein: L is  or ; J is $-(\text{CH}_2)_n$, $-(\text{CH}_2\text{-CHO})_n$, $-(\text{CH}_2\text{-CH-NH})_n$, $-\text{O}-(\text{CH}_2\text{-CHO})_n$, $-\text{NH}-(\text{CH}_2\text{-CH-NH})_n$, $-\text{NH}-(\text{CH}_2\text{-CHO})_n$, $-\text{O}-(\text{CH}_2\text{-CH-NH})_n$ or $-(\text{amino acid residue})_n$; and each n is independently a positive integer.

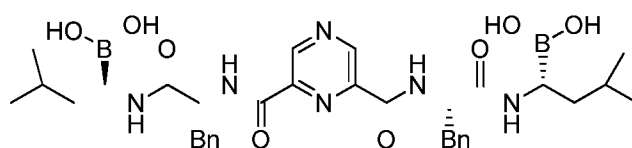
[000128] In certain embodiments provided herein are compounds according to Formula

1010, wherein L is , , , , or   ; where n is as described in the context of Formula 1010.

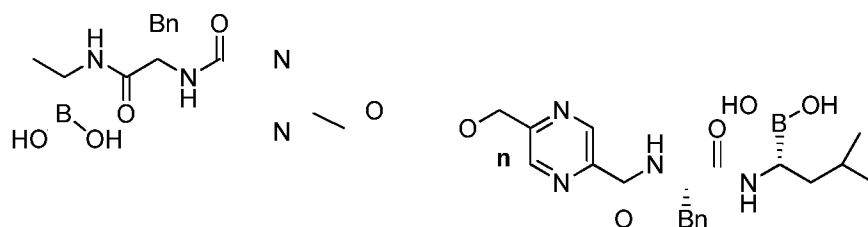
[000129] In certain embodiments provided herein are compounds according of any of Formulas 101-104:



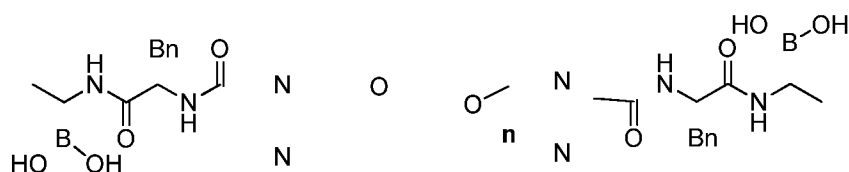
(101)



(102)



(103)



(104);

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomeric form, tautomeric form or polymorphic form thereof; where **n** is as described in the context of Formula 1010.

[000130] In certain embodiments provided herein are compounds according to any of Formulas 1010, 103 or 104, wherein each **n** is independently a positive integer selected from 1 to 10.

[000131] In some embodiments, provided herein is a process for the preparation of a compound as described herein, e.g., of any of Formula I-XXXIII, Va-Vd, VIIi-Xi, 1001-1004d, 1010 or 101-104 as described in more detail elsewhere herein.

Optically Active Compounds

[000132] It is appreciated that compounds provided herein have several chiral centers and are prepared or isolated in optically active forms, for example diastereomerically pure forms. Some compounds may exhibit polymorphism. It is well known in the art how to prepare optically active forms of the diastereomerically pure compounds provided herein, for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase, such as high-performance liquid chromatography.

[000133] Diastereomerically pure compounds of any of Formulas I-XXXIII, Va-Vd, VIIi-Xi, 1001-1004d, 1010 or 101-104 and purified compositions comprising the diastereomerically pure compounds of any of Formulas I-XXXIII, Va-Vd, VIIi-Xi, 1001-1004d, 1010 or 101-104 can be prepared according to techniques known to those of skill in the art. Examples of methods to obtain diastereomerically pure materials are known in the art, and include at least the following:

- a) *physical separation of crystals* - a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct;
- b) *simultaneous crystallization* - a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;
- c) *enzymatic resolutions* - a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;
- d) *enzymatic asymmetric synthesis* - a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;
- e) *chemical asymmetric synthesis* - a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;
- f) *diastereomer separations* - a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then

separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

- g) *first- and second-order asymmetric transformations* - a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;
- h) *kinetic resolutions* - this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;
- i) *enantiospecific synthesis from non-racemic precursors* - a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;
- j) *chiral liquid chromatography* - a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;
- k) *chiral gas chromatography* - a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;
- l) *extraction with chiral solvents* - a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;
- m) *transport across chiral membranes* - a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier.

Separation occurs as a result of the non-racemic chiral nature of the membrane which allows only one enantiomer of the racemate to pass through.

[000134] In some embodiments, provided are compositions of stereoisomerically pure compounds of any of Formulas I-XXXIII, Va-Vd, VIIi-Xi, 1001-1004d, 1010 or 101-104 that are substantially free of a designated stereoisomer of that compound. In certain embodiments, in the methods and compounds of this invention, the compounds are substantially free of other stereoisomers. In some embodiments, a composition includes a compound that is at least 85%, 90%, 95%, 98%, 99% or 100% by weight, of the compound, the remainder comprising other chemical species or stereoisomers.

Isotopically Enriched Compounds

[000135] Also provided herein are isotopically enriched compounds, including but not limited to isotopically enriched compounds of any of Formulas I-XXXIII, Va-Vd, VIIi-Xi, 1001-1004d, 1010 or 101-104.

[000136] Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C-H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). (See, e.g., Foster et al., Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner et al., Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999)).

[000137] The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C-H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon.

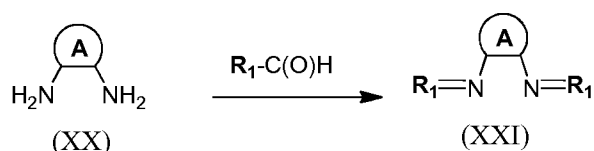
[000138] Tritium (“T”) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T₂O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium (“T”) for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ¹³C or ¹⁴C for carbon, ³³S, ³⁴S, or ³⁶S for sulfur, ¹⁵N for nitrogen, and ¹⁷O or ¹⁸O for oxygen, may lead to a similar kinetic isotope effect.

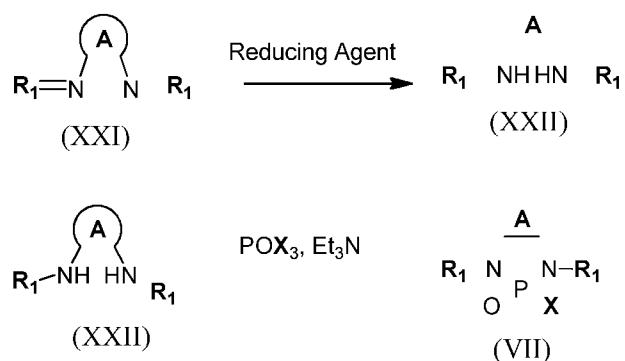
[000139] For example, the DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching. The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations prior to the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity.

Preparation of Compounds

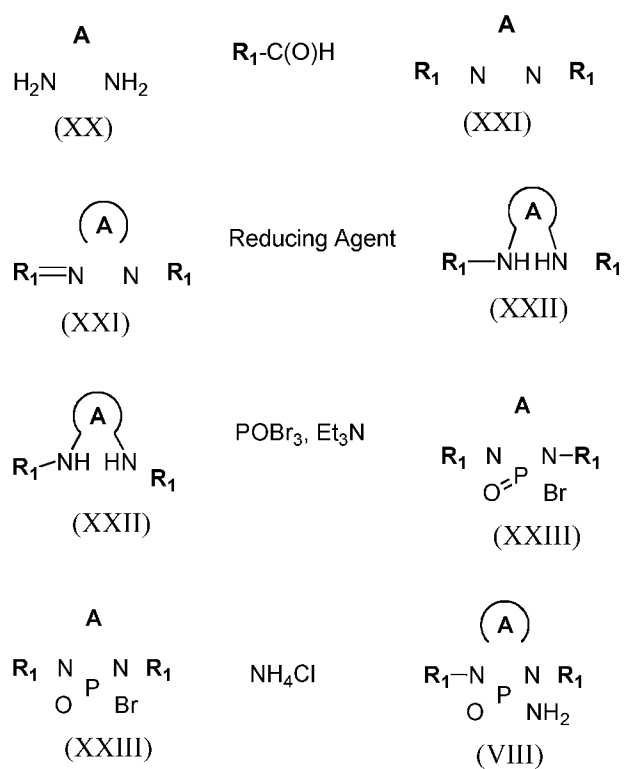
[000140] The compounds provided herein can be prepared, isolated or obtained as described herein. Exemplary methods of preparation are described in detail in the examples below. In certain embodiments, compounds provided herein can be prepared according to Exemplary Preparation Schemes **1a-1d**, as discussed further below.

Exemplary Preparation Scheme 1a

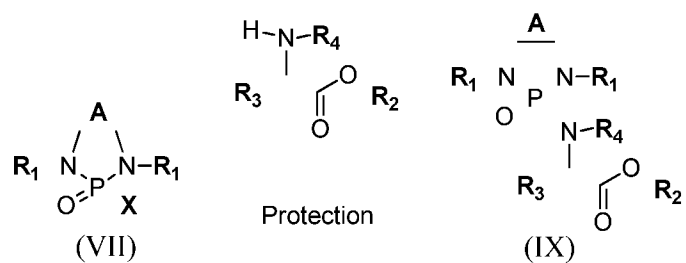


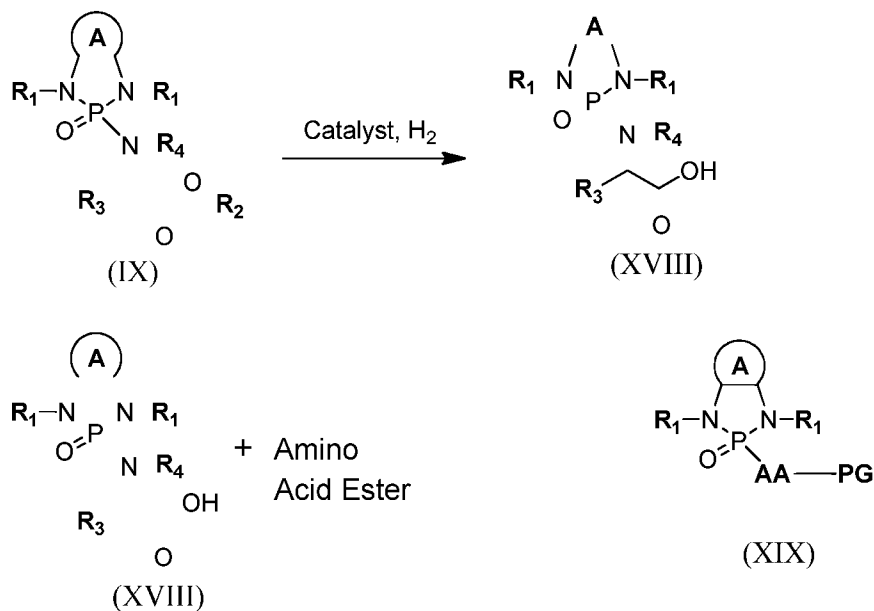


Exemplary Preparation Scheme 1b



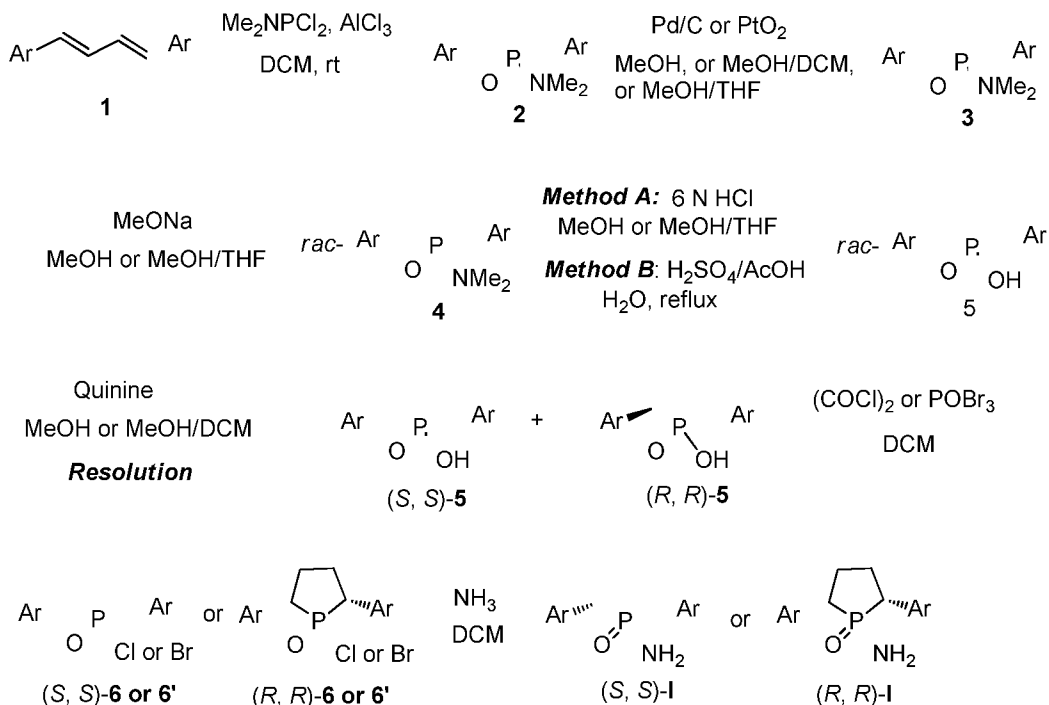
Exemplary Preparation Scheme 1c



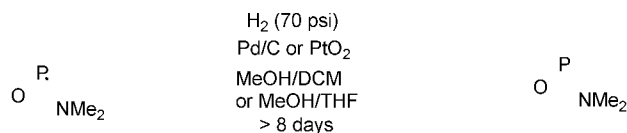
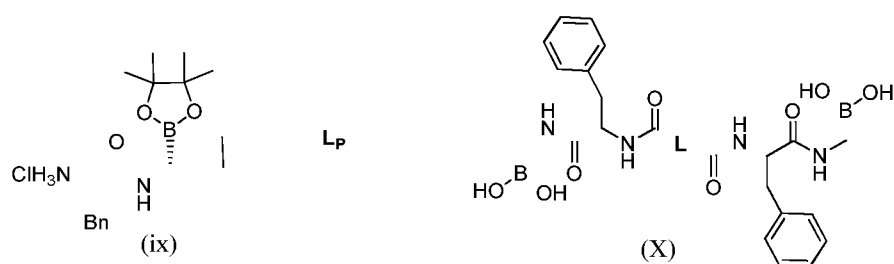
Exemplary Preparation Scheme 1d

[000141] In certain embodiments, one or more protection or deprotection steps may be included in the methods of preparation described in Exemplary Preparation Schemes 1a-1d. In certain embodiments, provided herein is a compound prepared according to the above Exemplary Preparation Schemes **1a-1d**.

[000142] The compounds provided herein can be prepared, isolated or obtained as described herein. Exemplary methods of preparation are described in detail in the examples below. In certain embodiments, compounds provided herein can be prepared according to Exemplary Preparation Schemes **1** and **2**, as discussed further below.

Exemplary Preparation Scheme 1

For (1*S*, 2*R*, 5*S*)-1-(dimethylamino)-2, 5-bis(5,6,7,8-tetrahydronaphthalen-1-yl) phospholane 1-oxide:

**Exemplary Preparation Scheme 2**

[000143] In certain embodiments, one or more protection or deprotection steps may be included in the methods of preparation described in Exemplary Preparation Schemes 1 and 2. In certain embodiments, provided herein is a compound prepared according to the above Exemplary Preparation Schemes 1 or 2.

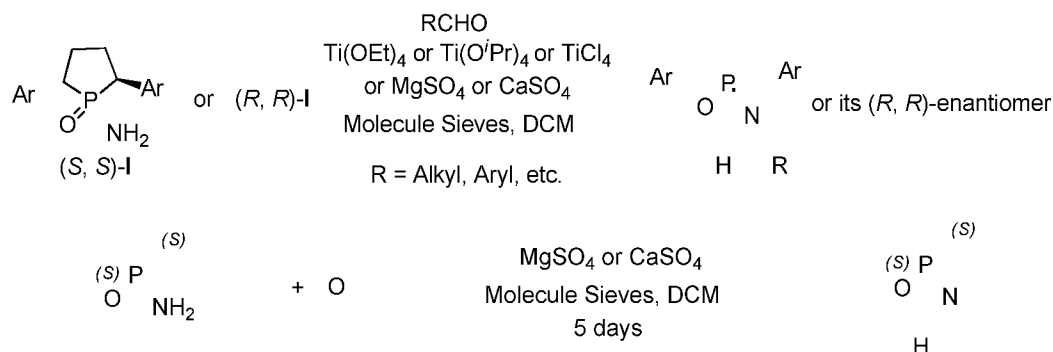
[000144] Provided herein are methods of synthesis of chiral phosphinic amides (Formula 1001) and their enantiomers (Exemplary Preparation Scheme 1). The synthetic

route was according to the literature. See Guillen, *et al. Tetrahedron*, **2002**, 58, 5895–5904 and Pindi, *et al. Chem Biol Drug Des*, **2011**, 77, 20–29.

[000145] The symmetrical (*E,E*)-1,4-diaryl-1,3-butadienes **1** were synthesized according to literature method (Hintermann, *et al. Advanced Synthesis & Catalysis* **2010**, 352, 2411–2415). The cis (1*S*, 2*R*, 5*S*)-2, 5-diaryl-1- (dimethylamino)-2, 5-dihydro-1*H*-phosphole 1-oxide **2** was synthesized from the diene and *N,N*-dimethylaminophosphinodichloridite, in which the two aryl groups and the dimethylamino group are on the same side. For those dienes possessing steric hindrance groups, more reacting time was necessary for complete conversion. To reduce the unsaturated double bond, the following step is the hydrogenation reaction with Pd/C or PtO₂ or other catalyst in methanol or other solvents. For the 1'-naphthyl substituted substrate, PtO₂ was proved as the preferable catalyst and DCM or THF or other solvents should be added to increase solubility. Extended reacting time can cause further reducing on the naphthyl group to produce the (1*S*, 2*R*, 5*S*)-1-(dimethylamino)-2, 5-bis(5, 6, 7, 8-tetrahydronaphthalen-1-yl)phospholane 1-oxide.

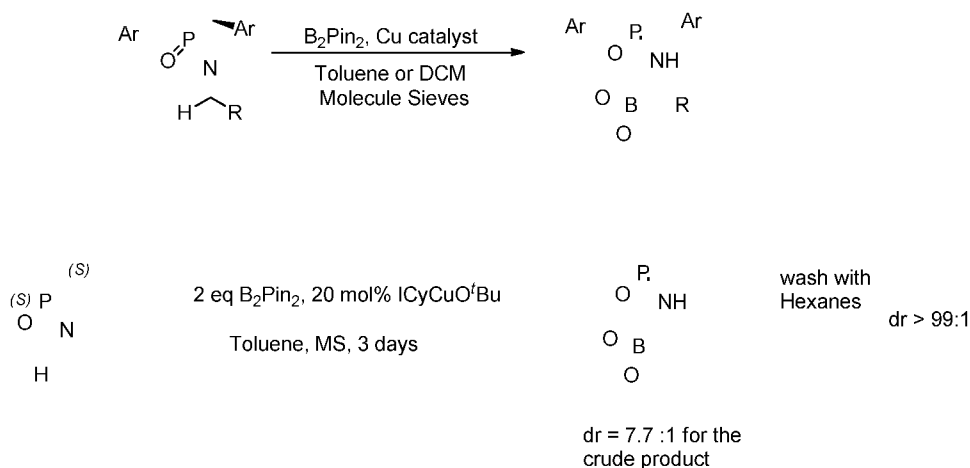
[000146] Sodium methanolate was proved as an efficient racemization reagent in the following step. In some cases, THF was added to increase the solubility or heating was necessary. For the hydrolysis step, 6 N aqueous HCl was usually good enough to give the acid product as a white suspending solid. But for several cases, heating and extended reacting time were necessary. In the resolution step, Quinine was proved as an efficient reagent for almost all the phosphinic acids. The (2*S*, 5*S*)-phosphinic acids can be separated as the precipitates, which were the related Quinine salt. Strong base like sodium was added to extract the acid to aqueous layer as its sodium salt from the Quinine salt DCM solution. After acidification with concentrated HCl, the optically pure acid was precipitated from the water solution. For the (2*R*, 5*R*)-phosphinic acids, similar operations were performed after concentration of the filtrate and re-dissolving in DCM. At least one of recrystallization in methanol was necessary to give the optically pure (2*R*, 5*R*)-phosphinic acids. With the optically pure phosphinic acids in hand, acyl halogenation and amination reactions were conducted successively to give the desired (2*R*, 5*R*)-1-amino-2,5-diaryl-phospholane 1-oxides and their (2*S*, 5*S*)-enantiomers.

Synthesis of phosphinic imines



[000147] With the optically pure 1-amino-2, 5-diaryl-phospholane 1-oxides in hand, aliphatic and the aromatic imines were synthesized. For the aromatic imines, most of the condensing conditions can be used because of the good stability of this kind of imines. On the other hand, only the mildest condition can be suitable for the aliphatic imines especially those possessing an adjacent CH₂ group. When strong condensation reagents were used, the byproducts increased quickly. With MgSO₄ or CaSO₄ for the condensation reagent, the aliphatic imine formed slowly and full conversion can be achieved after 8 or more days. To purify the aliphatic imine should be careful performed under dry conditions, in which all the solvent and the stationary phase must be dried before use. The aliphatic imine was not stable in air or moisture. Thus the storage must be conducted in an extremely dry condition. The best way is to use the aliphatic imine as soon as it is obtained. Purification was not necessary.

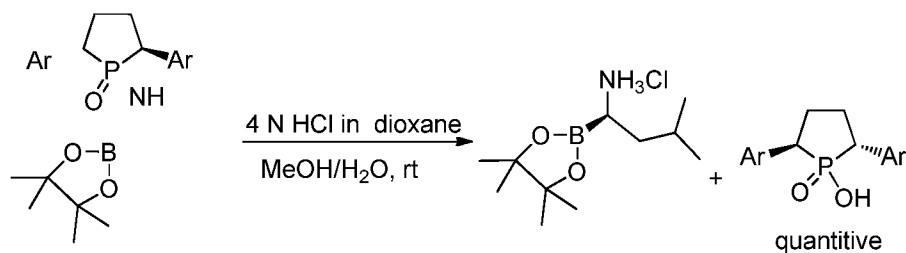
Asymmetric borylation of the phosphinic imines



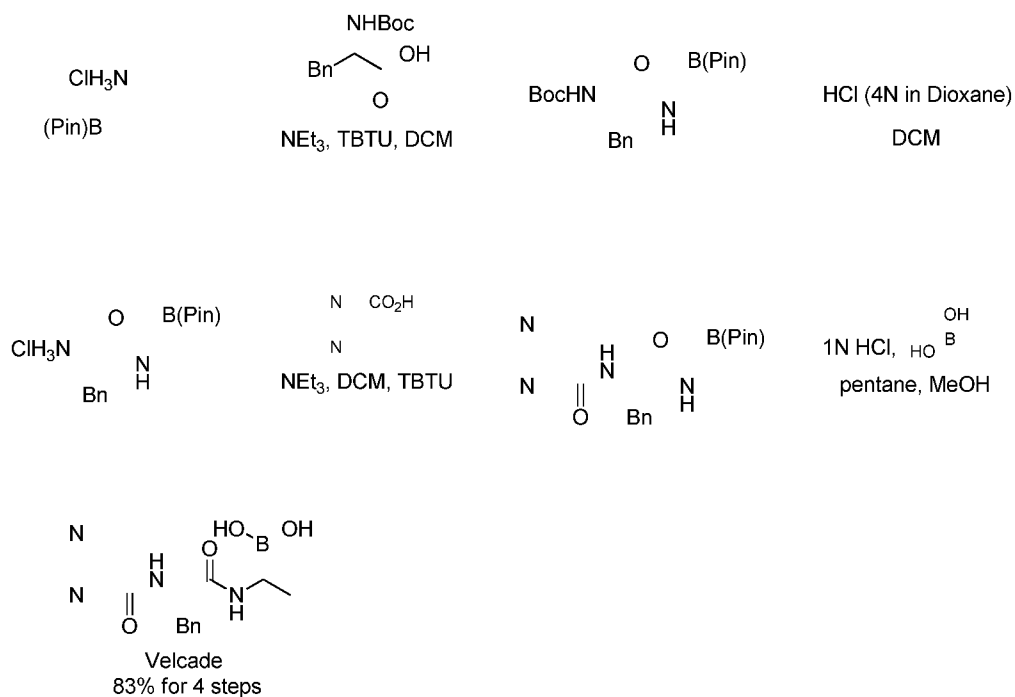
[000148] In the asymmetric borylation step, similar results were obtained with the crude imine and the purified imine. A lot of copper(I) catalyst can be used in the catalytic borylation reactions. The catalyst with NHC ligand, ICyCuO^tBu, had been proved as an

efficient catalyst in this kind of reaction. (Laitar, et al., *J. Am. Chem. Soc.*, **2006**, *128*, 11036–11037; Beenen, et al. *J. Am. Chem. Soc.*, **2008**, *130*, 6910–6911) Here, for the phenyl phosphinic imine with isobutyl group, a good diastereoselectivity was obtained (dr = 7.7:1) with ICyCuO'Bu. The dr value can be easily improved to more than 99% after wash with hexanes. Most of the byproducts and unreacted boron compound can be removed in the meantime. The desired optically pure α -amino boronic ester, the precursor of the key intermediate of Velcade, was obtained in 90-95% purity.

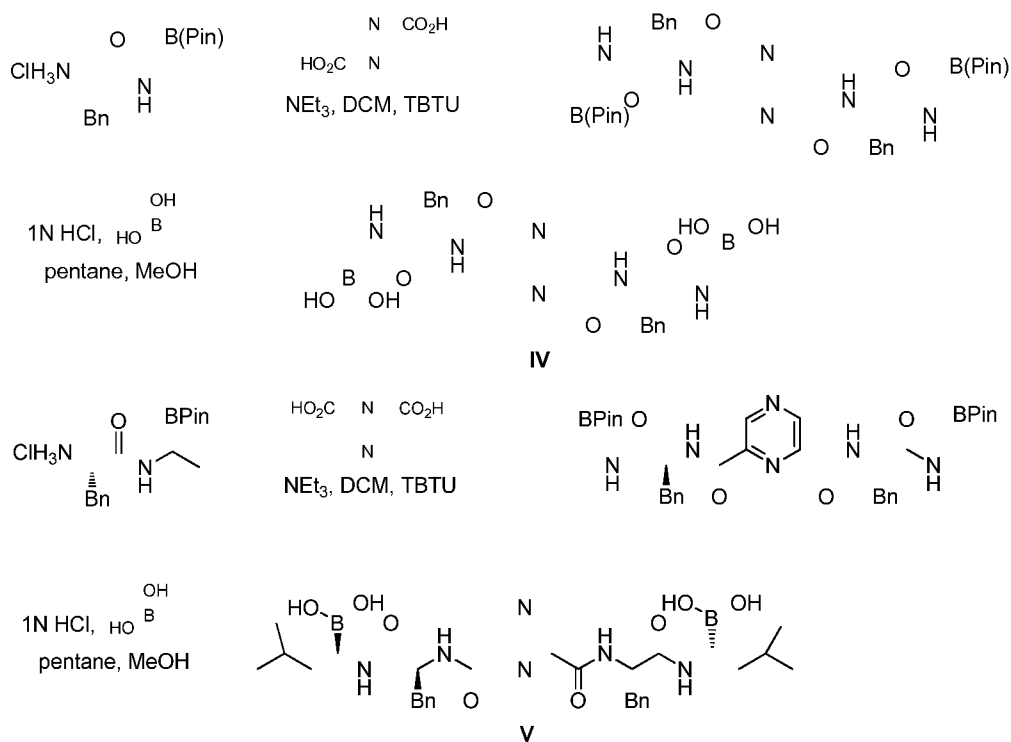
Deprotection of the amide and recycling of the chiral auxiliary

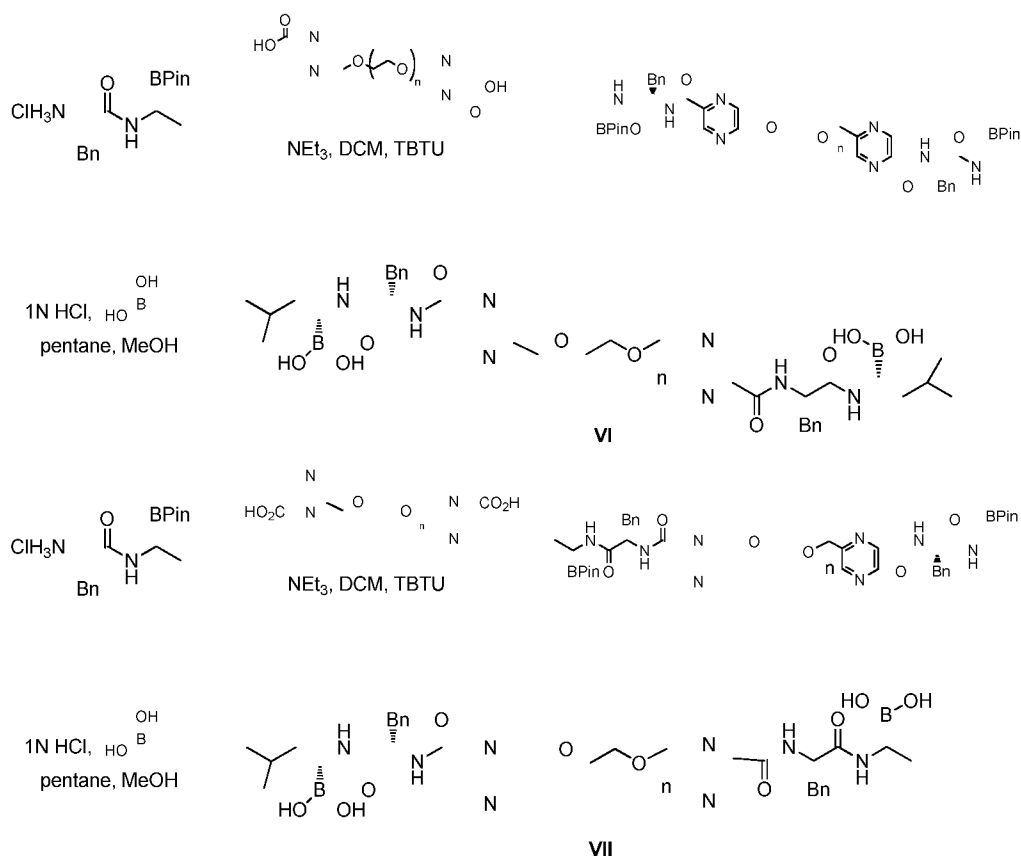


[000149] To deprotect the amino boronic ester, the method of Beenen was used: one equivalent HCl in the mixture of methanol and dioxane. This method produced a complex mixture according to the crude ³¹P and ¹H NMR. Next H₂O and MeOH (2:1) were used as the solvent. With 1.5 equivalents of HCl, the protection reaction was completed after 16 hours. The pure phosphinic acid was recycled by simple filtration in quantitative yield. The amine salt was obtained (92% yield) as a white solid by condensing the filtrate, followed by extracting with DCM from the residue.

Synthesis of Velcade

[000150] Velcade was synthesized according to Ellman in 83% yield after 4 steps. The ¹H NMR and ¹³C NMR were consistent with literature.

Synthesis of the analogs of Velcade

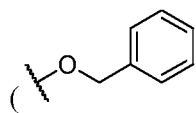


[000151] Also provided herein are new analogs of Velcade and methods of synthesizing the same which were similar as the route to Velcade.

EXAMPLES

[000152] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μL (microliters); mM (millimolar); μM (micromolar); Hz (Hertz); MHz (megahertz); mmol (millimoles); hr or hrs (hours); min (minutes); MS (mass spectrometry or molecular sieve); 4A MS ($4\text{\AA}$ aperture molecular sieve); ESI (electrospray ionization); TLC (thin layer chromatography); HPLC (high pressure liquid chromatography or high performance liquid chromatography); THF (tetrahydrofuran); RT, rt, or r.t. (room temperature); CDCl_3 (deuterated chloroform); AcOH (acetic acid); DCM (dichloromethane);

DMSO (dimethylsulfoxide); DMSO-d₆ (deuterated dimethylsulfoxide); OMe (–OCH₃); OBn



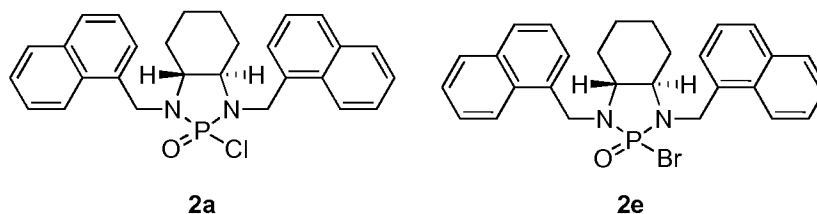
(); EtOAc (ethyl acetate); MeOH (methanol); and BOC (t-butyloxycarbonyl).

[000153] For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted at room temperature unless otherwise noted. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

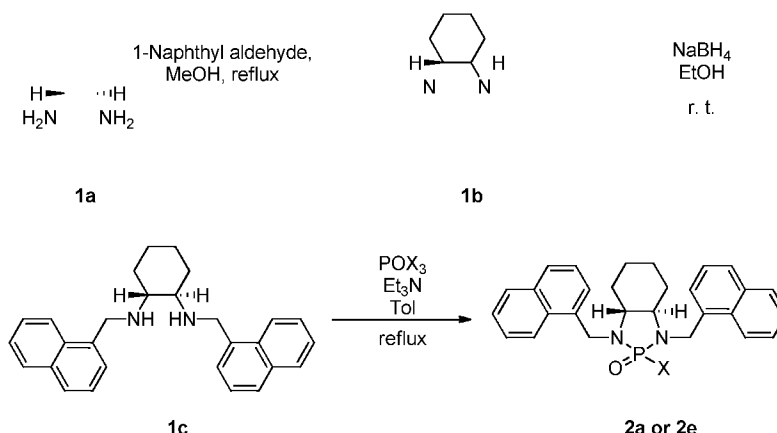
[000154] The Examples below provide methods of synthesis of phosphonyl chlorides and bromides without purification of chromatography or recrystallization, which is named the GAP (group assistant purification) process (scheme 1). The method also affords the protection of amino acid esters with the phosphonyl chlorides with GAP process. The method also provides, using similar synthetic approach, several peptides, such as *N*-protected proline-based peptides which can be synthesized with GAP process (scheme 2). In addition, the synthesis of phosphonyl amides from phosphonyl bromides using GAP process is provided, as the prior phosphonyl chlorides-NaN₃ approach was not safe in the industrial process.

Example 1

Synthesis of (3aR, 7aR)-2-chloro-1,3-bis(naphthalen-1-ylmethyl)octahydro-1H-benzo[d][1,3,2]diazaphosphole 2-oxide (**2a**) and (3aR, 7aR)-2-bromo-1,3-bis(naphthalen-1-ylmethyl)octahydro-1H-benzo[d][1,3,2]diazaphosphole 2-oxide (**2e**)



Scheme 1



[000155] Phosphonyl chlorides and bromides were synthesized starting from cyclohexyl diamine **1a**, as shown in the scheme 1. Diamine **1a** was converted into diimine **1b**, which was then reduced with NaBH_4 to produce diamine **1c**. Diamine **1c** was treated with POCl_3 or POBr_3 in presence of triethyl amine to produce chloride **2a** or bromide **2e**. All the products were purified by simple washing with appropriate solvent.

1. Synthesis of diimine **1b**

[000156] To a cyclohexanediamine MeOH solution (10 g cyclohexanediamine in 200 ml MeOH) in 500 ml single-necked flask, 28 g 1-naphthaldehyde was added with stirring vigorously. (A small amount of excess of aldehyde is necessary because the removal of diamine is difficult during work-up). The reaction solution was heated and refluxed overnight. The reaction mixture was cooled to r.t. and filtered through a clean Büchner funnel and solids in the Büchner funnel was washed with MeOH twice and hexanes three times. 22 g yellowish solid was obtained as the diimine **1b**.

2. Synthesis of diamine **1c**

[000157] To the diimine **1b** EtOH solution (19.5 g diimine in 150 ml absolute EtOH) in 500 ml single-necked flask, 5 g NaBH_4 was slowly added with stirring vigorously at 0°C . The reaction solution is stirred at r.t. for one day. Water was added to the reaction mixture slowly and the mixture was stirred at r.t. for another day. The white solid-liquid mixture was filtered through Celite in a Büchner funnel, and the filtrate cake was washed by EtOH three times. All filtrates were collected and evaporated to nearly only water on a rotavap. DCM was added to the residue and separated in two phases. The organic phase was dried over Na_2SO_4 and evaporated on a rotavap to give 16 g of pale yellow oil as the diamine **1c**.

3. Synthesis of chloride **2a**

[000158] To a diamine **1c** toluene solution (12 g **1c** in 120 ml toluene) in a 500 ml single-necked flask at 0°C, 4 ml POCl₃ followed by 10.1 ml Et₃N were slowly added with stirring vigorously. The reaction solution was stirred at refluxing until the reaction finished. The reaction mixture was filtered through celite in a Büchner funnel and the filtrate cake was washed by toluene three times. All filtrates were collected and evaporated on a rotavap. DCM was added to dissolve the residue and washed with 1 M HCl solution and brine. Solids were dried over Na₂SO₄ and evaporated. The solid obtained was purified by simple washing with a hexanes/DCM solution. 13 g of chloride **2a** was obtained as white solid.

Compound **2a**: $[\alpha]_D^{25} = -53.6^\circ$ (c = 1.0, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): δ = 8.25 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.76 (ddd, *J* = 23.1, 11.9, 5.0 Hz, 4H), 7.55 – 7.40 (m, 6H), 5.10 (dd, *J* = 16.5, 12.1 Hz, 1H), 4.93 (t, *J* = 15.1 Hz, 1H), 4.63 (dd, *J* = 16.7, 11.7 Hz, 1H), 4.24 (dd, *J* = 15.7, 8.8 Hz, 1H), 3.27 (dd, *J* = 14.3, 6.6 Hz, 1H), 3.05 (dd, *J* = 13.7, 7.4 Hz, 1H), 1.72 (d, *J* = 11.8 Hz, 1H), 1.59 (dd, *J* = 22.6, 12.5 Hz, 3H), 1.31– 1.12 (m, 2H), 1.11 – 0.92 (m, 2H). ¹³C NMR (CDCl₃, 101 MHz): δ = 133.75 (d, *J* = 11.8 Hz), 132.82, 132.73, 132.71, 131.38, 130.96, 128.88 (d, *J* = 10.7 Hz), 128.51, 128.07, 126.57, 126.41 (d, *J* = 8.8 Hz), 125.88 (d, *J* = 8.3 Hz), 125.47, 125.25, 123.57, 122.78, 64.91 (d, *J* = 9.2 Hz), 63.39 (d, *J* = 10.1 Hz), 46.65 (d, *J* = 3.1 Hz), 44.75 (d, *J* = 5.0 Hz), 29.34 (d, *J* = 7.1 Hz), 28.85 (d, *J* = 13.3 Hz), 24.26, 23.90. ³¹P NMR (CDCl₃, 162 MHz) ³¹P NMR (CDCl₃, 162 MHz) δ = 35.06.

4. Synthesis of bromide **2e**

[000159] To a diamine **1c** toluene solution (12 g diamine **1c** in 120 ml toluene) in 500 ml single-necked flask at 0°C, 6 g POBr₃ followed by 10.1 ml Et₃N were slowly added with stirring vigorously. The reaction solution was stirred at 0°C until the reaction finished. The reaction mixture was filtered through celite in a Büchner funnel and the filtrate cake was washed by toluene three times. All filtrates were collected and evaporated on a rotavap. DCM was added to dissolve the residue and washed with 1 M HCl solution and brine. Solids were dried over Na₂SO₄ and evaporated. The solid was purified by simple washing with hexanes/DCM solution. 9 g of bromide **2e** was obtained as brownish solid.

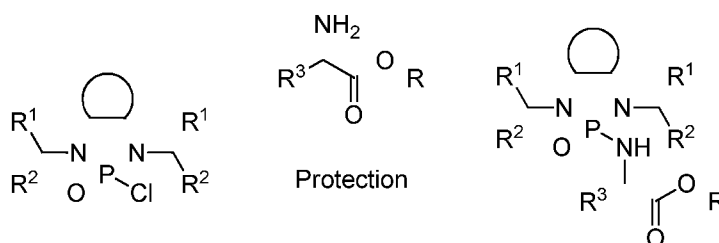
[000160] Compound **2e**: $[\alpha]_D^{25} = -42.6^\circ$ (c = 1.0, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): δ = 8.28 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.3 Hz, 2H),

7.76 (ddd, $J = 23.1, 11.9, 5.0$ Hz, 4H), 7.64 – 7.40 (m, 6H), 5.10 (dd, $J = 16.5, 12.1$ Hz, 1H), 4.93 (t, $J = 15.1$ Hz, 1H), 4.63 (dd, $J = 16.7, 11.7$ Hz, 1H), 4.24 (dd, $J = 15.7, 8.8$ Hz, 1H), 3.27 (dd, $J = 14.3, 6.6$ Hz, 1H), 3.05 (dd, $J = 13.7, 7.4$ Hz, 1H), 1.72 (d, $J = 11.8$ Hz, 1H), 1.59 (dd, $J = 22.6, 12.5$ Hz, 3H), 1.34 – 1.12 (m, 2H), 1.10 – 0.92 (m, 2H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 133.75$ (d, $J = 11.8$ Hz), 132.82, 132.73, 132.71, 131.38, 130.96, 128.88 (d, $J = 10.7$ Hz), 128.51, 128.07, 126.57, 126.41 (d, $J = 8.8$ Hz), 125.88 (d, $J = 8.3$ Hz), 125.47, 125.25, 123.57, 122.78, 64.91 (d, $J = 9.2$ Hz), 63.39 (d, $J = 10.1$ Hz), 46.65 (d, $J = 3.1$ Hz), 44.75 (d, $J = 5.0$ Hz), 29.34 (d, $J = 7.1$ Hz), 28.85 (d, $J = 13.3$ Hz), 24.26, 23.90. ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 25.03$.

Example 2

General procedure for the protection of amino acid esters

Scheme 2



[000161] To a flame dried flask, chloride (**2a**, **2b**, or **2d**, 0.474 g, 1.0 mmol), amino acid ester (1.2-1.5 mmol), triethyl amine (0.42 ml, 3 mmol), 4A MS (0.5 g) and dichloromethane (10 mL) was added in sequence. The reaction flask was sealed and stirred at 90°C until the chloride was consumed. After cooling to room temperature, the reaction mixture was filtered through celite and the filtrate cake was washed by three times. All filtrates were collected and washed with 1 M HCl solution and brine. Solids were dried over Na_2SO_4 and evaporated. The solid obtained was purified by simple washing with Hexane/DCM solution.

[000162] Results are provided in Table 1.

Table 1: GAP Protection of amino acid esters

Entry	Chloride	Amino Acid Ester	Product	Yield (%)
1	2a	Pro-OBn·HCl	3a	96
2	2a	Gly-OMe·HCl	3b	92
3	2a	D-Ala-OMe·HCl	3c	92

Entry	Chloride	Amino Acid Ester	Product	Yield (%)
4	2a	Phe-OMe·HCl	3d	86
5	2d	Gly-OMe·HCl	3e	86
6	2d	Phe-OMe·HCl	3f	82
7	2b	Gly-OMe·HCl	3g	98
8	2b	Gly-OBn·HCl	3h	95
9	2b	Phe-OMe·HCl	3i	92
10	2b	Pro-OBn·HCl	3j	98
11	2b	D-Ala-OMe·HCl	3k	96
12	2b	Val-OBn·HCl	3l	90
13	2b	Tyr-OBn·HCl	3m	90
14	2b	Leu-OBn·HCl	3n	88

[000163] Compound **3a**: $[\alpha]_D^{25} = -132.9^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.30 - 8.16$ (m, 2H), 7.93 – 7.79 (m, 5H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.60 – 7.41 (m, 6H), 7.13 – 6.97 (m, 5H), 5.36 – 5.16 (m, 2H), 4.82 (dd, $J = 30.5, 12.4$ Hz, 2H), 4.52 (ddd, $J = 20.1, 18.7, 10.1$ Hz, 2H), 4.16 (dd, $J = 16.7, 7.0$ Hz, 1H), 3.23 (dt, $J = 7.6, 3.6$ Hz, 1H), 3.19 – 3.08 (m, 1H), 3.00 (dd, $J = 14.9, 5.9$ Hz, 1H), 2.91 – 2.68 (m, 2H), 2.40 (d, $J = 11.9$ Hz, 1H), 1.87 (d, $J = 13.0$ Hz, 2H), 1.69 – 1.47 (m, 3H), 1.44 – 1.17 (m, 4H), 1.03 (dd, $J = 11.6, 8.8$ Hz, 1H), 0.69 – 0.40 (m, 2H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 174.47, 136.32$ (d, $J = 5.4$ Hz), 135.79, 133.72, 133.46 (d, $J = 10.6$ Hz), 132.15, 131.04, 128.98, 128.49 (d, $J = 3.0$ Hz), 128.14 (d, $J = 12.0$ Hz), 127.83, 127.62, 127.00, 125.66, 125.64, 125.61, 125.55, 125.43, 125.22, 124.13, 123.35, 66.17, 65.62 (d, $J = 10.5$ Hz), 63.43 (d, $J = 8.1$ Hz), 60.06 (d, $J = 6.4$ Hz), 46.07, 44.77 (d, $J = 4.7$ Hz), 44.43 (d, $J = 4.7$ Hz), 30.35 (d, $J = 8.5$ Hz), 29.85 (d, $J = 7.4$ Hz), 28.95 (d, $J = 10.3$ Hz), 24.35, 24.22 (d, $J = 8.2$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 27.10$.

[000164] Compound **3b**: $[\alpha]_D^{25} = -82.8^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.14$ (dd, $J = 8.3, 2.3$ Hz, 2H), 7.87 – 7.70 (m, 6H), 7.56 – 7.41 (m, 6H), 4.80 (dd, $J = 16.6, 11.2$ Hz, 1H), 4.68 (dd, $J = 14.5, 9.4$ Hz, 1H), 4.58 – 4.47 (m, 1H), 4.33 (dd, $J = 16.6, 8.6$ Hz, 1H), 3.45 (s, 3H), 3.24 (ddd, $J = 17.8, 9.3, 6.3$ Hz, 1H), 3.17 – 2.93 (m, 3H),

2.62 (dd, $J = 5.7, 3.9$ Hz, 1H), 2.02 (d, $J = 11.7$ Hz, 1H), 1.71 (d, $J = 11.4$ Hz, 1H), 1.59 (t, $J = 12.5$ Hz, 2H), 1.38 – 1.06 (m, 4H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 171.20$ (d, $J = 8.7$ Hz), 135.22 (d, $J = 4.7$ Hz), 133.76, 133.67, 133.63, 131.62, 131.04, 128.78, 128.07, 127.56, 127.26, 126.07 (d, $J = 1.8$ Hz), 125.58 (dd, $J = 7.6, 4.1$ Hz), 125.41, 123.48, 123.05, 65.26 (d, $J = 10.1$ Hz), 63.71 (d, $J = 8.8$ Hz), 53.60, 52.04, 45.39 (d, $J = 2.0$ Hz), 44.51 (d, $J = 4.5$ Hz), 42.61 (d, $J = 1.7$ Hz), 29.93 (d, $J = 8.3$ Hz), 29.37 (d, $J = 10.6$ Hz), 24.36 (d, $J = 9.9$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 27.59$.

[000165] Compound **3c**: $[\alpha]_D^{25} = -67.2^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.17 - 8.07$ (m, 2H), 7.89 – 7.71 (m, 6H), 7.57 – 7.43 (m, 6H), 4.82 – 4.68 (m, 2H), 4.51 (t, $J = 15.0$ Hz, 1H), 4.26 (dd, $J = 16.8, 8.4$ Hz, 1H), 3.69 – 3.53 (m, 4H), 3.16 – 2.96 (m, 2H), 2.79 (t, $J = 9.7$ Hz, 1H), 1.94 (dd, $J = 11.5, 9.1$ Hz, 1H), 1.68 (s, 1H), 1.56 (d, $J = 10.0$ Hz, 2H), 1.36 (s, 1H), 1.20 (dd, $J = 4.9, 3.2$ Hz, 2H), 1.14 – 0.95 (m, 1H), 0.82 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 174.81$ (d, $J = 5.3$ Hz), 135.38 (d, $J = 5.0$ Hz), 134.03 (d, $J = 3.9$ Hz), 133.69 (d, $J = 12.8$ Hz), 131.67, 130.97, 128.82 (d, $J = 9.1$ Hz), 127.89, 127.48, 126.72, 126.16 (d, $J = 13.9$ Hz), 125.61 (dd, $J = 15.6, 9.5$ Hz, 9H), 125.27, 123.38, 122.82, 64.80 (d, $J = 10.2$ Hz), 64.08 (d, $J = 8.7$ Hz), 52.21, 49.90, 45.26 (d, $J = 2.2$ Hz), 44.42 (d, $J = 4.8$ Hz), 29.98 (d, $J = 8.3$ Hz), 29.56 (d, $J = 10.4$ Hz), 24.38 (d, $J = 11.4$ Hz), 21.07 (d, $J = 4.8$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 27.10$.

[000166] Compound **3d**: $[\alpha]_D^{25} = -13.5^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.11$ (dd, $J = 13.7, 8.4$ Hz, 2H), 7.92 – 7.71 (m, 6H), 7.61 – 7.43 (m, 6H), 7.09 – 6.99 (m, 3H), 6.81 (dd, $J = 7.4, 1.8$ Hz, 2H), 4.74 (td, $J = 15.9, 11.7$ Hz, 2H), 4.43 (dd, $J = 16.4, 9.7$ Hz, 1H), 4.35 – 4.15 (m, 2H), 3.35 (s, 3H), 3.05 (dt, $J = 9.4, 4.9$ Hz, 2H), 2.89 (t, $J = 10.3$ Hz, 1H), 2.79 (dd, $J = 13.5, 6.3$ Hz, 1H), 2.59 (dd, $J = 13.5, 5.4$ Hz, 1H), 1.69 (d, $J = 11.4$ Hz, 1H), 1.63 – 1.48 (m, 3H), 1.34 – 0.96 (m, 4H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 173.97$ (d, $J = 3.4$ Hz), 136.10, 135.48 (d, $J = 5.5$ Hz), 134.46 (d, $J = 5.6$ Hz), 133.68 (d, $J = 10.4$ Hz), 131.36, 131.04, 129.47, 128.86 (d, $J = 15.8$ Hz), 128.43, 127.55 (d, $J = 17.7$ Hz), 126.92, 126.07 (d, $J = 19.5$ Hz), 125.73, 125.60 (d, $J = 3.9$ Hz), 125.41 (d, $J = 6.9$ Hz), 125.29, 123.15 (d, $J = 16.1$ Hz), 64.71 (d, $J = 9.9$ Hz), 64.42 (d, $J = 9.1$ Hz), 55.76, 51.95, 44.74 (dd, $J = 18.6, 3.8$ Hz), 40.98 (d, $J = 5.1$ Hz), 29.90 (dd, $J = 9.3, 6.4$ Hz), 24.36 (d, $J = 12.8$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 27.40$.

[000167] Compound **3e**: ^1H NMR (CDCl_3 , 400 MHz): $\delta = 3.66 - 3.47$ (m, 3H), 3.48 – 3.23 (m, 4H), 3.04 – 2.77 (m, 5H), 1.09 – 0.78 (m, 12H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta =$

172.05, 51.92, 43.84, 43.31, 38.42 (d, $J = 13.6$ Hz, 2H), 20.97. ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 21.55$.

[000168] Compound **3f**: $[\alpha]_D^{25} = -4.3^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.21$ (ddt, $J = 8.8, 6.4, 4.4$ Hz, 3H), 7.11 (d, $J = 6.1$ Hz, 2H), 4.00 – 3.85 (m, 1H), 3.69 – 3.53 (m, 3H), 3.44 – 3.24 (m, 2H), 3.15 – 2.77 (m, 7H), 1.22 – 0.88 (m, 12H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 174.10$ (d, $J = 2.7$ Hz), 136.32, 129.47, 128.55, 127.04, 56.02, 51.85, 43.83 (dd, $J = 9.5, 5.3$ Hz), 41.37 (d, $J = 6.3$ Hz), 38.09 (dd, $J = 21.8, 13.9$ Hz), 21.29 (dd, $J = 12.6, 6.1$ Hz), 21.01 (d, $J = 27.9$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 21.30$.

[000169] Compound **3g**: ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.23$ (d, $J = 8.3$ Hz, 2H), 7.84 (d, $J = 7.7$ Hz, 2H), 7.77 (d, $J = 8.1$ Hz, 2H), 7.56 – 7.38 (m, 8H), 4.65 – 4.51 (m, 4H), 3.65 – 3.52 (m, 5H), 3.39 – 3.29 (m, 1H), 3.06 – 2.92 (m, 4H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 171.79$ (d, $J = 7.6$ Hz), 133.91, 133.02 (d, $J = 7.2$ Hz), 131.79, 128.73, 128.41, 126.46 (d, $J = 11.5$ Hz), 125.92, 125.36, 123.62, 52.26, 46.81 (d, $J = 5.1$ Hz), 44.76 (d, $J = 12.4$ Hz), 43.16. ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 24.90$.

[000170] Compound **3h**: ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.25$ (d, $J = 8.2$ Hz, 2H), 7.79 (dt, $J = 24.3, 12.1$ Hz, 4H), 7.68 – 7.18 (m, 13H), 5.08 (s, 2H), 4.58 (d, $J = 6.1$ Hz, 4H), 3.63 (dd, $J = 9.8, 6.2$ Hz, 2H), 3.51 (dt, $J = 11.8, 6.1$ Hz, 1H), 2.95 (dd, $J = 9.2, 4.8$ Hz, 4H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 171.19$ (d, $J = 8.0$ Hz), 135.32, 133.94, 133.09 (d, $J = 7.2$ Hz), 131.83, 128.75 (d, $J = 1.9$ Hz), 128.65, 128.59, 128.43, 126.50 (d, $J = 15.0$ Hz), 125.95, 125.39, 123.68, 67.16, 46.84 (d, $J = 5.1$ Hz), 44.76 (d, $J = 12.3$ Hz), 43.38. ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 24.82$.

[000171] Compound **3i**: $[\alpha]_D^{25} = 5.1^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.26$ (d, $J = 8.4$ Hz, 1H), 8.13 (d, $J = 8.3$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 2H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.54 (ddd, $J = 16.7, 9.9, 5.6$ Hz, 5H), 7.46 – 7.40 (m, 3H), 7.22 – 7.07 (m, 5H), 4.57 – 4.44 (m, 2H), 4.38 – 4.19 (m, 3H), 3.52 (s, 3H), 3.21 – 3.08 (m, 1H), 3.07 – 2.87 (m, 6H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 174.26$ (d, $J = 2.4$ Hz, 1H), 136.48, 133.84 (d, $J = 5.3$ Hz), 133.10 (dd, $J = 10.0, 7.5$ Hz), 131.76 (d, $J = 17.0$ Hz), 129.57, 128.72 (d, $J = 4.1$ Hz), 128.66, 128.30, 128.04, 127.14, 126.38 (d, $J = 2.7$ Hz), 126.24, 125.92 (d, $J = 2.0$ Hz), 125.41 (d, $J = 1.8$ Hz), 125.16, 123.82, 123.45, 56.25, 52.21, 46.27 (dd, $J = 17.5, 5.1$ Hz), 44.53 (dd, $J = 12.2, 3.4$ Hz), 41.02 (d, $J = 6.7$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 24.21$.

[000172] Compound **3j**: $[\alpha]_D^{25} = -71.9^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.49$ (d, $J = 8.1$ Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 8.03 – 7.70 (m, 4H), 7.48 (dd, $J = 37.9$, 21.8 Hz, 8H), 7.25 (dd, $J = 28.0$, 6.7 Hz, 5H), 5.26 – 4.99 (m, 2H), 4.89 (dt, $J = 17.4$, 8.7 Hz, 1H), 4.61 – 4.31 (m, 3H), 4.12 (d, $J = 6.8$ Hz, 1H), 3.25 – 2.67 (m, 6H), 1.78 (s, 2H), 1.32 (s, 2H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 175.02$, 136.05, 133.96 (t, $J = 8.0$ Hz), 133.42 (d, $J = 5.6$ Hz), 132.12 (d, $J = 12.9$ Hz), 128.78, 128.58, 128.50, 128.22 (d, $J = 8.5$ Hz), 127.34, 126.97, 126.27, 125.95 (d, $J = 6.7$ Hz), 125.46 (d, $J = 21.5$ Hz), 124.59, 124.00, 66.67, 64.57, 60.71 (d, $J = 5.9$ Hz), 47.76, 46.94 (d, $J = 5.4$ Hz), 45.81 (d, $J = 12.7$ Hz), 44.73 (d, $J = 12.4$ Hz), 31.05 (d, $J = 9.4$ Hz), 25.11 (d, $J = 9.5$ Hz), 22.86. ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 22.96$.

[000173] Compound **3k**: $[\alpha]_D^{25} = -30.1^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.24$ (dd, $J = 23.0$, 8.4 Hz, 2H), 7.85 (d, $J = 8.1$ Hz, 2H), 7.78 (dd, $J = 8.0$, 3.5 Hz, 2H), 7.60 – 7.48 (m, 5H), 7.47 – 7.38 (m, 3H), 7.31 (dddd, $J = 7.9$, 5.2, 4.8, 0.9 Hz, 4H), 7.25 – 7.21 (m, 1H), 5.07 (d, $J = 13.1$ Hz, 3H), 4.65 – 4.50 (m, 3H), 4.41 (dd, $J = 15.1$, 6.3 Hz, 1H), 4.06 (td, $J = 9.6$, 7.2 Hz, 1H), 3.32 (t, $J = 10.1$ Hz, 1H), 3.07 – 2.87 (m, 4H), 1.36 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 174.60$ (d, $J = 4.3$ Hz), 135.44, 133.87 (d, $J = 2.7$ Hz), 133.05 (t, $J = 7.5$ Hz), 131.82 (d, $J = 4.6$ Hz), 128.70 (d, $J = 2.6$ Hz), 128.49, 128.29 (t, $J = 5.3$ Hz), 126.41 (d, $J = 2.3$ Hz), 126.31, 126.00, 125.95, 125.90, 125.39, 123.66 (d, $J = 12.9$ Hz), 67.10, 50.45, 46.88 (d, $J = 3.8$ Hz), 46.51 (d, $J = 5.1$ Hz), 44.60 (dd, $J = 30.9$, 12.1 Hz), 21.69 (d, $J = 5.5$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 23.99$.

[000174] Compound **3l**: $[\alpha]_D^{25} = -11.9^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.24$ (dd, $J = 29.7$, 8.3 Hz, 2H), 7.86 (d, $J = 7.8$ Hz, 2H), 7.78 (dd, $J = 8.0$, 3.0 Hz, 2H), 7.61 – 7.39 (m, 8H), 7.30 – 7.16 (m, 5H), 4.99 (q, $J = 12.2$ Hz, 2H), 4.64 (ddd, $J = 27.1$, 15.3, 5.6 Hz, 2H), 4.53 – 4.41 (m, 2H), 4.00 – 3.90 (m, 1H), 3.18 (dd, $J = 13.5$, 6.2 Hz, 1H), 3.09 – 2.87 (m, 4H), 2.06 (dd, $J = 12.7$, 6.3 Hz, 1H), 0.93 (dd, $J = 26.8$, 6.8 Hz, 6H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 173.89$ (d, $J = 2.1$ Hz), 135.39, 133.84 (d, $J = 2.6$ Hz), 133.00 (dd, $J = 7.6$, 6.3 Hz), 131.79 (d, $J = 10.2$ Hz), 128.70 (d, $J = 5.0$ Hz), 128.63, 128.50, 128.47, 128.20 (d, $J = 13.6$ Hz), 126.41 (d, $J = 5.8$ Hz), 126.13, 125.90 (d, $J = 2.1$ Hz), 125.58, 125.36 (d, $J = 6.8$ Hz), 123.72, 123.51, 66.99, 60.17, 46.62 (dd, $J = 20.2$, 5.2 Hz), 44.49 (dd, $J = 11.5$, 7.4 Hz), 32.68 (d, $J = 6.4$ Hz), 19.02, 17.97. ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 25.05$.

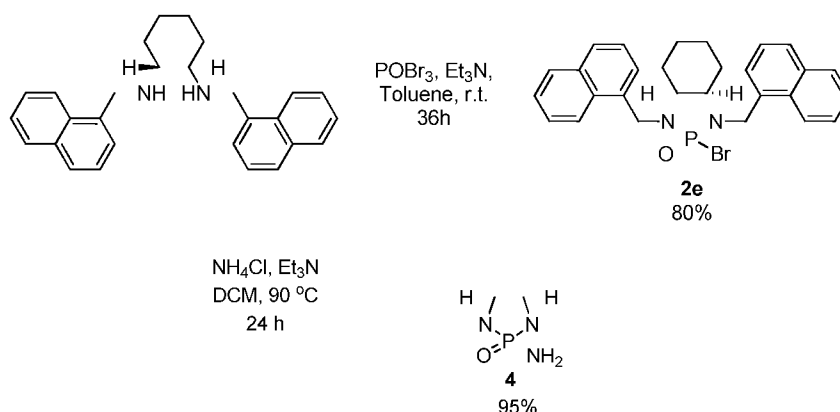
[000175] Compound **3m**: $[\alpha]_D^{25} = -71.9^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.93$ (s, 1H), 8.20 – 8.12 (m, 1H), 8.10 – 8.01 (m, 1H), 7.93 – 7.67 (m, 4H), 7.63 – 7.32 (m, 8H), 7.32 – 7.09 (m, 5H), 6.74 (d, $J = 8.5$ Hz, 4H), 4.99 – 4.85 (m, 2H), 4.49 (dd, $J = 12.1, 3.3$ Hz, 2H), 4.36 – 4.10 (m, 3H), 3.19 (t, $J = 10.2$ Hz, 1H), 3.07 – 2.72 (m, 7H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 173.72, 156.75, 135.19, 133.82$ (d, $J = 2.1$ Hz), 132.78 (d, $J = 7.4$ Hz), 131.72 (d, $J = 8.5$ Hz), 130.53, 128.72, 128.64 (d, $J = 6.3$ Hz), 128.54, 128.23 (d, $J = 19.5$ Hz), 126.58, 126.41 (d, $J = 8.3$ Hz), 126.04 (d, $J = 17.4$ Hz), 125.41, 123.70, 123.48, 115.86, 67.23, 56.26, 46.15 (d, $J = 18.6$ Hz), 44.50 (dd, $J = 28.6, 15.1$ Hz), 40.03. ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 24.47$.

[000176] Compound **3n**: $[\alpha]_D^{25} = -32.9^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.28$ (dd, $J = 19.9, 8.4$ Hz, 2H), 7.94 – 7.78 (m, 4H), 7.66 – 7.41 (m, 9H), 7.28 – 7.22 (m, 4H), 5.12 – 5.00 (m, 2H), 4.76 – 4.39 (m, 4H), 4.16 – 3.99 (m, 1H), 3.16 – 2.90 (m, 5H), 1.79 – 1.40 (m, 3H), 0.89 (dd, $J = 9.6, 6.4$ Hz, 6H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 174.78$ (d, $J = 2.5$ Hz), 135.39, 133.85 (d, $J = 4.2$ Hz), 133.05 (t, $J = 7.4$ Hz), 131.81 (d, $J = 10.1$ Hz), 128.44 (dt, $J = 19.6, 8.7$ Hz), 126.41 (d, $J = 8.0$ Hz), 126.24, 125.90 (d, $J = 2.2$ Hz), 125.82, 125.36 (d, $J = 1.3$ Hz), 123.63 (d, $J = 18.3$ Hz), 66.99, 53.56, 46.68 (d, $J = 5.1$ Hz), 46.41 (d, $J = 5.2$ Hz), 44.72, 44.60, 44.47, 44.38, 44.35, 44.31, 24.82, 22.51 (d, $J = 11.2$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 24.33$.

Example 3

General procedure for phosphonyl amide synthesis

Scheme 3



[000177] To a flame dried flask, bromide **2e** (0.519 g, 1.0 mmol), ammonium chloride (2 mmol), triethyl amine (0.42 ml, 3 mmol), 4A MS (0.5 g) and dichloromethane (10 mL) was added in sequence. The reaction flask was sealed and stirred at 90°C until the bromide

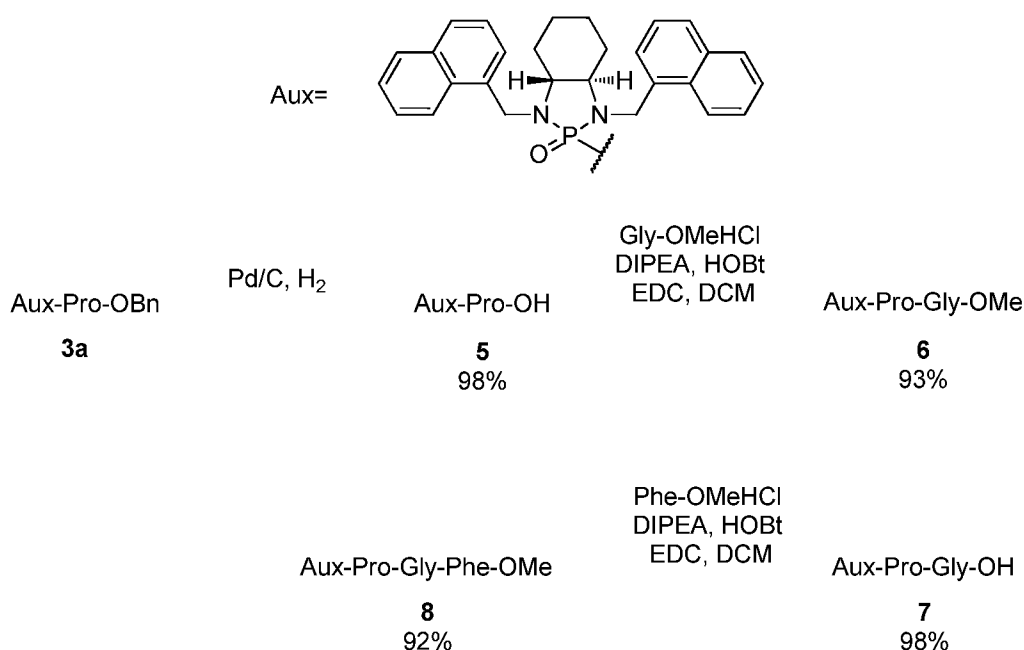
was consumed. After cooling to room temperature, the reaction mixture was filtered through celite and the filtrate cake was washed by dichloromethane three times. All filtrates were collected and washed with 1 M HCl solution and brine. Solids were dried over Na₂SO₄ and evaporated. The solid was purified by simple washing with hexanes/DCM solution.

[000178] Compound 4: $[\alpha]_D^{25} = -78.9^\circ$ ($c = 1.0$, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): $\delta = 8.16$ (dd, $J = 15.1, 8.2$ Hz, 2H), 7.85 (t, $J = 7.8$ Hz, 2H), 7.75 (dd, $J = 12.6, 6.4$ Hz, 4H), 7.57 – 7.40 (m, 6H), 4.86 (ddd, $J = 17.2, 11.1, 6.1$ Hz, 2H), 4.55 – 4.43 (m, 1H), 4.35 (dd, $J = 16.5, 8.0$ Hz, 1H), 3.08 (dd, $J = 12.9, 6.4$ Hz, 1H), 2.95 (t, $J = 9.9$ Hz, 1H), 2.31 (d, $J = 3.9$ Hz, 2H), 1.84 (d, $J = 8.1$ Hz, 1H), 1.70 – 1.50 (m, 3H), 1.15 (ddd, $J = 49.0, 21.0, 12.3$ Hz, 5H). ¹³C NMR (CDCl₃, 101 MHz): $\delta = 135.08$ (d, $J = 5.3$ Hz), 134.56 (d, $J = 4.9$ Hz), 133.68 (d, $J = 3.0$ Hz), 131.46, 131.18, 128.80 (d, $J = 7.7$ Hz), 127.83, 127.60, 126.08 (d, $J = 3.5$ Hz), 125.63 (d, $J = 7.5$ Hz), 125.46 (d, $J = 2.4$ Hz), 125.40, 123.23 (d, $J = 9.4$ Hz), 100.00, 64.68 (d, $J = 9.8$ Hz), 63.96 (d, $J = 8.9$ Hz), 45.15 (dd, $J = 11.5, 3.5$ Hz), 29.63 (dd, $J = 9.8, 6.2$ Hz), 24.33 (d, $J = 2.6$ Hz). ³¹P NMR (CDCl₃, 162 MHz) $\delta = 28.32$.

Example 4

General procedure for deprotection of benzyl esters, coupling reaction for peptide synthesis, and deprotection of methyl esters

Scheme 4



[000179] To a flask, *N*-phosphonyl proline benzyl ester (0.643 g, 1.0 mmol) was charged with Pd/C (10%, 0.2g) in THF solution. The reaction proceeded under hydrogen for 4 hours. The reaction mixture was filtered through celite and the filtrate cake was washed by

THF three times. All filtrates were collected, dried over Na₂SO₄, and evaporated to give the *N*-phosphonyl proline.

[000180] Compound **5**: $[\alpha]_D^{25} = -89.9^\circ$ (*c* = 1.0, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): δ = 8.22 – 8.14 (m, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.79 (m, 3H), 7.74 (d, *J* = 7.5 Hz, 3H), 7.56 – 7.40 (m, 6H), 4.67 (dd, *J* = 28.3, 12.4 Hz, 1H), 4.53 (dd, *J* = 16.5, 11.0 Hz, 1H), 4.36 – 4.24 (m, 2H), 3.21 – 3.10 (m, 1H), 3.04 – 2.94 (m, 1H), 2.73 – 2.61 (m, 1H), 2.57 – 2.40 (m, 2H), 2.31 (ddd, *J* = 8.3, 6.7, 3.0 Hz, 1H), 1.90 (d, *J* = 13.4 Hz, 1H), 1.75 (ddd, *J* = 16.2, 7.0, 3.7 Hz, 1H), 1.69 – 1.52 (m, 3H), 1.47 – 1.18 (m, 3H), 1.06 (qd, *J* = 12.1, 3.5 Hz, 1H), 0.76 – 0.64 (m, 1H), 0.02 – -0.13 (m, 1H). ¹³C NMR (CDCl₃, 101 MHz): δ = 174.29, 133.90 (d, *J* = 13.8 Hz), 132.67, 131.89, 131.79 (d, *J* = 20.2 Hz), 130.36 (dd, *J* = 287.7, 13.5 Hz), 129.17 (ddd, *J* = 226.5, 160.9, 56.3 Hz), 125.52, 125.14, 123.74 (d, *J* = 6.0 Hz), 60.60 (d, *J* = 4.6 Hz), 48.58 (d, *J* = 3.2 Hz), 46.61 (d, *J* = 11.5 Hz), 46.11 (t, *J* = 4.9 Hz), 44.24 (d, *J* = 13.8 Hz), 30.40, 28.32 (d, *J* = 7.3 Hz), 25.16 (d, *J* = 8.9 Hz). ³¹P NMR (CDCl₃, 162 MHz) δ = 29.81.

[000181] The *N*-phosphonyl proline, glycine methyl ester hydrochloride, hydroxybenzotriazole (HOBt) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) was dissolved in dichloromethane, and diisopropyl ethylamine was added to the reaction mixture. The solution was stirred for 12 hours and washed with 1 M HCl solution, 1M NaOH solution and brine. Solids were dried over Na₂SO₄ and evaporated to give the *N*-phosphonyl proline-glycine methyl ester.

[000182] Compound **6**: $[\alpha]_D^{25} = -102.1^\circ$ (*c* = 0.1, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): δ = 8.29 – 8.11 (m, 2H), 7.93 – 7.74 (m, 6H), 7.57 – 7.45 (m, 6H), 4.70 (ddd, *J* = 34.4, 21.5, 12.0 Hz, 2H), 4.43 (dd, *J* = 12.7, 7.0 Hz, 1H), 4.27 (dd, *J* = 17.1, 9.8 Hz, 1H), 3.33 (dd, *J* = 17.9, 5.7 Hz, 1H), 3.25 – 3.13 (m, 5H), 3.10 – 2.94 (m, 2H), 2.69 (ddd, *J* = 12.6, 7.3, 4.8 Hz, 2H), 2.45 (d, *J* = 11.2 Hz, 1H), 1.95 – 1.09 (m, 11H), 0.81 (dd, *J* = 7.4, 3.5 Hz, 1H). ¹³C NMR (CDCl₃, 101 MHz): δ = 174.18, 169.94, 136.74 (d, *J* = 5.3 Hz), 133.72, 133.37, 133.04, 131.48, 130.53, 128.34 (d, *J* = 11.8 Hz), 127.81 (d, *J* = 12.6 Hz), 126.79, 125.83, 125.68 (d, *J* = 3.9 Hz), 125.45, 125.27 (d, *J* = 10.0 Hz), 124.89, 123.85, 123.53, 64.66 (d, *J* = 10.2 Hz), 63.10 (d, *J* = 8.0 Hz), 59.91 (d, *J* = 5.6 Hz), 54.90, 51.32, 45.36, 44.67, 43.76, 40.23, 30.08 (d, *J* = 8.8 Hz), 28.90 (d, *J* = 7.1 Hz), 28.48 (d, *J* = 10.0 Hz), 24.10 (d, *J* = 8.3 Hz), 23.79 (d, *J* = 10.1 Hz). ³¹P NMR (CDCl₃, 162 MHz) δ = 30.78.

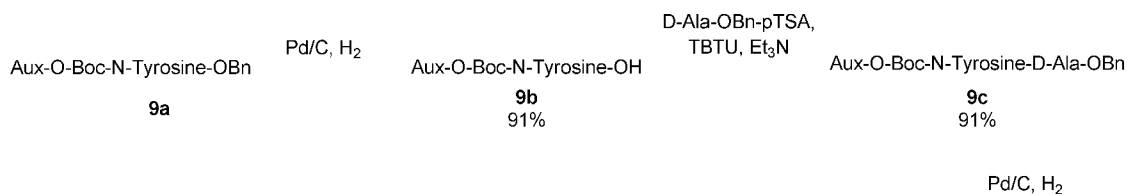
[000183] Compound **8**: $[\alpha]_D^{25} = -104.1^\circ$ ($c = 0.05$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.28$ (dd, $J = 43.7, 6.7$ Hz, 2H), $8.06 - 7.64$ (m, 5H), $7.65 - 7.40$ (m, 5H), 7.36 (t, $J = 7.7$ Hz, 2H), 7.16 (dt, $J = 17.8, 6.8$ Hz, 5H), 5.10 (dd, $J = 16.8, 12.0$ Hz, 1H), 4.57 (dd, $J = 21.4, 13.7$ Hz, 1H), $4.42 - 4.18$ (m, 2H), $3.64 - 3.22$ (m, 9H), $3.14 - 2.64$ (m, 6H), 2.22 (s, 1H), 1.70 (s, 1H), 1.34 (ddd, $J = 48.4, 32.8, 14.2$ Hz, 9H), 0.81 (dd, $J = 17.1, 9.6$ Hz, 2H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 173.99, 171.61, 168.87, 137.03, 136.72$ (d, $J = 5.6$ Hz), $133.86, 133.39, 133.04, 131.36, 130.44, 129.04, 128.38$ (d, $J = 6.5$ Hz), $128.12, 127.78, 127.51, 126.70, 126.43, 125.85, 125.70$ (d, $J = 4.6$ Hz), $125.46, 125.13, 124.55, 123.79, 123.37, 64.76$ (d, $J = 10.3$ Hz), 62.97 (d, $J = 8.1$ Hz), 60.48 (d, $J = 5.8$ Hz), $53.85, 51.61, 45.25, 44.89, 43.57, 41.48, 36.65, 30.14$ (d, $J = 8.9$ Hz), 29.74 (d, $J = 7.7$ Hz), 28.51 (d, $J = 10.0$ Hz), 24.52 (d, $J = 8.5$ Hz), 23.77 . ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 27.84$.

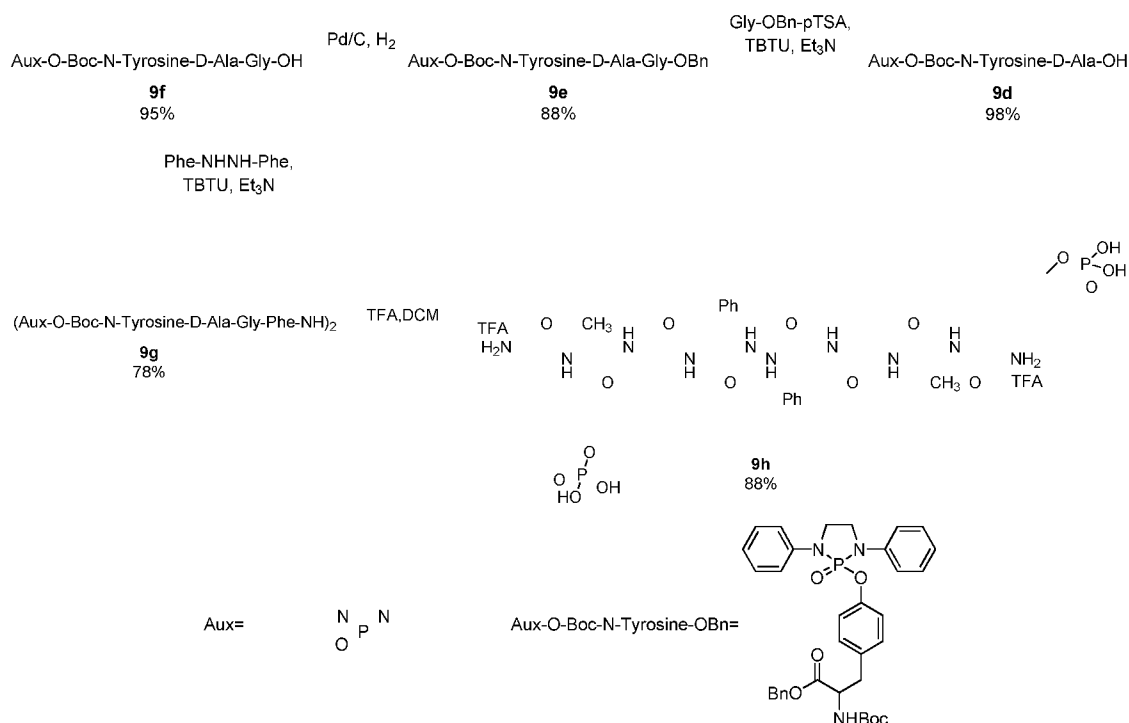
[000184] The *N*-phosphonyl proline-glycine methyl ester was dissolved in THF and treated with LiOH (4N) solution at 0°C for 2 hours. The solution was neutralized by addition of 1 M HCl. The aqueous phase was extracted with DCM three times. All organic phases were combined and evaporated to give the *N*-phosphonyl proline-glycine.

[000185] Compound **7**: $[\alpha]_D^{25} = -75.2^\circ$ ($c = 0.05$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.13$ (dt, $J = 21.5, 10.1$ Hz, 2H), 7.82 (ddd, $J = 23.7, 17.3, 8.1$ Hz, 5H), 7.44 (ddd, $J = 57.7, 19.3, 12.7$ Hz, 7H), $4.89 - 4.15$ (m, 3H), $3.40 - 3.10$ (m, 4H), 3.02 (s, 2H), $2.83 - 2.36$ (m, 3H), $2.00 - 1.02$ (m, 10H), 0.86 (d, $J = 32.2$ Hz, 1H), -0.05 (s, 1H). ^{13}C NMR (CDCl_3 , 101 MHz): $\delta = 173.94, 170.96, 136.73$ (d, $J = 5.5$ Hz), $133.73, 133.38, 133.08, 131.47, 130.59, 128.35$ (d, $J = 11.9$ Hz), 127.80 (d, $J = 15.0$ Hz), $126.85, 125.77$ (d, $J = 16.6$ Hz), 125.27 (dd, $J = 30.8, 17.4$ Hz), $123.84, 123.61, 64.66$ (d, $J = 10.2$ Hz), 63.11 (d, $J = 8.0$ Hz), 60.03 (d, $J = 5.4$ Hz), $54.90, 45.36, 44.72, 43.87, 40.36, 30.10$ (d, $J = 8.7$ Hz), $28.95, 28.48$ (d, $J = 9.9$ Hz), 24.18 (d, $J = 8.3$ Hz), 23.78 (d, $J = 7.4$ Hz). ^{31}P NMR (CDCl_3 , 162 MHz) $\delta = 28.76$.

Example 5

General procedure for synthesis of biphelines





[000186] 12g of **9a** was added to a mixture of dichloromethane (90 mL) and methanol (10 mL), followed by the addition of 1.5 g of 10% Pd/C. The mixture was stirred under H₂ atmosphere (1 atm) for 12 hours before filtered through a pack of celite. The filtrate was evaporated. The residue was then dissolved in a mixture of EtOAc (90 mL) and hexanes (60 mL). The solution was extracted by sat. aqueous NaHCO₃ (75 mL×3). The aqueous phase was acidified with citric acid to pH~2, and extracted by dichloromethane (100 mL×4). The dichloromethane phase was dried over Na₂SO₄, filtered, evaporated to give **9b** as a white solid, 9.4 g, 91 % yield.

[000187] Compound **9b**: a white solid, 9.4 g, 91 % yield. ¹H NMR (400 MHz, DMSO-d₆): δ 7.42 (t, J = 7.80 Hz, 4 H), 7.27 (d, J = 7.80 Hz, 4 H), 7.08 (t, J = 6.88 Hz, 4 H), 6.52 (d, J = 7.32 Hz, 2 H), 4.02-3.95 (m, 1 H), 3.80-3.73 (m, 2 H), 3.35-3.26 (m, 2 H), 2.94-2.87 (m, 1 H), 2.75-2.67 (m, 1 H), 1.29 (s, 9 H). ¹³C NMR (100 MHz, DMSO-d₆): 174.0, 155.8, 149.2, 149.1, 141.2, 141.1, 136.0, 131.0, 130.5, 130.0, 122.4, 120.6, 116.6, 115.4, 78.5, 55.6, 42.1, 36.2, 28.7. ³¹P NMR (162 MHz, DMSO-d₆): 7.46. ESI-HRMS calcd. for C₂₈H₃₂N₃O₆P ([M+Na]⁺): 560.1921; found: 560.1932.

[000188] Et₃N (2.2 mmol, 0.31 mL), D-Ala-OBn-PTSA (1 mmol, 0.54 g) and **9b** (1 mmol, 0.18 g) were dissolved in 5 mL of dry dichloromethane. The mixture was cooled to 0 °C. TBTU (1.1 mmol, 0.35 g) was added in portion at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours and room temperature for 10 hours. The mixture was then washed by 5%

citric acid aqueous solution, sat. NaHCO₃ aqueous solution, H₂O and then brine. The organic phase was dried over Na₂SO₄, filtered and evaporated to give **9c** as a white solid, 0.63 g, 91% yield.

[000189] Compound **9c**: a white solid, 0.63 g, 91% yield. ¹H NMR (400 MHz, DMSO-d₆): δ 8.35 (d, J = 7.32 Hz, 1 H), 7.41 (t, J = 8.24 Hz, 4 H), 7.36-7.31 (m, 5 H), 7.27 (d, J = 8.24 Hz, 4 H), 7.08 (t, J = 7.36 Hz, 4 H), 6.82 (d, J = 8.72 Hz, 1 H), 6.51 (d, J = 7.32 Hz, 2 H), 5.11 (s, 2 H), 4.32-4.24 (m, 1 H), 4.18-4.12 (m, 1 H), 3.80-3.73 (m, 2 H), 3.32-3.25 (m, 2 H), 2.84-2.76 (m, 1 H), 2.67-2.60 (m, 1 H), 1.27 (s, 9 H), 1.21 (d, J = 7.32 Hz, 3 H). ¹³C NMR (100 MHz, DMSO-d₆): δ 172.8, 171.8, 170.9, 155.5, 149.2, 149.1, 141.2, 141.1, 136.5, 135.8, 131.0, 130.0, 128.9, 128.5, 128.2, 122.4, 120.5, 116.6, 78.5, 66.4, 60.3, 55.7, 48.2, 42.1, 42.0, 37.8, 28.6, 28.3, 21.3, 17.6, 14.6. ³¹P NMR (162 MHz, DMSO-d₆): δ 7.43. ESI-HRMS calcd. for C₃₈H₄₃N₄O₇P ([M+Na]⁺): 721.2762; found: 721.2775.

[000190] To a mixture of 4 mL of dichloromethane and 1 mL of methanol was added 700 mg of **9c**, followed by the addition of 80 mg of 10% Pd/C. The resulting mixture was stirred under H₂ atmosphere (1 atm) at room temperature for 12 hours. The mixture was then filtered through a pack of celite. The filtrate was evaporated to give **9d** as a white solid, 598 mg, 98% yield.

[000191] Compound **9d**: a white solid, 598 mg, 98% yield. ¹H NMR (400 MHz, DMSO-d₆): δ 8.15 (d, J = 7.32 Hz, 1 H), 7.42 (t, J = 8.28 Hz, 4 H), 7.27 (d, J = 8.24 Hz, 4 H), 7.08 (t, J = 7.40 Hz, 4 H), 6.81 (d, J = 9.16 Hz, 1 H), 6.51 (d, J = 7.80 Hz, 2 H), 4.21-4.11 (m, 2 H), 3.81-7.30 (m, 2 H), 3.34-3.26 (m, 2 H), 2.86-2.80 (m, 1 H), 2.67-2.61 (m, 1 H), 1.28 (s, 9 H), 1.18 (d, J = 8.28 Hz, 3 H). ¹³C NMR (100 MHz, DMSO-d₆): δ 174.5, 171.5, 170.9, 155.5, 149.2, 149.1, 141.2, 141.1, 135.9, 131.0, 130.0, 122.4, 120.5, 116.6, 78.5, 60.3, 55.7, 48.0, 42.1, 42.0, 37.7, 28.6, 28.3, 21.3, 18.0, 14.6. ³¹P NMR (162 MHz, DMSO-d₆): δ 7.45. ESI-HRMS calcd. for C₃₁H₃₇N₄O₇P ([M+Na]⁺): 631.2293; found: 631.2307.

[000192] Et₃N (2.2 mmol, 0.31 mL), **9d** (1 mmol, 0.61 g) and Gly-OBn-PTSA (1.05 mmol, 0.35 g) were dissolved in 5 mL of dry dichloromethane. The mixture was cooled to 0 °C. TBTU (1.1 mmol, 0.35 g) was added in portion at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours and room temperature for 10 hours. The mixture was then washed by 5% citric acid aqueous solution, sat. NaHCO₃ aqueous solution, H₂O and then brine. The organic phase was dried over Na₂SO₄, filtered and evaporated to give **9e** as a white solid, 0.67 g, 88% yield.

[000193] Compound **9e**: a white solid, 0.67 g, 88% yield. ¹H NMR (400 MHz, DMSO-d₆): δ 8.33 (t, J = 5.96 Hz, 1 H), 8.12 (d, J = 7.76 Hz, 1 H), 7.44-7.26 (m, 13 H), 7.10-7.07 (m, 4 H), 6.95 (d, J = 8.24 Hz, 1 H), 6.52 (d, J = 7.32 Hz, 2 H), 5.12 (s, 2 H), 4.32-4.24 (m, 1 H), 4.12-4.08 (m, 1 H), 3.92-3.86 (m, 2 H), 3.80-3.74 (m, 2 H), 3.32-3.26 (m, 2 H), 2.85-2.79 (m, 1 H), 2.65-2.62 (m, 1 H), 1.27 (s, 9 H), 1.09 (d, J = 7.32 Hz, 3 H). ¹³C NMR (100 MHz, DMSO-d₆): δ 173.1, 171.5, 170.1, 170.0, 165.1, 155.8, 149.2, 149.1, 141.2, 141.1, 136.4, 135.8, 131.0, 130.0, 128.9, 128.6, 128.5, 122.4, 120.5, 116.6, 78.7, 66.4, 56.1, 48.3, 42.2, 42.1, 41.2, 38.8, 37.3, 28.6, 28.3, 18.8. ³¹P NMR (162 MHz, DMSO-d₆): δ 7.43. ESI-HRMS calcd. for C₄₀H₄₆N₅O₈P ([M+Na]⁺): 778.2977; found: 778.2994.

[000194] To a mixture of 4 mL of dichloromethane and 1 mL of methanol was added 756 mg of **9e**, followed by the addition of 80 mg of 10% Pd/C. The resulting mixture was stirred under H₂ atmosphere (1 atm) at room temperature for 12 hours. The mixture was then filtered through a pack of celite. The filtrate was evaporated to give **9f** as a white solid, 632 mg, 95% yield.

[000195] Compound **9f**: a white solid, 632 mg, 95% yield. ¹H NMR (400 MHz, DMSO-d₆): δ 8.17 (t, J = 5.92 Hz, 1 H), 8.10 (d, J = 7.80 Hz, 1 H), 7.42 (t, J = 8.24 Hz, 4 H), 7.27 (d, J = 8.24 Hz, 4 H), 7.08 (t, J = 6.88 Hz, 4 H), 6.96 (d, J = 7.80 Hz, 1 H), 6.51 (d, J = 7.32 Hz, 2 H), 4.30-4.23 (m, 1 H), 4.11-4.06 (m, 1 H), 3.80-3.72 (m, 4 H), 3.35-3.26 (m, 2 H), 2.86-2.78 (m, 1 H), 2.68-2.62 (m, 1 H), 1.28 (s, 9 H), 1.10 (d, J = 6.88 Hz, 3 H). ¹³C NMR (100 MHz, DMSO-d₆): δ 172.8, 171.5, 171.4, 165.1, 155.8, 149.2, 149.1, 141.2, 141.1, 135.8, 131.0, 130.0, 122.4, 120.5, 116.6, 78.7, 56.2, 48.3, 42.1, 42.0, 41.1, 38.8, 37.2, 28.6, 28.3, 18.9. ³¹P NMR (162 MHz, DMSO-d₆): δ 7.43. ESI-HRMS calcd. for C₃₃H₄₀N₅O₈P ([M+H]⁺): 666.2687; found: 666.2701.

[000196] The Phe-NHNH-Phe (0.5mmol) was added 5 mL of dichloromethane, followed by the addition of **9f** (1 mmol, 666 mg) and Et₃N (1.6 mmol, 0.22 mL). The mixture was cooled to 0 °C. To this mixture was added TBTU (1.1 mmol, 353 mg) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours and room temperature for 10 hours. 5 mL dichloromethane was added to the reaction mixture, the solution was then washed by H₂O, 0.5 M HCl, sat. aqueous NaHCO₃ and brine, 5 mL each, respectively. The organic phase was dried over Na₂SO₄, filtered, and evaporated. The residue was washed by dichloromethane/hexanes (5 : 1, v/v) to give **9g** as a white solid, 632 mg, 78% yield. No further purification needed.

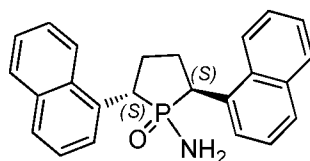
[000197] Compound **9g**: a white solid, 632 mg, 78% yield. No further purification needed. ^1H NMR (400 MHz, DMSO- d_6): δ 10.20 (s, 2 H), 8.15 (d, J = 8.24 Hz, 2 H), 8.06-8.01 (m, 4 H), 7.41 (t, J = 7.80 Hz, 8 H), 7.32-7.16 (m, 20 H), 7.13-7.04 (m, 8 H), 6.90 (d, J = 7.76 Hz, 2 H), 6.50 (d, J = 7.80 Hz, 4 H), 4.63-4.54 (m, 2 H), 4.55-4.20 (m, 2 H), 4.12-4.05 (m, 2 H), 3.80-3.68 (m, 6 H), 3.58-3.51 (m, 2 H), 3.31-3.26 (m, 4 H), 3.06-3.01 (m, 2 H), 2.85-2.76 (m, 4 H), 2.66-2.60 (m, 2 H), 1.25 (s, 18 H), 1.07 (d, J = 7.32 Hz, 6 H). ^{31}P NMR (162 MHz, DMSO- d_6): δ 7.43. ESI-HRMS calcd. for $\text{C}_{84}\text{H}_{98}\text{N}_{14}\text{O}_{16}\text{P}_2$ ($[\text{M}+\text{H}]^+$): 1621.6833; found: 1621.6852.

[000198] **9g** (150 mg) was dissolved in TFA (1 mL) and DCM (1 mL). The mixture was stirred at 23 °C for 24 hours. The reaction mixture was then evaporated and 5 ml of H_2O was added. The mixture was then extracted by DCM (10 mL $\times$ 5). The aqueous phase was evaporated under reduced pressure to give **9h** as a white solid, 103 mg, 88% yield.

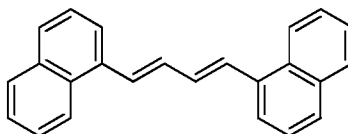
[000199] Compound **9h**: a white solid, 103 mg, 88% yield. ^1H NMR (400 MHz, DMSO- $d_6/\text{D}_2\text{O}$ = 10/1 (v/v)): δ 7.33-7.17 (m, 14 H), 7.09 (d, J = 7.80 Hz, 4 H), 4.58-4.54 (m, 2 H), 4.27-4.22 (m, 2 H), 4.00 (t, J = 6.88 Hz, 2 H), 3.73 (d, J = 16.96 Hz, 2 H), 3.56 (d, J = 16.96 Hz, 2 H), 3.58-2.96 (m, 6 H), 2.82-2.76 (m, 2 H), 1.03 (d, J = 7.36 Hz, 6 H). ^{31}P NMR (162 MHz, DMSO- $d_6/\text{D}_2\text{O}$ = 10/1 (v/v)): δ -5.93. ESI-HRMS calcd. for $\text{C}_{46}\text{H}_{58}\text{N}_{10}\text{O}_{16}\text{P}_2$ ($[\text{M}-2\text{TFA}+\text{H}]^+$): 1069.3580; found: 1069.3605.

Example 6

Synthesis of (2*S*, 5*S*)-1-amino-2, 5-di(naphthalen-1-yl)phospholane 1-oxide and its enantiomer



Step 1 (1E, 3E)-1, 4-di(naphthalen-1-yl)buta-1, 3-diene

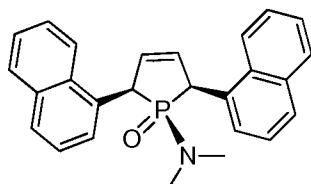


[000200] To an argon-filled dry 1 L three-necked round bottle with mounted reflux condenser containing magnesium turnings (99.98% purity; 8.1 g, 333 mmol), dry Et_2O (50 mL) and iodine (2–3 crystals), a solution of 1-bromonaphthalene (69.0 g, 333 mmol) in Et_2O (100 mL) was added with stirring at a rate sufficient to maintain the exothermal reaction

without becoming too vigorous. After completion of the addition, stirring was continued until the reaction mixture had solidified and cooled to room temperature. Dry degassed toluene (500 mL) was added. A solution of $\text{NiCl}_2(\text{PCy}_3)_2$ (2.6 g, 3.8 mmol) and thiophene (10.0 mL, 125 mmol) in dry toluene (100 mL) was transferred under argon to the reaction mixture with a steel bridge. The reaction mixture was heated to 80 °C for 48 h with vigorous stirring. After cooling, the dark brown reaction mixture was carefully added saturated aq NH_4Cl (~ 200 mL). The mixture was filtered through Celite pad, then transferred to a 2 L separatory funnel. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3×100 mL). The combined organic phase was washed with 2 M HCl , followed by 2 M NaOH aq and water (1×200 mL each). The organic phase was dried (MgSO_4), filtered and evaporated. The residue was taken up in CH_2Cl_2 (100 mL) with stirring. The pure product (32.9 g, 86%) was obtained after filtration and drying in high vacuum as yellow solid.

[000201] ^1H NMR (400 MHz, CDCl_3): δ 7.14–7.25 (m, 2H), 7.48–7.58 (m, 8H), 7.76–7.82 (m, 4H), 7.86–7.88 (m, 2H), 8.22 (d, J = 8.4 Hz, 2H).

Step 2 (1s, 2R, 5S)-1-(dimethylamino)-2, 5-di(naphthalen-1-yl)-2, 5-dihydro-1H-phosphole 1-oxide

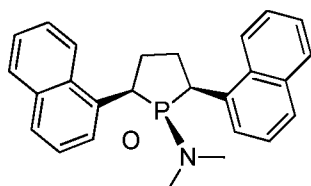


[000202] To an argon-filled dry 1 L three-necked round was added AlCl_3 (10.4 g, 77.7 mmol) and 100 mL anhydrous CH_2Cl_2 , followed by addition of *N, N*-dimethylaminophosphinodichloridite (12.0 g, 82.2 mmol). After stirring for 30 minutes at room temperature, 400 mL CH_2Cl_2 was added and the solution was placed in an ice bath. (1*E*, 3*E*)-1, 4-di(naphthalen-1-yl)buta-1, 3-diene (23.0 g, 75 mmol) was then slowly added in portions. The reaction mixture was stirred at 0 °C under argon for 48 hours, then poured in to a 400 mL of aqueous EDTA-Na_4 (0.2 M) at 0 °C in portions. After 30 minutes, saturated NaHCO_3 (400 mL) was added cautiously in portions to the stirring mixture. The bath was then removed, and the mixture was allowed to warm to RT. After 3h, the reaction mixture was filtered through Celite pad, washed with 500 mL CH_2Cl_2 . The two layers was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The organic layers combined were washed with saturated NaHCO_3 , 1 M HCl and brine, then dried over MgSO_4 and concentrated under vacuum. The resulting yellow solid was treated with CH_2Cl_2 (50 mL).

The slightly yellowish precipitate of (1*s*, 2*R*, 5*S*)-1-(dimethylamino)-2, 5-di(naphthalen-1-yl)-2, 5-dihydro-1*H*-phosphole 1-oxide was collected by filtration. After drying under vacuum, the pure product (28.3 g, 95%) was obtained.

[000203] ^1H NMR (400 MHz, CDCl_3): δ 1.14 (s, CH_3 , 3H), 1.17 (s, CH_3 , 3H), 4.91 (d, J = 20.4 Hz, PCH, 2H), 6.86 (d, J = 29.7 Hz, $\text{CH}=\text{CH}$, 2H), 7.38–7.66 (m, 6H), 7.74 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H), 8.38 (d, J = 8.4 Hz, 2H). ^{31}P NMR (122 MHz, CDCl_3): δ 63.2 (s).

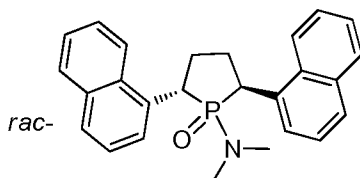
*Step 3 (1*s*, 2*R*, 5*S*)-1-(dimethylamino)-2, 5-di(naphthalen-1-yl)phospholane 1-oxide*



[000204] A pressure reactor was charged with (1*s*, 2*R*, 5*S*)-1-(dimethylamino)-2, 5-di(naphthalen-1-yl)-2, 5-dihydro-1*H*-phosphole 1-oxide (8.0 g, 20.1 mmol), PtO_2 (1.0 g, 4.4 mmol), methanol (200 mL) and CH_2Cl_2 (100 mL). The reactor was purged with hydrogen, then pressurized to 70 psi of hydrogen. After 94 hours, the reacting mixture was checked by crude NMR. If the reaction was not complete, another more 24 hours was needed for this reaction. The reaction mixture was filtered through Celite pad and the solvent was removed in vacuo, giving 8.2 g of white solid, which was washed by 20 mL methanol. The solid was collected by filtration and dried in vacuum to give 7.9 g of pure product (98%).

[000205] ^1H NMR (400 MHz, CDCl_3): δ 1.16 (s, CH_3 , 3H), 1.18 (s, CH_3 , 3H), 2.72–2.88 (m, CH_2 , 2H), 2.98–3.12 (m, CH_2 , 2H), 4.29–4.41 (m, PCH, 2H), 7.39–7.63 (m, 8H), 7.73 (d, J = 7.8 Hz, 2H), 7.82 (d, J = 7.8 Hz, 2H), 8.51 (d, J = 8.4 Hz, 2H). ^{31}P NMR (122 MHz, CDCl_3): δ 67.1 (s).

Step 4 trans-1-(dimethylamino)-2, 5-di(naphthalen-1-yl)phospholane 1-oxide

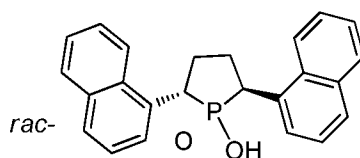


[000206] To a 500 mL round-bottom flask was added (1*s*, 2*R*, 5*S*)-1-(dimethylamino)-2, 5-di(naphthalen-1-yl)phospholane 1-oxide (7.0 g, 17.5 mmol), methanol (200 mL) and THF (100 mL). Sodium methanolate (4.75 g, 88.0 mmol) was added at once. The resulting

suspension was stirred for 5 hours at room temperature and then heated to reflux for overnight. The reaction mixture was placed in an ice bath and slowly poured into 400 mL HCl (2 M). The solid was collected by filtration. After drying in vacuo, a white solid product (6.8 g, 97%) was obtained.

[000207] ^1H NMR (400 MHz, CDCl_3): δ 2.02 (s, CH_3 , 3H), 2.04 (s, CH_3 , 3H), 2.60–2.70 (m, CH_2 , 4H), 4.20–4.51 (m, PCH, 2H), 7.47–7.62 (m, 7H), 7.80–7.84 (m, 2H), 7.89–7.93 (m, 4H), 8.72 (d, $J = 7.8$ Hz, 1H). ^{31}P NMR (122 MHz, CDCl_3): δ 60.2 (s).

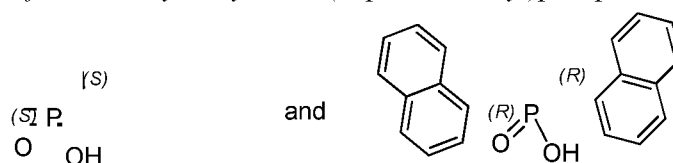
Step 5 trans-1-hydroxy-2,5-di(naphthalen-1-yl)phospholane 1-oxide



[000208] To a 500 mL round-bottom flask was added $\text{CH}_3\text{CO}_2\text{H}$ (60 mL), H_2O (180 mL), conc. H_2SO_4 (120 mL). *trans*-1-(dimethylamino)-2, 5-di(naphthalen-1-yl)phospholane 1-oxide (6.5 g, 16.3 mmol) was added to the mixture. The resulting suspension was heated to reflux overnight. The solid was collected by filtration and washed with H_2O for several times. After drying in vacuo, the white solid product (5.5 g, 90%) was obtained.

[000209] ^1H NMR (400 MHz, $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 2.53–2.67 (m, CH_2 , 4H), 4.28–4.38 (m, PCH, 2H), 7.50–7.61 (m, 6H), 7.72–7.91 (m, 6H), 8.40 (d, $J = 6.9$ Hz, 1H). ^{31}P NMR (122 MHz, $\text{CD}_3\text{OD}/\text{CDCl}_3 = 1/1$): δ 62.3 (s).

Step 6 Resolution of trans-1-hydroxy-2,5-di(naphthalen-1-yl)phospholane 1-oxide

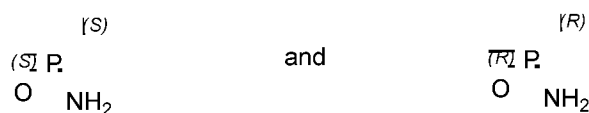


[000210] To a 1 L round-bottom flask was added (*rac*)-*trans*-1-hydroxy-2, 5-di(naphthalen-1-yl)phospholane 1-oxide (5.0 g, 13.4 mmol) and MeOH (500 mL). The suspension was heated to reflux. The least amount of DCM was added until the solution became clear. Quinine (4.4 g, 13.4 mmol) was added to the solution. The oil bath was removed and the solution cooled to room temperature in air. The resulting suspension was filtered. The solid was dried and added slowly to 6 M HCl (200 mL). The mixture was stirred vigorously for 3 hours, then filtered to give the crude (*S,S*)-1-hydroxy-2, 5-di(naphthalen-1-yl)phospholane 1-oxide. After treatment with MeOH (20 mL) and drying in high vacuo, the

pure (*S, S*)-1-hydroxy-2, 5-di(naphthalen-1-yl)phospholane 1-oxide (1.9 g, 74%, 99.3% ee) was obtained. To determine the ee value, the corresponding methyl ester was made. HPLC conditions: AD, 1 ml/min, 254 nm, *i*PrOH / Hexane = 10:90, $t_{R,R}$ = 11.9 min, $t_{S,S}$ = 13.0 min.

[000211] To obtain optically pure (*R, R*)-1-hydroxy-2, 5-di(naphthalen-1-yl)phospholane 1-oxide, Quinidine was used as the resolution reagent. Similar procedures was performed. The pure (*R, R*)-1-hydroxy-2, 5-di(naphthalen-1-yl)phospholane 1-oxide (1.4 g, 56%, 99.5% ee) was obtained.

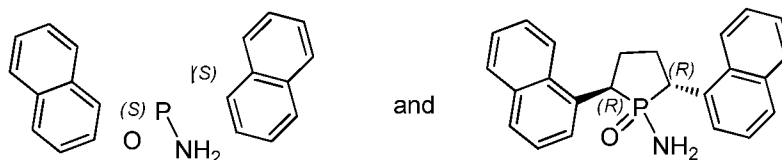
*Step 7 (2*S, 5S*)-1-amino-2, 5-di(naphthalen-1-yl)phospholane 1-oxide or its enantiomer*



[000212] The crude product of step 6 was re-dissolved in anhydrous DCM (30 mL). The flask was equipped with a Dewar condenser. The solution was cooled to -78 °C, ammonia gas was condensed using the Dewar condenser and approximately 2 mL was added. The reaction mixture was stirred at -78 °C for 5 h, allowed to warm slowly to room temperature and stirred overnight. The solution was diluted with dichloromethane and filtered through celite pad with the solvent evaporated under vacuum. A pale yellow solid was obtained and washed with ethyl acetate to afford (*2S, 5S*)-1-amino-2, 5-di(naphthalen-1-yl)phospholane 1-oxide (0.95g, 95%) or its (*2R, 5R*) enantiomer as white cottony crystals.

[000213] ^1H NMR (400 MHz, CDCl_3): δ 2.51–2.84 (m, CH_2 , 4H), 4.58–4.70 (m, PCH, 2H), 7.50–7.89 (m, 12 H), 8.19 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 8.4 Hz, 1H). ^{31}P NMR (122 MHz, CDCl_3): δ 80.0 (s).

*Step 8 (2*S, 5S*)-1-amino-2, 5-di(naphthalen-1-yl)phospholane 1-oxide or its enantiomer*



[000214] The crude product of step 7 was re-dissolved in anhydrous DCM (30 mL). The flask was equipped with a Dewar condenser. The solution was cooled to -78 °C, and ammonia gas was condensed using the Dewar condenser and approximately 2 mL was added. The reaction mixture was stirred at -78 °C for 5 h and allowed to warm slowly to room

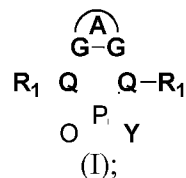
temperature and stirred overnight. The solution was diluted with dichloromethane and filtered through celite pad and solvent evaporated under vacuum. A pale yellow solid was obtained, and washed with ethyl acetate to afford (2*S*, 5*S*)-1-amino-2, 5-di(naphthalen-1-yl)phospholane 1-oxide (0.95g, 95%) or its (2*R*, 5*R*) enantiomer as white cottony crystals.

[000215] ^1H NMR (400 MHz, CDCl_3): δ 2.27 (br, NH_2 , 2H), 2.48–2.70 (m, CH_2 , 4H), 4.02–4.12 (m, PCH, 1H), 4.32–4.42 (m, PCH, 1H), 7.42–7.58 (m, 7 H), 7.75–7.86 (m, 5 H), 8.07–8.09 (m, 1H), 8.53 (d, $J = 8.7$ Hz, 1H). ^{31}P NMR (122 MHz, CDCl_3): δ 54.5 (s).

[000216] All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to be incorporated by reference. While the claimed subject matter has been described in terms of various embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the claimed subject matter is limited solely by the scope of the following claims, including equivalents thereof.

WHAT IS CLAIMED IS:

1. A compound according to Formula I:



wherein:

each R_1 is independently hydrogen, alkyl, aryl or arylalkyl;

ring A is a carbocyclic ring or absent;

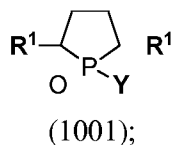
each Q is nitrogen, carbon, or oxygen;

each G is carbon; or when ring A is absent and Q is oxygen, then G is absent;

and

Y is hydroxyl, halogen, amide, imine, an amino acid sequence or an amino acid, or ester thereof.

2. The compound of claim 1 according to Formula 1001:

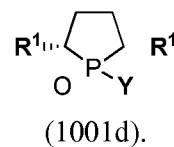
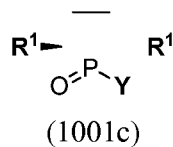
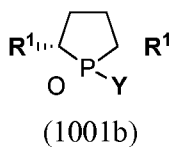
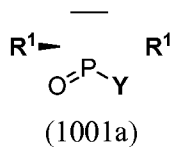


wherein:

each R^1 is independently aryl or arylalkyl; and

Y is hydroxyl, halogen, amine, or imine.

3. The compound of any of claims 1-2 according to any of Formulas 1001a, 1001b, 1001c or 1001d:

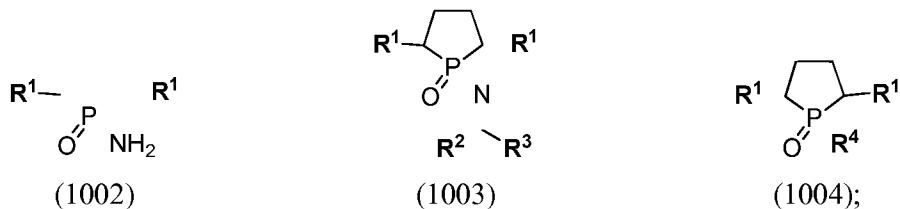


4. The compound according to any of claims 1-3, wherein:

each Y is independently hydroxyl, chloro, bromo, $-\text{NH}_2$ or $-\text{N}=\text{CH}-\text{R}^3$; and

R^3 is C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, or C_6 - C_{12} aryl.

5. The compound of any of claims 1-2 according to any of Formulas 1002, 1003, or 1004:



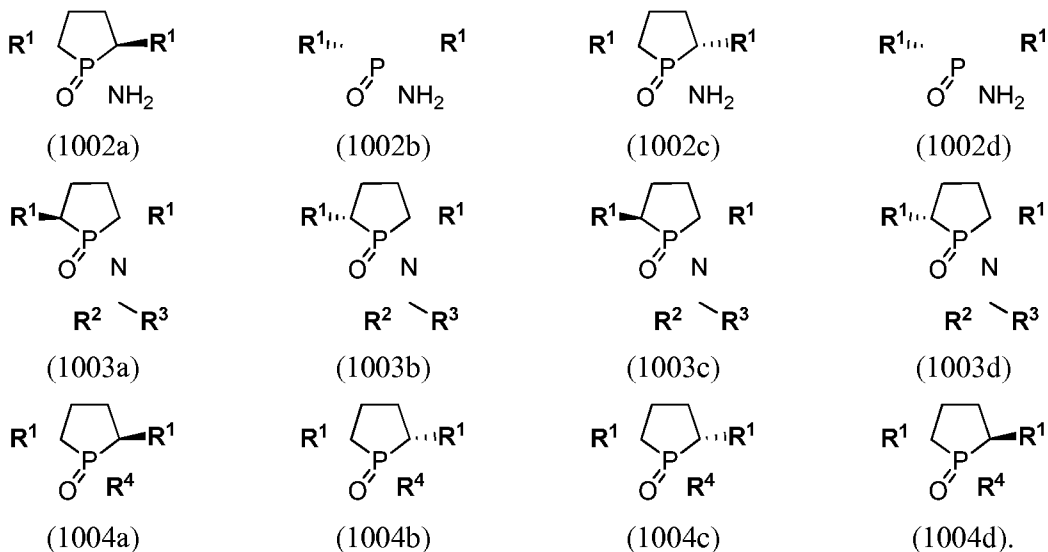
wherein:

R^2 is hydrogen or C_1 - C_8 alkyl;

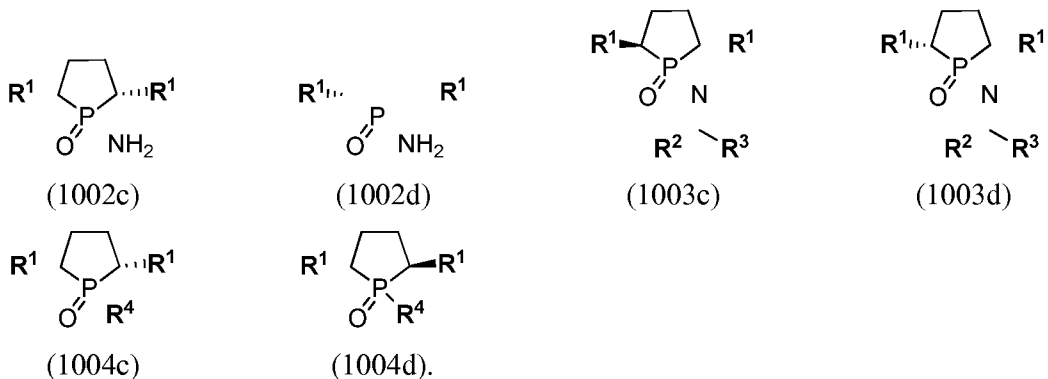
R^3 is C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, or C_6 - C_{12} aryl; and

R^4 is hydroxyl or halogen.

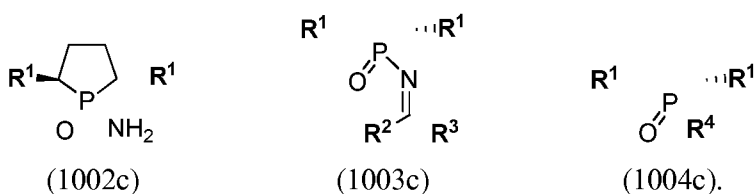
6. The compound of claim 5, according to any of Formulas 1002a-1004d:



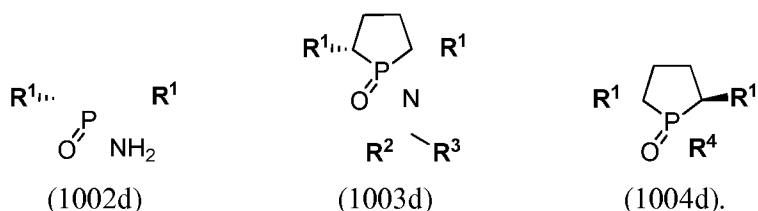
7. The compound of claim 5, according to any of Formulas 1002c-1004d:



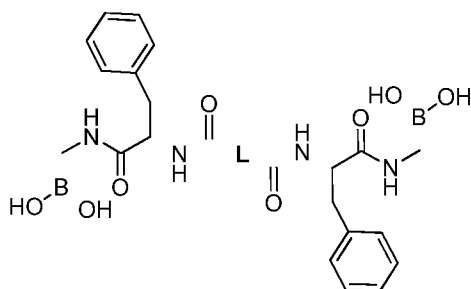
8. The compound of claim 5, according to any of Formulas 1002c-1004c:



9. The compound of claim 5, according to any of Formulas 1002d-1004d:

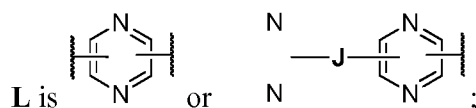


10. The compound of any of claims 1-9, wherein each R^1 is independently phenyl, 1'-naphthyl, 5',6',7',8'-tetrahydronaphthalen-1-yl, 2',4',6'-trimethylphenyl, 4'-biphenyl, or 2',6'-di-tert-butyl-phenyl.
11. The compound of any of claims 5-10, wherein R^4 is hydroxyl, chloro, or bromo.
12. The compound of any of claims 4-11, wherein each R^3 is independently C_1 - C_8 alkyl.
13. The compound of any of claims 4-11, wherein each R^3 is $-\text{CH}_2\text{CH}(\text{CH}_3)_2$.
14. The compound of any of claims 5-9, wherein R^2 is hydrogen and R^3 is C_1 - C_8 alkyl.
15. A compound according to Formula 1010:



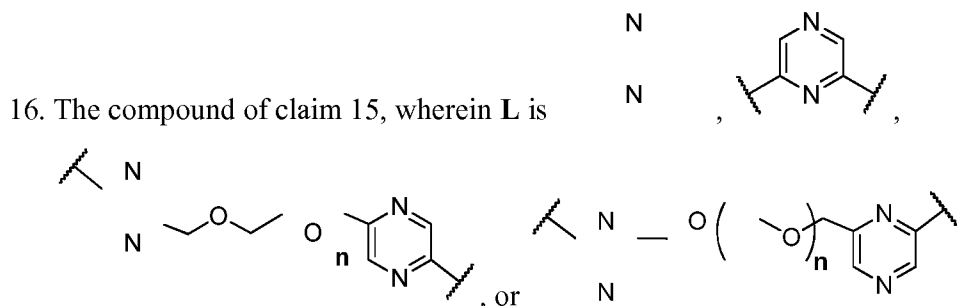
(1010);

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomeric form, tautomeric form or polymorphic form thereof; wherein:

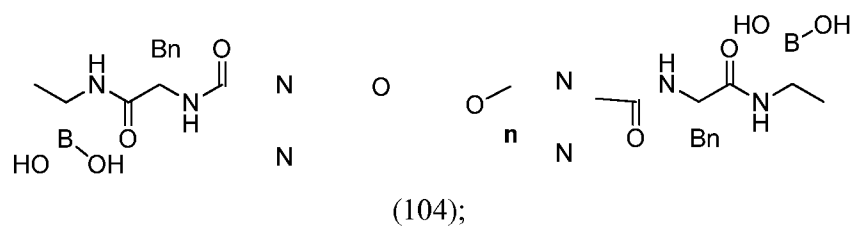
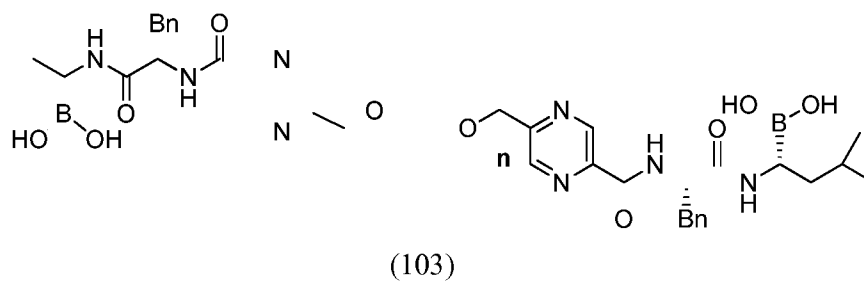
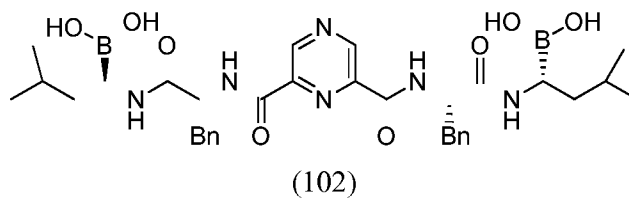
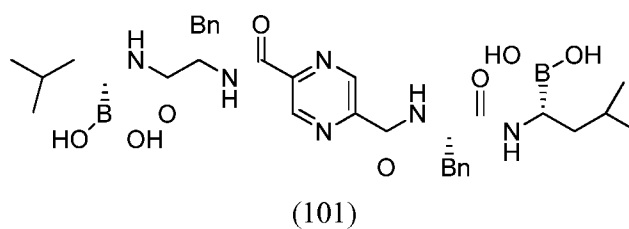


J is $-(\text{CH}_2)_n-$, $-(\text{CH}_2\text{-CHO})_n-$, $-(\text{CH}_2\text{-CH-NH})_n-$, $-\text{O}-(\text{CH}_2\text{-CHO})_n-$, $-\text{NH}-(\text{CH}_2\text{-CH-NH})_n-$, $-\text{NH}-(\text{CH}_2\text{-CHO})_n-$, $-\text{O}-(\text{CH}_2\text{-CH-NH})_n-$ and $-(\text{amino acid residue})_n-$; and

each n is independently a positive integer.



17. The compound of claim 15 according to any of Formulas 101-104:

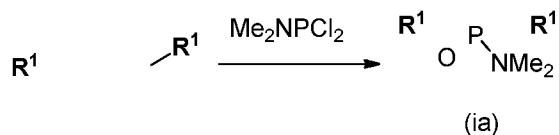


or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomeric form, tautomeric form or polymorphic form thereof.

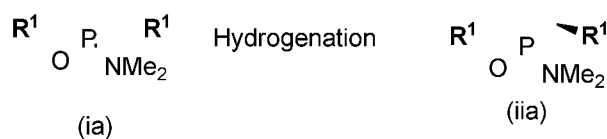
18. The compound of any of claims 15-17 wherein each n is independently a positive integer selected from 1 to 10.

19. A method of synthesizing a compound of Formula 1002 comprising:

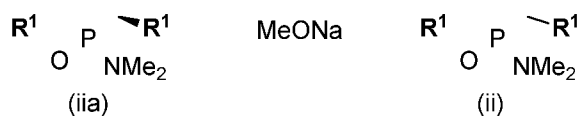
(a) reacting R^1  with Me_2NPCl_2 to form a compound of Formula (ia):



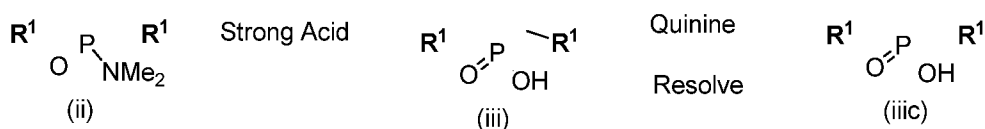
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



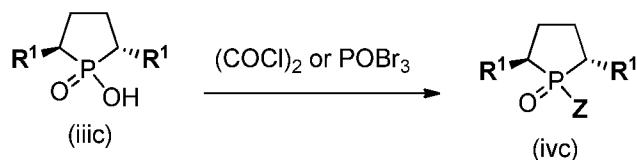
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



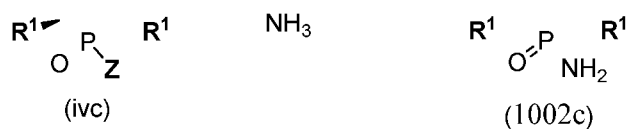
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiic):



(e) reacting the compound of Formula (iiic) with $(\text{COCl})_2$ or POBr_3 to form a compound of Formula (ivc):



(f) reacting the compound of Formula (ivc) with NH_3 to form a compound of Formula (1002c):



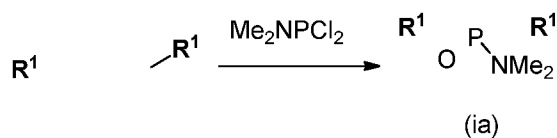
wherein:

Z is chloro or bromo; and

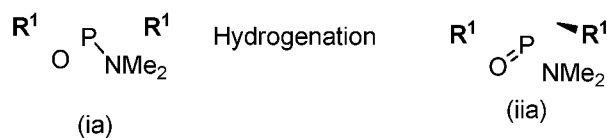
each R^1 is independently aryl or arylalkyl.

20. A method of synthesizing a compound of Formula 1002 comprising:

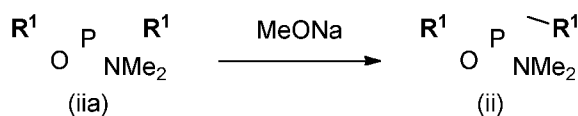
(a) reacting R^1 with Me_2NPCl_2 to form a compound of Formula (ia):



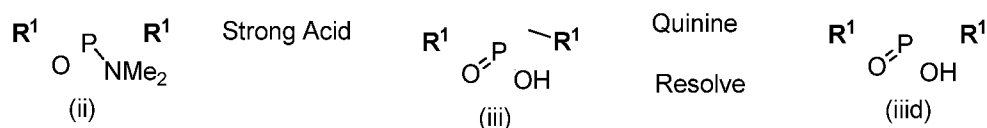
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



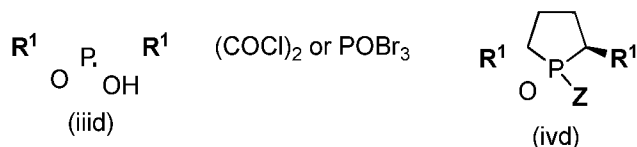
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



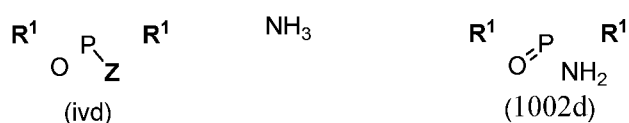
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiid):



(e) reacting the compound of Formula (iiid) with $(\text{COCl})_2$ or POBr_3 to form a compound of Formula (ivd):



(f) reacting the compound of Formula (ivd) with NH_3 to form a compound of Formula (1002d):

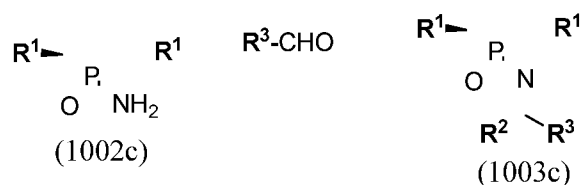


wherein:

Z is chloro or bromo; and

each **R**¹ is independently aryl or arylalkyl.

21. A method of synthesizing a compound of Formula 1003c comprising reacting a compound of Formula 1002c with **R**³-CHO to form a compound of Formula 1003c:



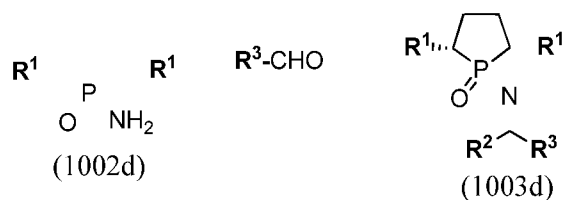
wherein:

each **R**¹ is independently aryl or arylalkyl;

R² is hydrogen; and

R³ is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, or C₆-C₁₂ aryl.

22. A method of synthesizing a compound of Formula 1003d comprising reacting a compound of Formula 1002d with **R**³-CHO to form a compound of Formula 1003d:



wherein:

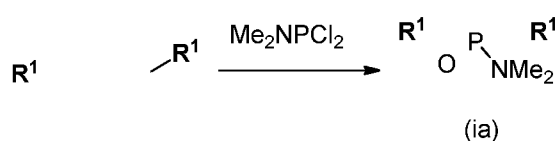
each R^1 is independently aryl or arylalkyl;

R^2 is hydrogen; and

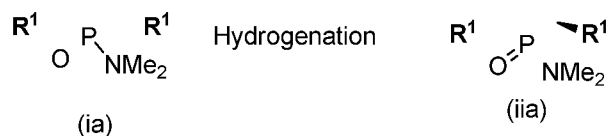
R^3 is C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, or C_6 - C_{12} aryl.

23. A method of synthesizing Velcade comprising:

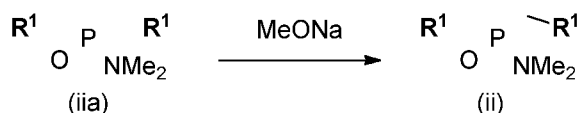
(a) reacting R^1  with Me_2NPCl_2 to form a compound of Formula (ia):



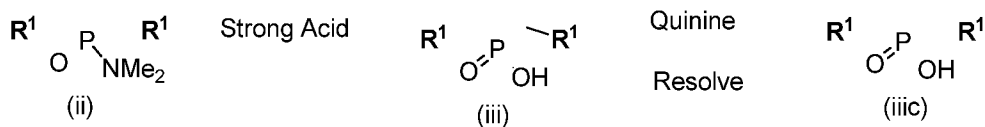
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



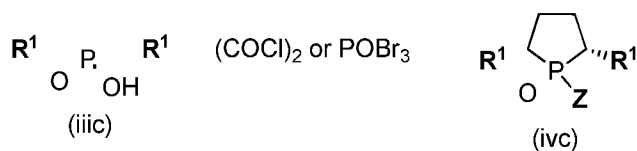
(c) reacting the compound of Formula (iia) with $MeONa$ to form a compound of Formula (ii):



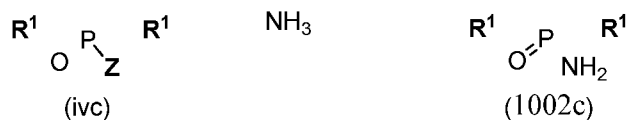
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiic):



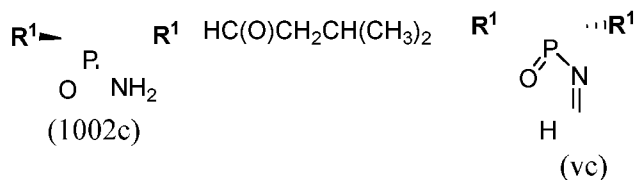
(e) reacting the compound of Formula (iiic) with $(COCl)_2$ or $POBr_3$ to form a compound of Formula (ivc):



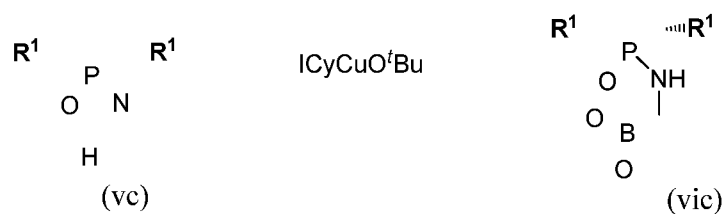
(f) reacting the compound of Formula (ivc) with NH_3 to form a compound of Formula (1002c):



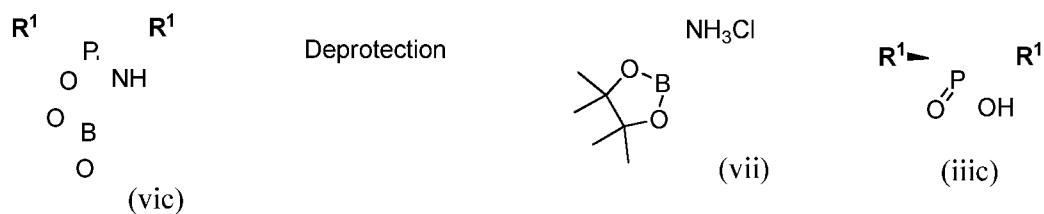
(g) reacting the compound of Formula 1002c with $\text{HC(O)CH}_2\text{CH(CH}_3)_2$ to form a compound of Formula vc:



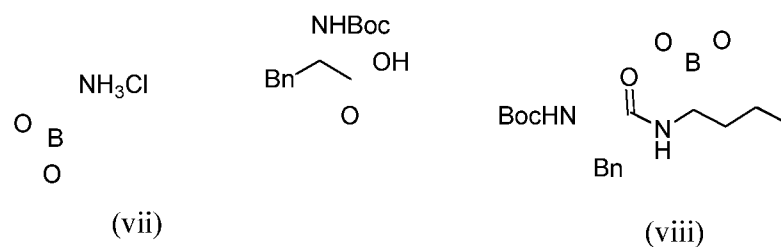
(h) reacting a compound of Formula (vc) with ICyCu^tBu to form a compound of Formula (vic):



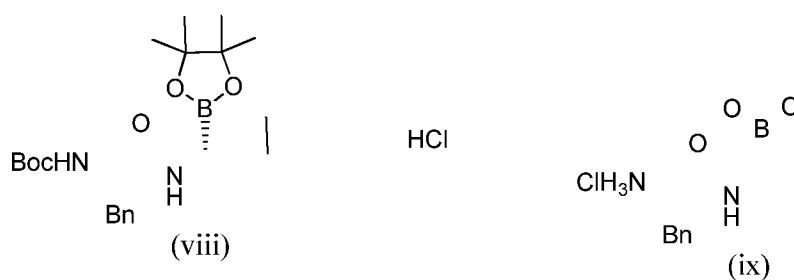
(i) deprotecting the compound of Formula (vic) to form a compound of Formula (vii) and a compound of Formula (iiic):

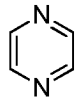


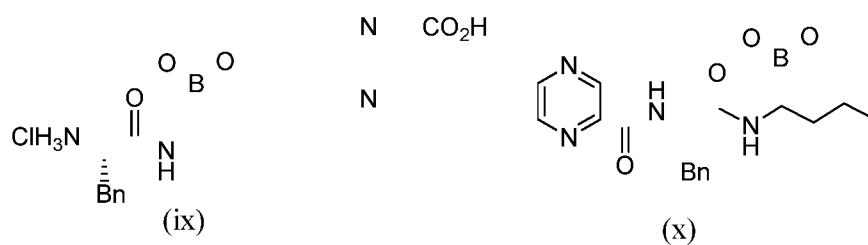
(j) reacting the compound of Formula (vii) with BnCH(NHBoc)C(O)OH to form a compound of Formula (viii):



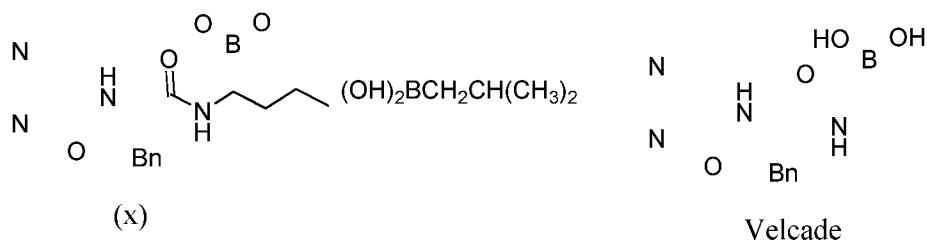
(k) reacting the compound of Formula (viii) with HCl to form a compound of Formula (ix):



(l) reacting the compound of Formula (ix) with  to form a compound of Formula (x):



(m) reacting the compound of Formula (x) with $(\text{OH})_2\text{BCH}_2\text{CH}(\text{CH}_3)_2$ to form Velcade:



wherein:

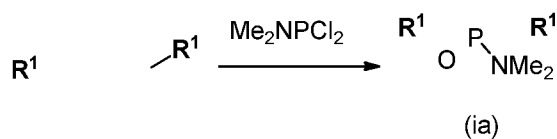
Z is chloro or bromo; and

each **R**¹ is independently aryl or arylalkyl.

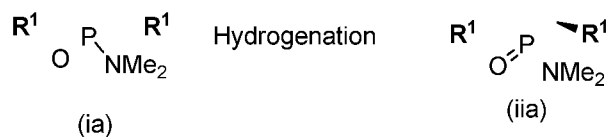
24. The method of claim 23, further comprising using the compound of Formula (iiic) produced in step (i) in step (e).

25. A method of synthesizing Velcade comprising:

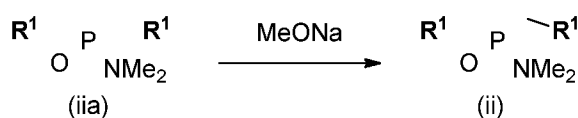
(a) reacting **R**¹  with Me₂NPCl₂ to form a compound of Formula (ia):



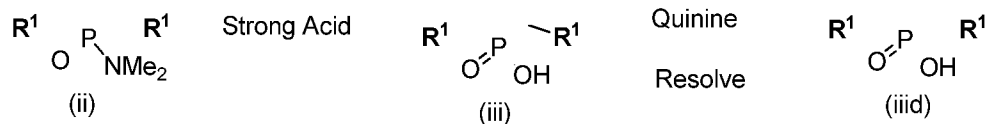
(b) hydrogenating the compound of Formula (ia) to form a compound of Formula (iia):



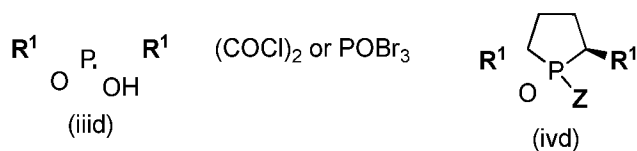
(c) reacting the compound of Formula (iia) with MeONa to form a compound of Formula (ii):



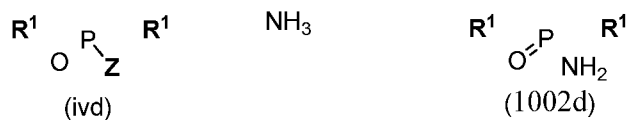
(d) reacting the compound of Formula (ii) with a strong acid in the presence of an alcohol or water to form a compound of Formula (iii) and resolving the compound of Formula (iii) by reaction with quinine to a compound of Formula (iiid):



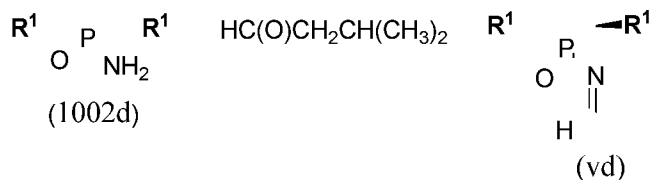
(e) reacting the compound of Formula (iiid) with (COCl)₂ or POBr₃ to form a compound of Formula (ivd):



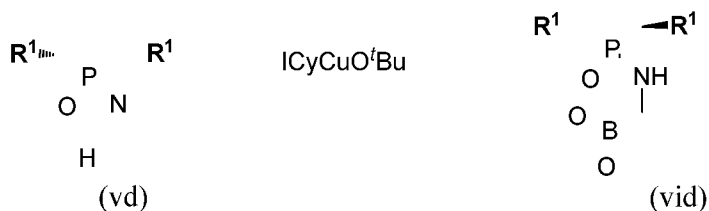
(f) reacting the compound of Formula (ivd) with NH_3 to form a compound of Formula (1002d):



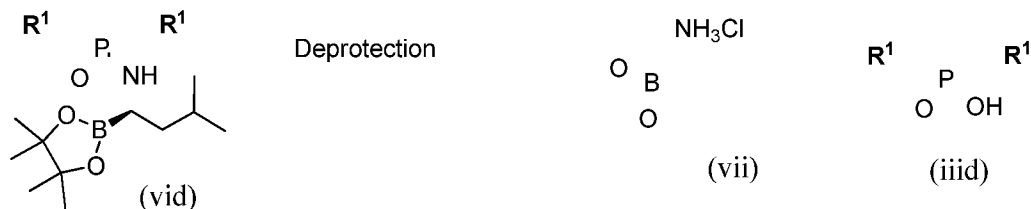
(g) reacting the compound of Formula 1002d with $\text{HC(O)CH}_2\text{CH(CH}_3)_2$ to form a compound of Formula vd:



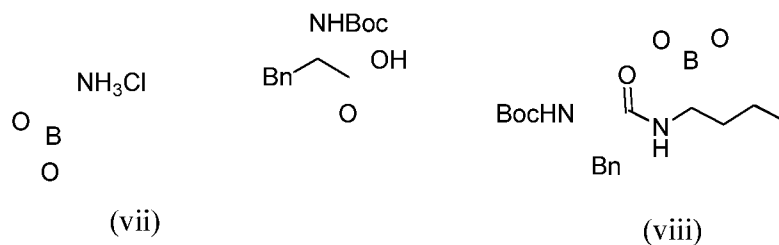
(h) reacting a compound of Formula (vd) with ICyCu^tBu to form a compound of Formula (vid):



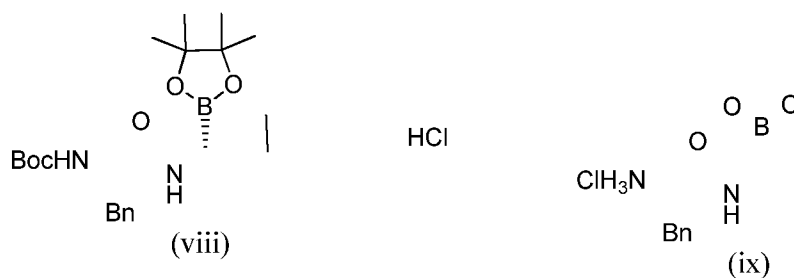
(i) deprotecting the compound of Formula (vid) to form a compound of Formula (vii) and a compound of Formula (iiid):



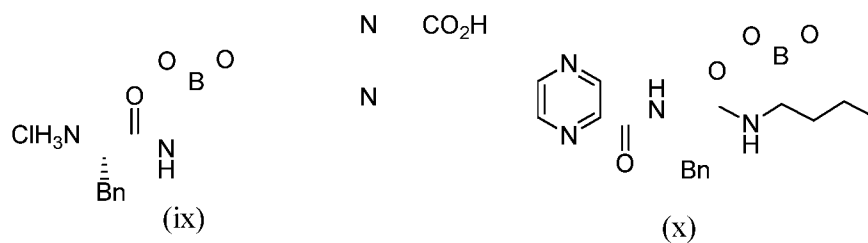
(j) reacting the compound of Formula (vii) with BnCH(NHBoc)C(O)OH to form a compound of Formula (viii):



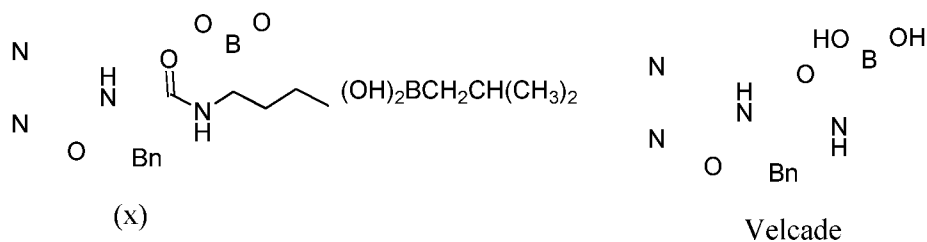
(k) reacting the compound of Formula (viii) with HCl to form a compound of Formula (ix):



(l) reacting the compound of Formula (ix) with  to form a compound of Formula (x):



(m) reacting the compound of Formula (x) with $(\text{OH})_2\text{BCH}_2\text{CH}(\text{CH}_3)_2$ to form Velcade:

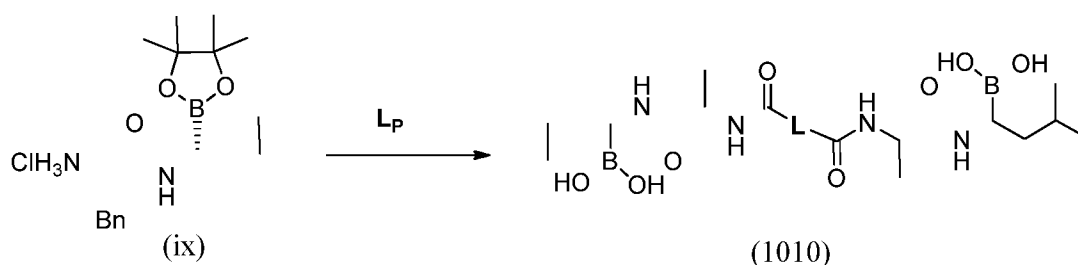


wherein:

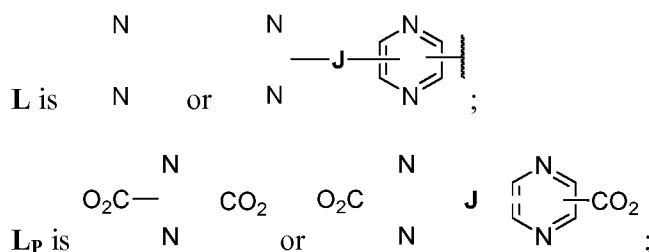
Z is chloro or bromo; and

each **R**¹ is independently aryl or arylalkyl.

26. The method of claim 25, further comprising using the compound of Formula (iiid) produced in step (i) in step (e).
27. The method of any of claims 19-26, wherein each **R**¹ is independently phenyl, 1'-naphthyl, 5',6',7',8'-tetrahydronaphthalen-1-yl, 2',4',6'-trimethylphenyl, 4'-biphenyl, or 2',6'-di-tert-butyl-phenyl.
28. The method of any of claims 19-22, wherein each **R**³ is independently C₁-C₈ alkyl.
29. The method of any of claims 19-22 or 28, wherein each **R**³ is -CH₂CH(CH₃)₂.
30. A method of synthesizing a compound of Formula 1010 comprising reacting a compound of Formula (ix) with **L_P**:

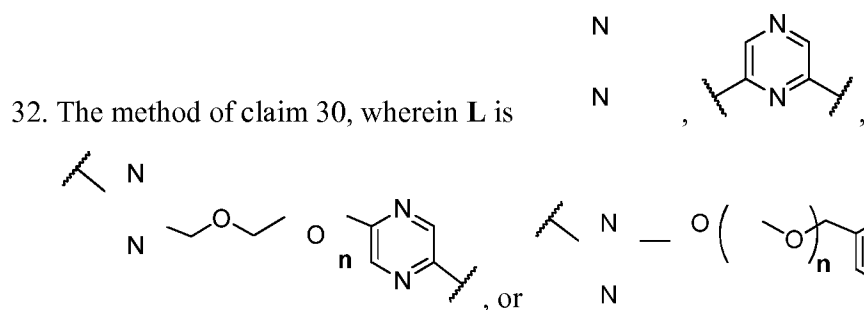
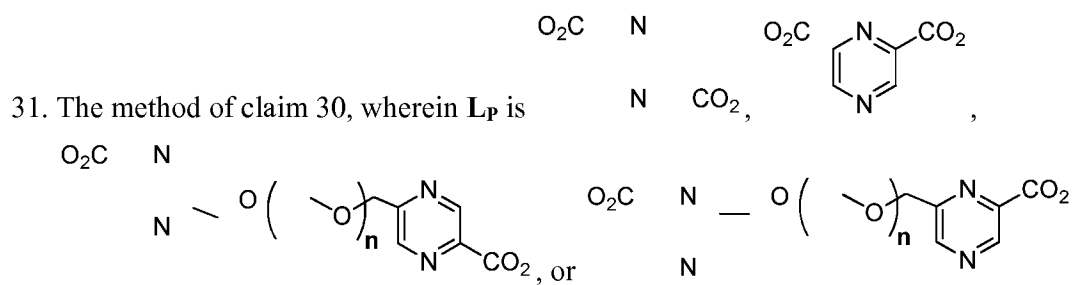


wherein:



J is -(CH₂)_n-, -(CH₂-CHO)_n-, -(CH₂-CH-NH)_n-, -O-(CH₂-CHO)_n-, -NH-(CH₂-CH-NH)_n-, -NH-(CH₂-CHO)_n-, -O-(CH₂-CH-NH)_n- and -(amino acid residue)_n-; and

each **n** is independently a positive integer.



33. The method of any of claims 30-32, wherein each n is independently a positive integer selected from 1 to 10.

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT
(PCT Article 17(2)(a), Rules 13ter.1(c) and (d) and 39)

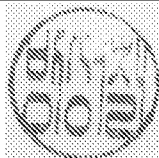
Applicant's or agent's file reference 385568995040	IMPORTANT DECLARATION	Date of mailing (<i>day/month/year</i>) 10 March 2014 (10.03.2014)
International application No. PCT/US2013/074830	International filing date (<i>day/month/year</i>) 12 December 2013 (12.12.2013)	(Earliest) Priority date (<i>day/month/year</i>) 12 December 2012 (12.12.2012)
International Patent Classification (IPC) or both national classification and IPC C07F 9/36(2006.01)i, C07F 9/34(2006.01)i, C07F 9/06(2006.01)i, A61K 33/42(2006.01)i, A61P 35/00(2006.01)i		
Applicant NANJING UNIVERSITY		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. ☐ The subject matter of the international application relates to:
 - a. ☐ scientific theories
 - b. ☐ mathematical theories
 - c. ☐ plant varieties
 - d. ☐ animal varieties
 - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes
 - f. ☐ schemes, rules or methods of doing business
 - g. ☐ schemes, rules or methods of performing purely mental acts
 - h. ☐ schemes, rules or methods of playing games
 - i. ☐ methods for treatment of the human body by surgery or therapy
 - j. ☐ methods for treatment of the animal body by surgery or therapy
 - k. ☐ diagnostic methods practised on the human or animal body
 - l. ☐ mere presentation of information
 - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art
2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

☒ the description
☒ the claims
☐ the drawings
3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
4. Further comments:

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