PROCESSES AND INTERMEDIATES

CROSS-REFERENCE

[001] This application claims priority under 35 U.S.C. 119(e) to U.S. Serial Numbers 60/709,964, filed Aug. 19, 2005, and 60/810,042, filed June 1, 2006, each of which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[002] This invention relates to processes and intermediates for the preparation of protease inhibitors, in particular, serine protease inhibitors.

BACKGROUND OF THE INVENTION

[003] Infection by hepatitis C virus ("HCV") is a compelling human medical problem. HCV is recognized as the causative agent for most cases of non-A, non-B hepatitis, with an estimated human sero-prevalence of 3% globally (A. Alberti et al., "Natural History of Hepatitis C," *J. Hepatology*, 31 (Suppl. 1), pp. 17-24 (1999)). Nearly four million individuals may be infected in the United States alone. (M.J. Alter et al., "The Epidemiology of Viral Hepatitis in the United States," *Gastroenterol. Clin. North Am.*, 23, pp. 437-455 (1994); M. J. Alter "Hepatitis C Virus Infection in the United States," *J. Hepatology*, 31 (Suppl. 1), pp. 88-91 (1999)).

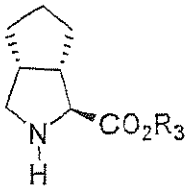
[004] Upon first exposure to HCV, only about 20% of infected individuals develop acute clinical hepatitis while others appear to resolve the infection spontaneously. In almost 70% of instances, however, the virus establishes a chronic infection that may persist for decades. (S. Iwarson, "The Natural Course of Chronic Hepatitis," *FEMS Microbiology Reviews*, 14, pp. 201-204 (1994); D. Lavanchy, "Global Surveillance and Control of Hepatitis C," *J. Viral Hepatitis*, 6, pp. 35-47 (1999)). Prolonged chronic infection can result in recurrent and progressively worsening liver inflammation, which often leads to more severe disease states such as cirrhosis and hepatocellular carcinoma. (M.C. Kew, "Hepatitis C and Hepatocellular Carcinoma", *FEMS Microbiology Reviews*, 14, pp. 211-220 (1994); I. Saito et. al., "Hepatitis C Virus Infection is Associated with the Development of Hepatocellular Carcinoma," *Proc. Natl. Acad. Sci. USA*, 87, pp. 6547-6549 (1990)). Unfortunately, there are no broadly effective treatments for the debilitating progression of chronic HCV.

[005] Compounds described as protease inhibitors, and in particular serine protease inhibitors, useful in the treatment of HCV infections are disclosed in WO 02/18369. Also disclosed therein in this publication are processes and intermediates for the preparation of these compounds, which lead to racemization of certain steric carbon centers. See, e.g.,

pages 223-22. There remains however, a need for economical processes for the preparation of these compounds.

SUMMARY

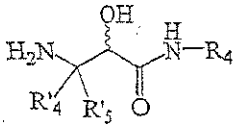
[006] The disclosure provides processes and intermediates for producing a bicyclic pyrrolidine derivative of Formula **1**, which is useful in producing protease inhibitors.



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In Formula **1**, R_3 is an acid protecting group which can be removed under acidic, basic, or hydrogenation conditions. Under acidic conditions, R_3 is, for example, *t*-butyl; under basic conditions, R_3 is, for example, methyl or ethyl; under hydrogenation conditions, R_3 is, for example, benzyl.

[007] Another embodiment of the disclosure includes processes and intermediates for the preparation of a compound of Formula **2**, which is also useful in producing protease inhibitors.



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In Formula 2,

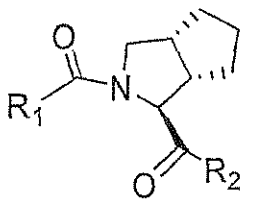
R_4 is H, an optionally substituted aliphatic, an optionally substituted cycloaliphatic, an optionally substituted aryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl;

R'_4 is H, an optionally substituted aliphatic, an optionally substituted aryl, an optionally substituted aralkyl or an optionally substituted heteroaralkyl; and

R'_5 is an optionally substituted aliphatic, an optionally substituted cycloaliphatic, an optionally substituted aryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl; or

R'_4 and R'_5 together with the atom to which they are attached may form a 3- to 7-membered optionally substituted cycloaliphatic ring.

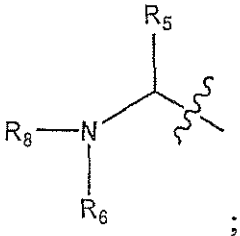
[008] The processes and intermediates described herein are also useful for a process for preparating a protease-inhibiting compound of Formula 3 shown below.



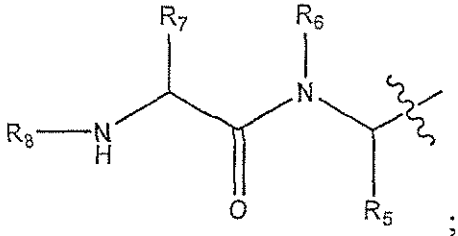
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Referring to Formula 3,

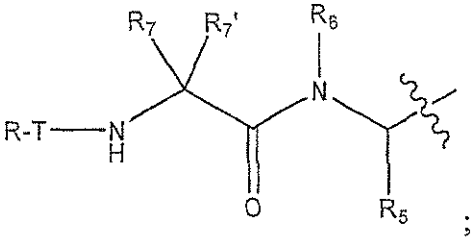
R_1 is RW-, P_2-, P_3-L_2-P_2-, or P_4-L_3-P_3-L_2-P_2-;



P_2- is ;



P_3-L_2-P_2 is ;



P_4-L_3-P_3–L_2-P_2 is ;

W is a bond, -CO-, -O-CO-, -NR^X-,-NR^X-CO-, -O-, or -S-;

T is -C(O)-, -O-C(O)-, -NHC(O)-, -C(O)C(O)-, or -SO_2-;

R is H, an optionally substituted aliphatic, an optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, an optionally substituted aryl, or an optionally substituted heteroaryl;

R_5 is H, an aliphatic, a cycloaliphatic, a heterocycloaliphatic, an aryl, or a heteroaryl; each of which, except for H, is optionally substituted with one or more substituents each independently selected from Group J, wherein Group J includes halo, cycloaliphatic, aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl, nitro, cyano, amido, amino, sulfonyl, sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, and hydroxy;

R_6 is an optionally substituted aliphatic, an optionally substituted heteroalkyl, an optionally substituted heteroaryl, an optionally substituted phenyl; or R_5 and R_6, together with

the atoms to which they are attached, may form a 5- to 7-membered, optionally substituted monocyclic heterocycle, or a 6- to 12-membered, optionally substituted bicyclic heterocycle, in which each heterocycle ring optionally contains an additional heteroatom selected from -O-, -S-, or -NR^X-;

Each of R_7 and R_7' is independently H, an optionally substituted aliphatic, an optionally substituted heteroalkyl, an optionally substituted heteroaryl, or an optionally substituted phenyl; or R_7 and R_7', together with the atom to which they are attached, may form a 3- to 7-membered cycloaliphatic or heterocycloaliphatic ring; or

R_7 and R_6, together with the atoms to which they are attached, may form a 5- to 7-membered optionally substituted monocyclic heterocycle, a 5- to 7-membered optionally substituted monocyclic aryl, a 6- to 12-membered optionally substituted bicyclic heterocycle, or a 6- to 12-membered optionally substituted bicyclic aryl, in which each heterocycle or aryl ring optionally contains an additional heteroatom selected from -O-, -S-, or -NR^X-; or

When R_5 and R_6 together with the atoms to which they are attached form a ring, R_7 and the ring system formed by R_5 and R_6 may form an 8- to 14-membered optionally substituted bicyclic fused ring system, wherein the bicyclic fused ring system may further fuse with an optionally substituted phenyl to form an optionally substituted 10- to 16-membered tricyclic fused ring system;

R_8 is H or a protecting group;

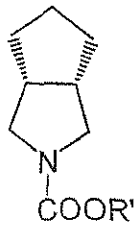
R^X is H, aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl;

R_2 is -(NH-$CR_4'R_5'$-C(O)-C(O))-NHR_4 or -(NH-$CR_4'R_5'$-CH(OH)-C(O))-NHR_4;

R_4 is H, an optionally substituted aliphatic, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, an optionally substituted aralkyl or an optionally substituted heteroaralkyl; and

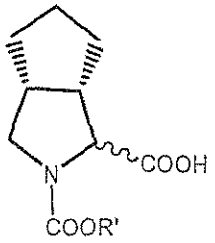
Each of R'_4 and R'_5 is independently H, an optionally substituted aliphatic, an optionally substituted cycloaliphatic, an optionally substituted heterocycloaliphatic, an optionally substituted aryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, or an optionally substituted heteroaralkyl; or R_4' and R_5', together with the atom to which they are attached, may form a 3- to 7-membered optionally substituted cycloaliphatic ring.

[009] In some embodiments, the process for preparing compounds of Formula 3 includes the step of carboxylation of an azabicyclooctane of formula **6**,



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wherein R' is a C_{1-5} alkyl, to give a racemic mixture of *cis*- and *trans*-octahydrocyclopenta[c]pyrrole-1-carboxylic acids of formula 7.



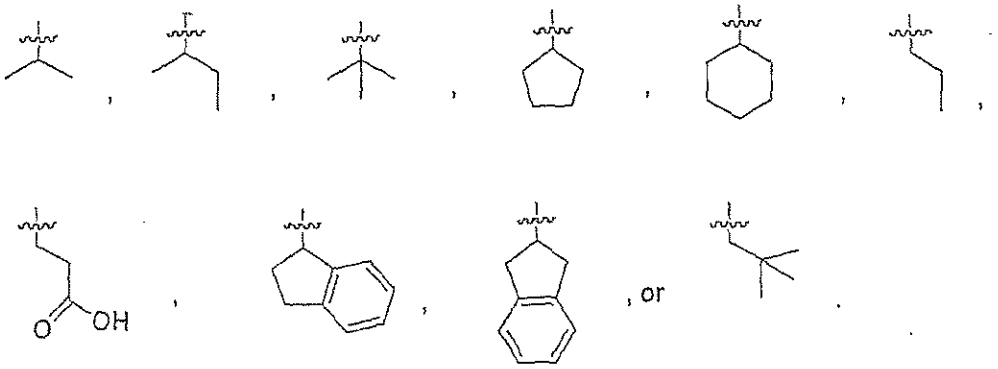
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[0010] In some embodiments, each of P_2, P_3 and P_4 is independently a bond, H, an optionally substituted aliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkoxy, an optionally substituted alkylsufanyl, an optionally substituted aralkoxy, an optionally substituted aralkylsulfanyl, an optionally substituted mono- or dialkylamino, an optionally substituted mono- or diarylamino, or an optionally substituted mono- or diheteroarylamino.

[0011] In some embodiments, each of L_2 and L_3 is independently a bond, -C(O)-, or -SO_2-.

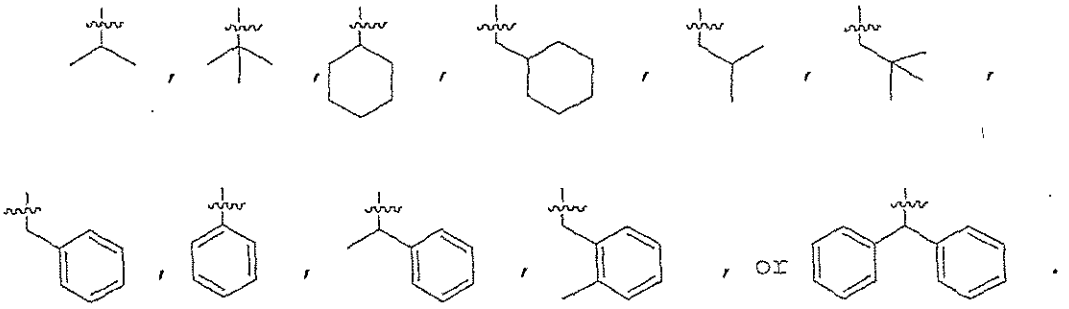
[0012] In some embodiments, R_5 is a C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-12} alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{3-10} heterocyclyl, C_{6-10} heterocyclyl-C_{1-6} alkyl, C_{5-10} heteroaryl, or C_{5-10} heteroaryl-C_{1-6} alkyl; each of which is optionally substituted with one to three substituents each independently selected from Group J; and up to three aliphatic carbon atoms in R_5 may be independently replaced by a heteroatom or group selected from O, NH, S, SO, or SO_2, in a chemically stable arrangement.

[0013] In some further embodiments, R_5 is

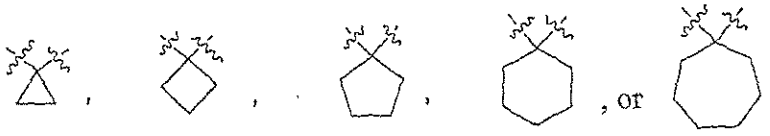


[0014] In some embodiments, R_7' is H; R_7 is a C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-12} alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{3-10} heterocyclyl, C_{6-10} heterocyclyl-C_{1-6} alkyl, C_{5-10} heteroaryl, or C_{5-10} heteroaryl-C_{1-6} alkyl; and R_1 is optionally substituted with one to three substituents each independently selected from Group J; and up to three aliphatic carbon atoms in R_1 may be replaced by a heteroatom or group selected from O, NH, S, SO, or SO_2 in a chemically stable arrangement.

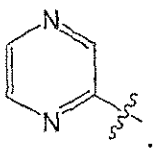
[0015] In some further embodiments, R_7 is



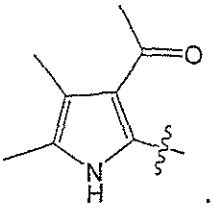
[0016] In still some further embodiments, R_7 and R_7', together with the atom to which they are attached, form



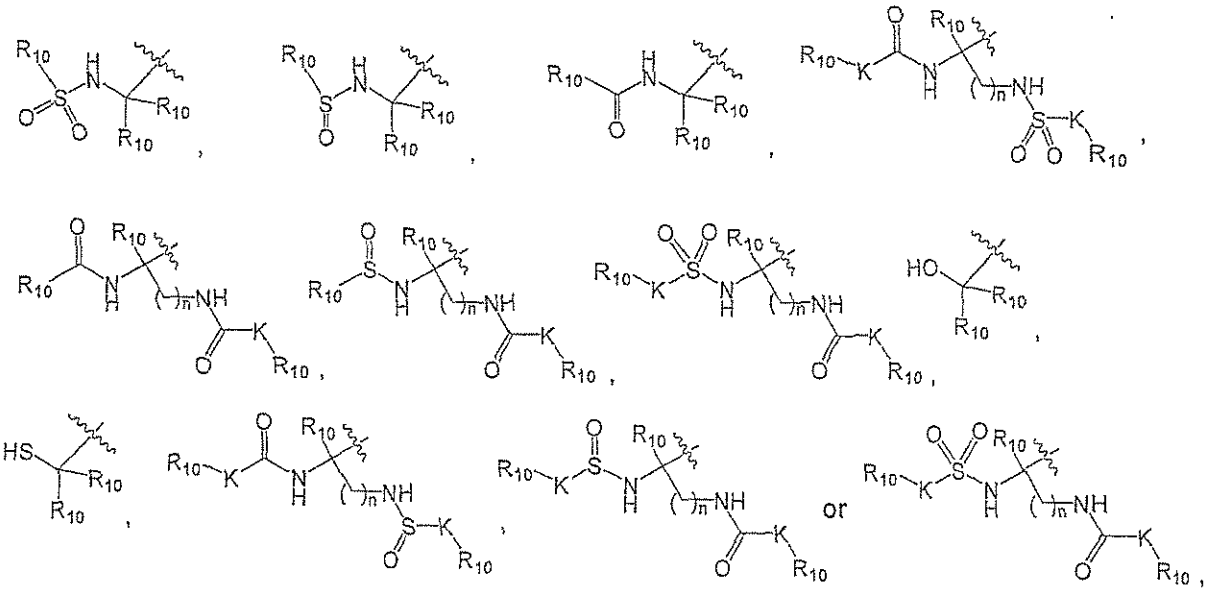
[0017] In some embodiments, R is a C_{6-10} aryl, C_{6-10} aryl-C_{1-12} aliphatic, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{3-10} cycloalkyl-C_{1-12} aliphatic, C_{3-10} cycloalkenyl-C_{1-12} aliphatic, C_{3-10} heterocyclyl, C_{3-10} heterocyclyl-C_{1-12} aliphatic, C_{5-10} heteroaryl, or C_{5-10} heteroaryl-C_{1-12} aliphatic; each of which is optionally substituted with one to three substituents each independently selected from Group J.

[0018] In some further embodiments, R is 

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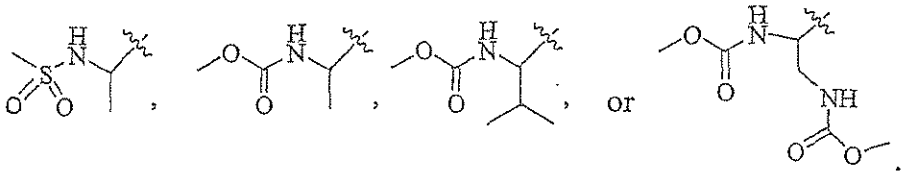
[0019] In still some further embodiments, R is .

[0020] In yet still some further embodiments, R is

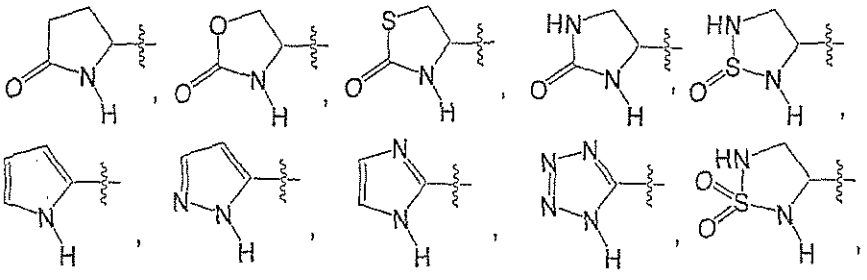


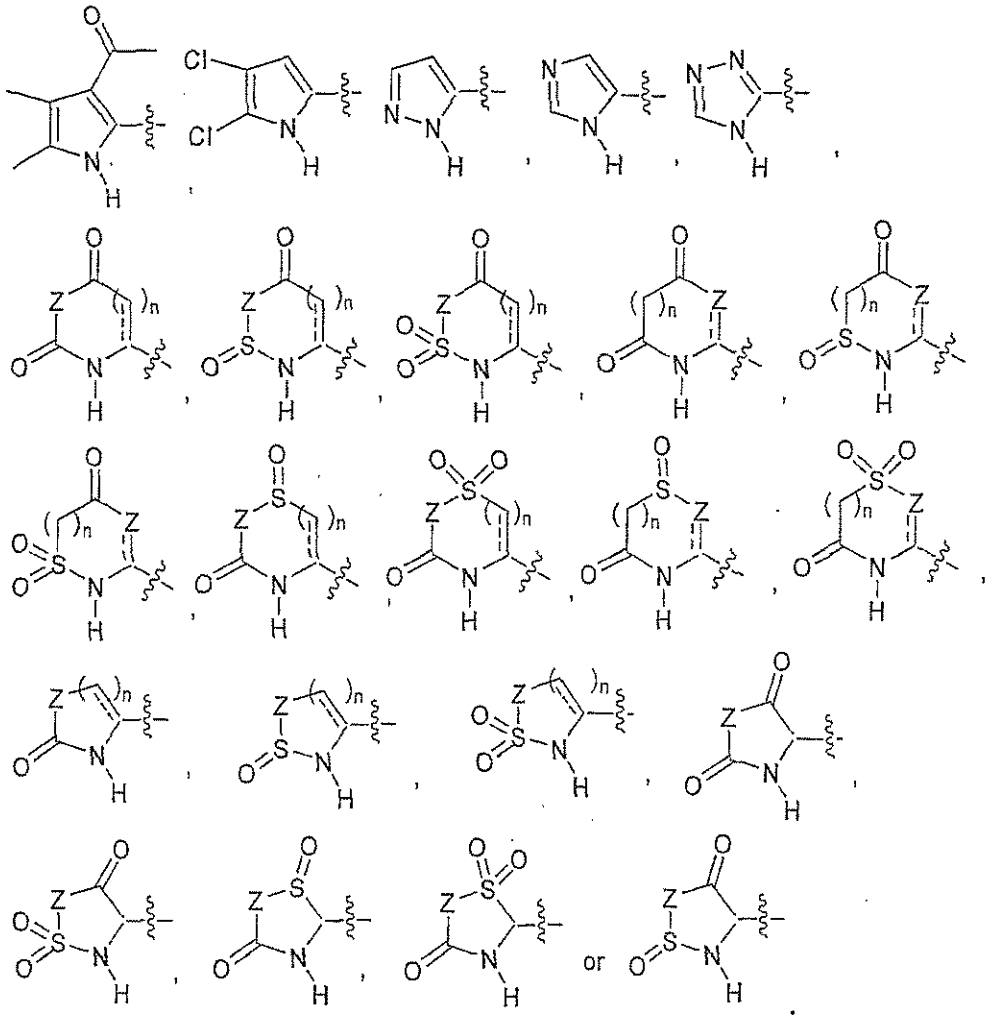
and R_{10} is H, C_{1-12} aliphatic, C_{6-10} aryl, C_{6-10} aryl-C_{1-12} aliphatic, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{3-10} cycloalkyl-C_{1-12} aliphatic, C_{3-10} cycloalkenyl-C_{1-12} aliphatic, C_{3-10} heterocyclyl, C_{3-10} heterocyclyl-C_{1-12} aliphatic, C_{5-10} heteroaryl, or C_{5-10} heteroaryl-C_{1-12} aliphatic.

[0021] In still some further embodiments, R is

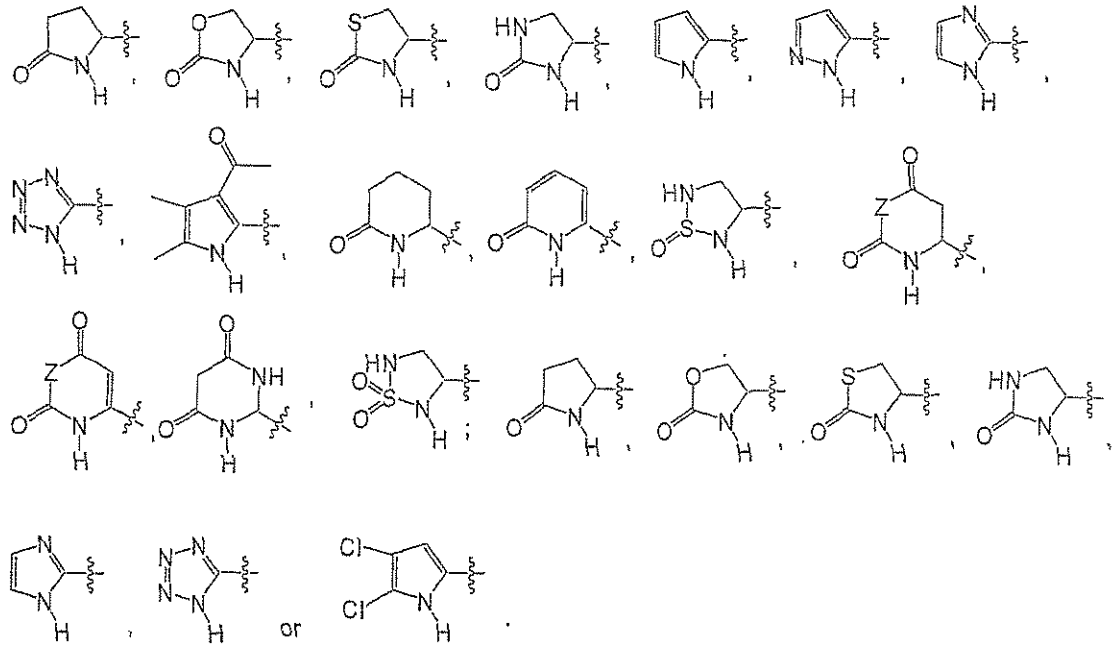


[0022] In yet still some further embodiments, R is





[0023] In some further embodiments, R is

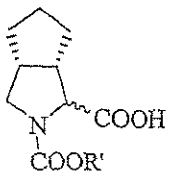


[0024] In some embodiments, the carboxylation step in the process for preparing compounds of Formula **3** includes forming a 2-anion of the compound of formula **6**



6

in the presence of a complexing agent, and then treating the 2-anion with carbon dioxide to produce a racemic mixture of *trans-/cis*-octahydrocyclopenta[c]pyrrole-1-carboxylic acids of formula 7



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[0025] In some further embodiments, the 2-anion of the compound of formula **6** is prepared by treating the compound of formula **6** with a strong lithium base in the presence of a complexing agent and an aprotic solvent.

[0026] In still some further embodiments, the base used in preparing the 2-anion is *sec*-butyl lithium.

[0027] In still some further embodiments, the complexing agent used in preparing the 2-anion is tetramethylethylenediamine, tetraethylethylenediamine, tetramethyl-1,2-cyclohexyldiamine, sparteine, or a 3,7-di(C_{1-6} alkyl)-3,7-diazabicyclo[3.3.1]nonane such as, for example, 3,7-di(*n*-propyl)-3,7-diazabicyclo[3.3.1]nonane.

[0028] In still some further embodiments, the complexing agent is tetramethylethylenediamine, tetraethylethylenediamine, tetramethyl-1,2-cyclohexyldiamine, or 3,7-di(C_{1-6} alkyl)-3,7-diazabicyclo[3.3.1]nonane.

[0029] In still some further embodiments, the complexing agent is D-sparteine.

[0030] In some embodiments, the *trans-/cis-* ratio in the racemic mixture of compounds of formula 7 is 1 to 2.

[0031] In some embodiments, the *trans-/cis-* ratio in the racemic mixture of compounds of formula 7 is 40 to 60.

[0032] In still some further embodiments, the *trans-/cis-* ratio in the racemic mixture of compounds of formula 7 is 1 to 1.

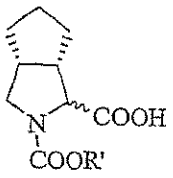
[0033] In still some further embodiments, the *trans-/cis-* ratio is 60 to 40.

[0034] In still some further embodiments, the *trans-/cis-* ratio is 80 to 20.

[0035] In still some further embodiments, the *trans-/cis-* ratio is 90 to 10.

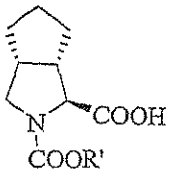
[0036] In still some further embodiments, the *trans-/cis-* ratio is greater than 98 to 2.

[0037] In some other embodiments, the process for preparing compounds of Formula **3** further includes equilibrating a *trans-/cis-* mixture of the compounds of formula 7



7

in the presence of a suitable base to produce a predominantly *trans-cis* racemic acid of formula **8**



8 (rac)

wherein the *trans-/cis-* ratio is greater than 80 to 20.

[0038] In some other embodiments, the process for preparing compounds of Formula **3** further includes equilibrating a *trans-/cis-* mixture of the compounds of formula 7 in the presence of a suitable base to produce a predominantly *trans-cis racemic* acid of formula **8** wherein the *trans-/cis-* ratio is greater than 90 to 10.

[0039] In some other embodiments, the process for preparing compounds of Formula **3** further includes equilibrating a *trans-/cis-* mixture of formula 7 in the presence of a suitable base to produce a predominantly *trans-cis racemic* acid of formula **8** wherein the *trans-/cis-* ratio is greater than 98 to 2.

[0040] In some further embodiments, the base used in equilibrating the *trans-/cis-* mixture of formula 7 is lithium hexamethyldisilazide, lithium di-isopropylamide, or lithium 2,2,6,6-tetramethylpiperidide.

[0041] In some further embodiments, the base is lithium hexamethyldisilazide.

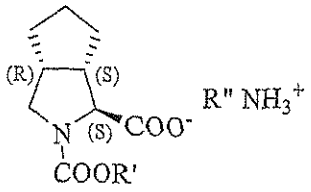
[0042] In some further embodiments, the base is *sec*-butyl lithium and the complexing agent is 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane to give a mixture of racemic *trans-/cis*-N-alkoxycarbonyl-octahydrocyclopenta[c]pyrrole-1-carboxylic acids of formula 7, in which the *trans-/cis-* ratio is greater than 90 to 10.

[0043] In some further embodiments, the *trans*-N-alkoxycarbonyl-octahydrocyclopenta[c]pyrrole-1-carboxylic acid is *trans*-N-*t*-butoxycarbonyl-octahydrocyclopenta[c]pyrrole-1-carboxylic acid.

[0044] In some other embodiments, the process for preparing compounds of Formula **3** further includes resolving racemic *trans*-N-alkoxycarbonyl-octahydrocyclopenta[c]pyrrole-1-

carboxylic acid to produce a (1S, 2S, 3R) *trans*-N-alkoxycarbonyl-octahydrocyclopenta[c]pyrrole-1-carboxylic acid.

[0045] In some further embodiments, the resolution of a racemic mixture of compounds includes the steps of **i)** forming a salt with an optically active base; and **ii)** crystallizing the salt formed by step **i)** to provide an optically active salt of formula **9.**

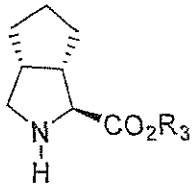


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[0046] In some further embodiments, the optically active base used in resolving a racemic mixture of compounds is (R) α-aminoethylbenzene.

[0047] In some further embodiments, the optically active base is (S) 1,2,3,4-tetrahydro-1-naphthylamine.

[0048] In some further embodiments, the process for preparing compounds of Formula **3** further includes the steps of esterifying the caboxylic acid of formula **9** with a compound containing the R_3 group; and removing the -COOR' protecting group to produce a compound of Formula **1,**

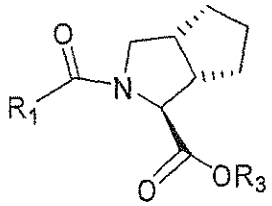


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wherein R_3 is an optionally substituted alkyl or aralkyl.

[0049] In still some further embodiments, R_3 is *t*-butyl.

[0050] In some embodiments, the process for preparing compounds of Formula **3** further includes reacting the amino-ester of Formula **1** with R_1COOH in the presence of a coupling reagent to produce a compound of Formula **1a.**



1a

[0051] In some embodiments, the reaction between the amino-ester of Formula **1** and R_1COOH can be carried out further in the presence of histamine, glycine, or lysine, in addition to a coupling agent.

[0052] In some further embodiments, R_1 is P_2-.

[0053] In some further embodiments, R_1 is P_3–L_2-P_2-.

[0054] In some further embodiments, R_1 is P_4-L_3-P_3–L_2-P_2-.

[0055] In some further embodiments, R_1 is RW-.

[0056] In some embodiments, the process for preparing compounds of Formula 3 further includes the steps of hydrolyzing the ester of a compound of Formula **1a**; to provide a carboxylic acid and reacting the carboxylic acid thus obtained with a compound containing the R_2 group, wherein R_2 is -(NH-$CR_4'R_5'$-CH(OH)C(O))-NHR_4, in the presence of a coupling reagent to produce the compound of Formula **3**.

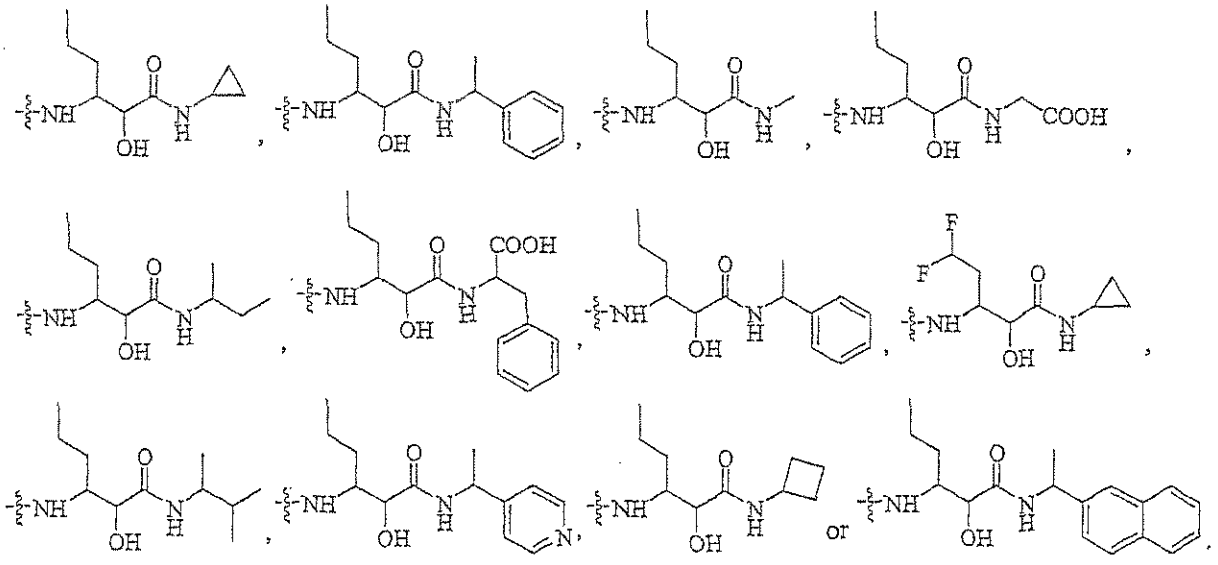
[0057] In some further embodiments, R_4 is H, an optionally substituted aliphatic, optionally substituted cycloaliphatic, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl;

R_4' is H, an optionally substituted aliphatic, an optionally substituted aryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl; and

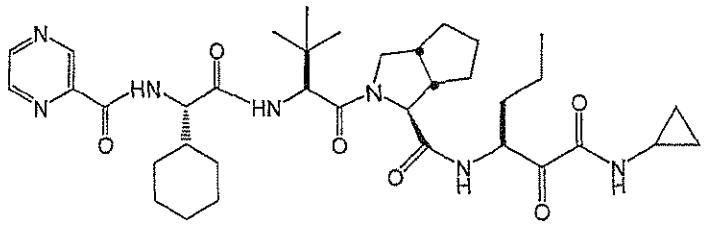
R_5' is H, an optionally substituted aliphatic, an optionally substituted cycloaliphatic, an optionally substituted aryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl; or

R_4' and R_5', together with the atom to which they are attached, form a 3- to 7-membered optionally substituted cycloaliphatic ring.

[0058] In some further embodiments, R_2 is



[0059] The disclosure further relates to a process for preparing a compound of Formula **4**



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[0060] In some embodiments, the process for preparing compounds of Formula **4** includes the steps of:

i) providing an N-alkoxycarbonyl-3-azabicyclo[3.3.0]octane;

ii) forming a 2-anion of the N-alkoxycarbonyl-3-azabicyclo[3.3.0]octane in the presence of a chelating agent;

iii) treating the anion of step **ii)** with carbon dioxide to produce a *cis-/trans-* mixture of N-alkoxycarbonyl-octahydrocyclopenta[c]pyrrole-1-carboxylic acids;

iv) treating the mixture of step **iii)** with a strong base to produce an essentially pure *trans-* N-alkoxycarbonyl-octahydrocyclopenta[c]pyrrole-1-carboxylic acid;

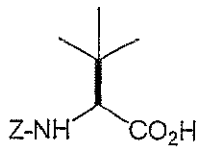
v) forming a salt of the carboxylic acid with an optically active amine;

vi) crystallizing the salt;

vii) esterifying the salt provided in step **vi)**;

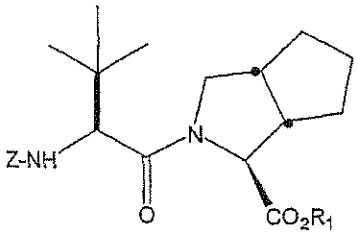
viii) removing the N-alkoxycarbonyl group to produce (1S,3aR,6aS)-*t*-butyl-octahydrocyclopenta[c]pyrrole-1-carboxylate, *t*-butyl ester;

ix) reacting the bicyclic of step **viii)** with a protected amino acid of formula **26**,



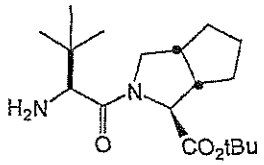
26

wherein Z is an amine protecting group, in the presence of a coupling reagent, to produce an amide-ester of formula **27**;



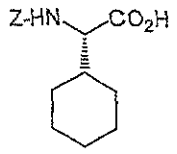
27

x) removing the protecting group Z from the amide-ester of step **ix)** to produce the amino compound of formula **28**;



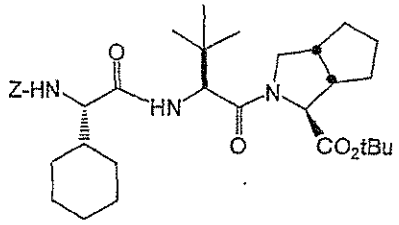
28

xi) reacting the amino compound of formula **28** with a protected amino acid of formula **29**



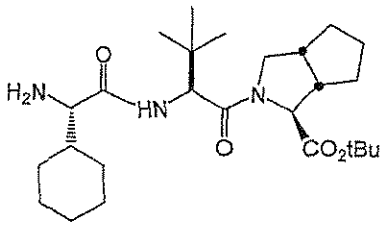
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in the presence of a coupling reagent to produce a tripeptide of formula **30**;



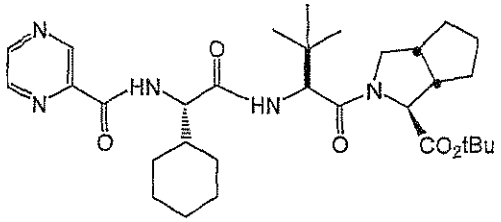
30

xii) removing the protecting group Z in the tripeptide of Formula 30 to produce a free amino-tripeptide of formula **31**;



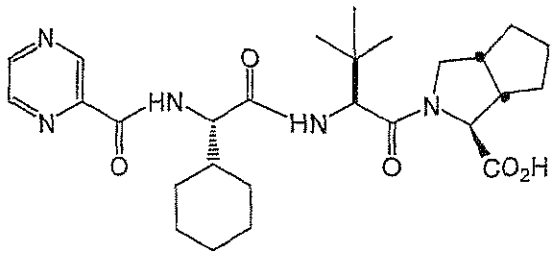
31

xiii) reacting the amino-tripeptide of formula **31** with pyrazine-2-carboxylic acid in the presence of a coupling reagent to produce an amide-tripeptide ester of formula **33**;



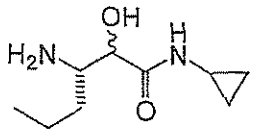
33

xiv) hydrolyzing the ester of the amide-tripeptide ester of formula **33** to produce an amide-tripeptide acid of formula **34**;



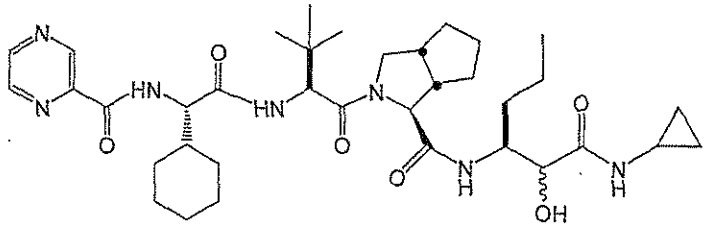
34

xv) reacting the amide-tripeptide acid of formula **34** with an aminohydroxy-amide of formula **18**



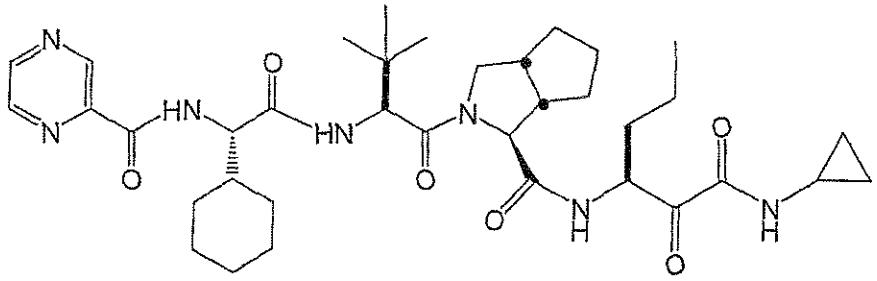
18

in the presence of a coupling reagent to produce a hydroxy-tetrapeptide of formula **35**; and



35

xvi) oxidizing the hydroxy group of formula **35** to produce the compound of Formula **4**.



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[0061] In some embodiments, the oxidizing reagent used in step **xvi)** described above is sodium hypochlorite, and the oxidation is carried out in the presence of 2,2,6,6-tetramethylpiperidinyloxy free radical (TEMPO).

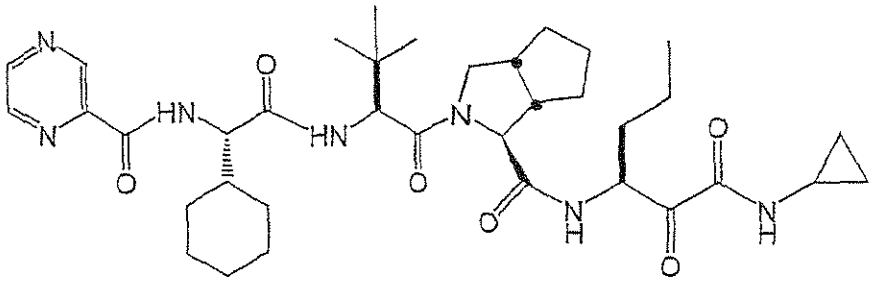
[0062] In some other embodiments, the oxidizing reagent used in step **xvi)** described above is 1,1-dihydro-1,1,1-triacetoxy-1,2-benzoiodooxol-3(1H)-one.

[0063] In some further embodiments, the process further includes dissolving the compound of Formula **4** in an organic solvent to obtain its solution, and then adding an acid to the solution. A suitable organic solvent can be any solvent in which the compound of Formula 4

dissolves, e.g., methylene chloride. The acid can be any acid, inorganic or organic, e.g., acetic acid or propionic acid.

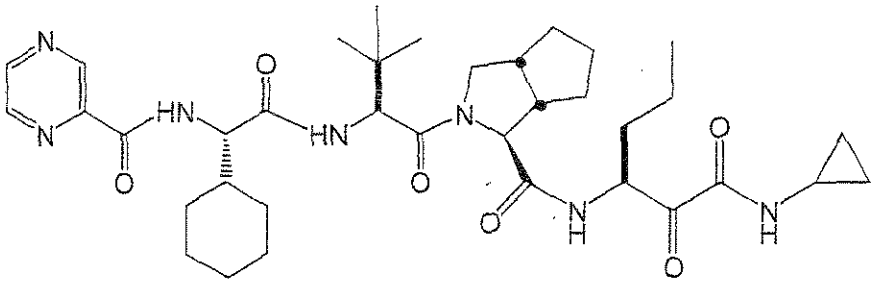
[0064] In still some further embodiments, the process further includes concentrating the solution of the compound of Formula 4 to obtain the compound in a solid form. Such a concentrating process can be, e.g., distillation of the solvent under reduced pressure (e.g., vacuum) by natural evaporation of the solvent. The solid form in which hthe compound of Formula 4 is obtained can be, e.g., crystalline or semicrystalline, and can be of higher purity than that before being dissolved into an organic solvent and then concentrated in acid condition.

[0065] As such, the disclosure also relates to process of purifying the compound of Formula 4.



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[0065a] In one aspect, there is provided a process of purifying the compound of Formula 4, comprising:



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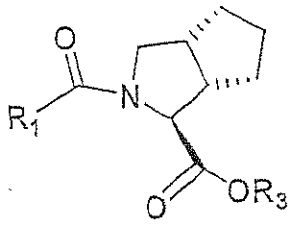
a) dissolving the compound of Formula 4 in an organic solvent to obtain a solution of the compound of Formula 4,

b) adding an acid to the solution of the compound of Formula 4, and

c) concencentrating the solution of the compound of Formula 4 to obtain the compound in a solid form.

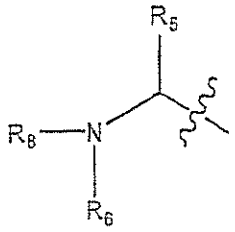
[0066] In some embodiments, the process includes first dissolving the compound of Formula 4 in an organic solvent to obtain its solution, adding an acid to the solution of the compound of Formula 4, and then concencentrating the solution of the compound of Formula 4 to obtain the compound in a solid form. Examples of sutiable organic solvents, acids, and solid forms have been provided above.

[0067] The disclosure further feathers compounds of Formula **1a**,



1a

Wherein R_1 is P_2-;



P_2- is :

R_5 is H, an aliphatic, a cycloaliphatic, a heterocycloaliphatic, an aryl, or a heteroaryl; each of which, except for H, is optionally substituted with one or more substituents each independently selected from Group J consisting of halo, cycloaliphatic, aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl, nitro, cyano, amido, amino, sulfonyl, sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, and hydroxy;

R_6 is an optionally substituted aliphatic, an optionally substituted heteroalkyl, an optionally substituted heteroaryl, an optionally substituted phenyl; or R_5 and R_6, together with the atoms to which they are attached, may form a 5- to 7-membered, optionally substituted monocyclic heterocycle, or a 6- to 12-membered, optionally substituted bicyclic heterocycle, in which each heterocycle ring optionally contains an additional heteroatom selected from -O-, -S-, or -NR^X-;

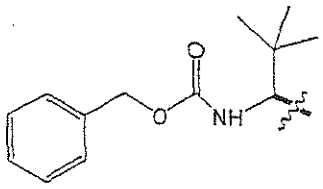
R^X is H, aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl;

R_8 is H or a protecting group; and

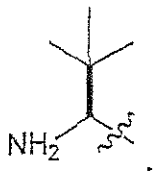
R_3 is an optionally substituted alkyl.

[0068] In some embodiments, R_3 is *t*-butyl.

[0069] In some other embodiments, P_2- is

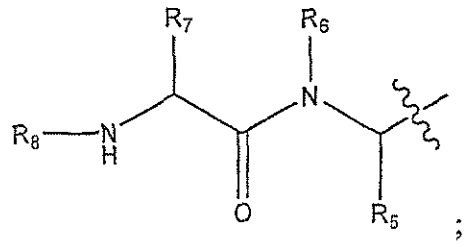


[0070] In some further embodiments, P_2- is



[0071] The disclosure further relates to compounds of Formula **1a** show above, in which

R_1 is P_3-L_2-P_2-;

P_3-L_2-P_2- is  ;

R_5 is H, an aliphatic, a cycloaliphatic, a heterocycloaliphatic, an aryl, or a heteroaryl; each of which, except for H, is optionally substituted with one or more substituents each independently selected from Group J consisting of halo, cycloaliphatic, aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl, nitro, cyano, amido, amino, sulfonyl, sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, and hydroxy;

R_6 is an optionally substituted aliphatic, an optionally substituted heteroalkyl, an optionally substituted heteroaryl, an optionally substituted phenyl; or R_5 and R_6, together with the atoms to which they are attached, may form a 5- to 7-membered, optionally substituted monocyclic heterocycle, or a 6- to 12-membered, optionally substituted bicyclic heterocycle, in which each heterocycle ring optionally contains an additional heteroatom selected from -O-, -S-, or -NR^X-;

R_7 is H, an optionally substituted aliphatic, an optionally substituted heteroalkyl, an optionally substituted heteroaryl, or an optionally substituted phenyl; or

R_7 and R_6, together with the atoms to which they are attached, may form a 5- to 7-membered optionally substituted monocyclic heterocycle, a 5- to 7-membered optionally substituted monocyclic aryl, a 6- to 12-membered optionally substituted bicyclic heterocycle, or a 6- to 12-membered optionally substituted bicyclic aryl, in which each heterocycle or aryl ring optionally contains an additional heteroatom selected from -O-, -S-, or -NR^X-; or

When R_5 and R_6 together with the atoms to which they are attached form a ring, R_7 and the ring system formed by R_5 and R_6 may form an 8- to 14-membered optionally substituted bicyclic fused ring system, wherein the bicyclic fused ring system may further fuse with an optionally substituted phenyl to form an optionally substituted 10- to 16-membered tricyclic fused ring system;

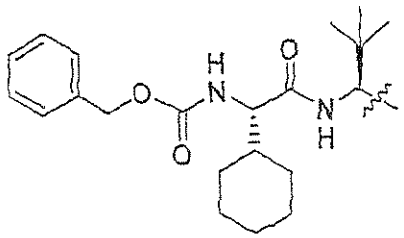
R^X is H, aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl;

R_8 is H or a protecting group; and

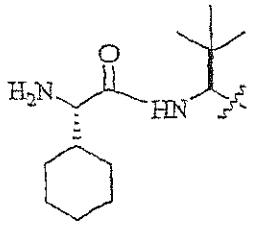
R_3 is an optionally substituted alkyl.

[0072] In some embodiments, R_3 is *t*-butyl.

[0073] In some embodiments, P_3-L_2-P_2- is



[0074] In some embodiments, P_3-L_2-P_2- is



[0075] Also within the scope of the present disclosure are the compounds of 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane, and 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonan-9-one.

DESCRIPTION OF THE INVENTION

I. *Definitions*

[0076] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described by Thomas Sorrell in Organic Chemistry, University Science Books, Sausalito (1999), and by M.B. Smith and J. March in Advanced Organic Chemistry, 5th Ed., John Wiley & Sons, New York (2001), the entire contents of which are hereby incorporated by reference.

[0077] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention.

[0078] As used herein the term "aliphatic" encompasses the terms alkyl, alkenyl, and alkynyl, each of which is optionally substituted as set forth below.

[0079] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-8 (e.g., 1-6 or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl,

be substituted (i.e., optionally substituted) with one or more substituents selected from the group J ("Group J") which consists of halo, cycloaliphatic (e.g., cycloalkyl or cycloalkenyl), heterocycloaliphatic (e.g., heterocycloalkyl or heterocycloalkenyl), aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl (e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl), nitro, cyano, amido (e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl), amino (e.g., aliphaticamino, cycloaliphaticamino, or heterocycloaliphaticamino), sulfonyl (e.g., aliphatic-SO_2-), sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, and hydroxy. Without limitation, some examples of substituted alkyls include carboxyalkyl (such as HOOC-alkyl, alkoxycarbonylalkyl, and alkylcarbonyloxyalkyl), cyanoalkyl, hydroxyalkyl, alkoxyalkyl, acylalkyl, aralkyl, (alkoxyaryl)alkyl, (sulfonylamino)alkyl (such as (alkyl-SO_2-amino)alkyl), aminoalkyl, amidoalkyl, (cycloaliphatic)alkyl, or haloalkyl.

[0080] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, allyl, isoprenyl, 2-butenyl, and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents selected from Group J such as halo, cycloaliphatic (e.g., cycloalkyl or cycloalkenyl), heterocycloaliphatic (e.g., heterocycloalkyl or heterocycloalkenyl), aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl (e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl), nitro, cyano, amido (e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl), amino (e.g., aliphaticamino, cycloaliphaticamino, heterocycloaliphaticamino, or aliphaticsulfonylamino), sulfonyl (e.g., alkyl-SO_2-, cycloaliphatic-SO_2-, or aryl-SO_2-), sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkenyls include cyanoalkenyl,

alkoxyalkenyl, acylalkenyl, hydroxyalkenyl, aralkenyl, (alkoxyaryl)alkenyl, (sulfonylamino)alkenyl (such as (alkyl-SO_2-amino)alkenyl), aminoalkenyl, amidoalkenyl, (cycloaliphatic)alkenyl, or haloalkenyl.

[0081] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl and butynyl. An alkynyl group can be optionally substituted with one or more substituents selected from Group J such as aroyl, heteroaroyl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, nitro, carboxy, cyano, halo, hydroxy, sulfo, mercapto, sulfanyl (e.g., aliphaticsulfanyl or cycloaliphaticsulfanyl), sulfinyl (e.g., aliphaticsulfinyl or cycloaliphaticsulfinyl), sulfonyl (e.g., aliphatic-SO_2-, aliphaticamino-SO_2-, or cycloaliphatic-SO_2-), amido (e.g., aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, cycloalkylcarbonylamino, arylaminocarbonyl, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (cycloalkylalkyl)carbonylamino, heteroaralkylcarbonylamino, heteroarylcarbonylamino or heteroarylaminocarbonyl), urea, thiourea, sulfamoyl, sulfamide, alkoxycarbonyl, alkylcarbonyloxy, cycloaliphatic, heterocycloaliphatic, aryl, heteroaryl, acyl (e.g., (cycloaliphatic)carbonyl or (heterocycloaliphatic)carbonyl), amino (e.g., aliphaticamino), sulfoxy, oxo, carboxy, carbamoyl, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, or (heteroaryl)alkoxy.

[0082] As used herein, an "amido" encompasses both "aminocarbonyl" and "carbonylamino." These terms, when used alone or in connection with another group, refer to an amido group such as -$N(R^X)$-C(O)-R^Y or -C(O)-$N(R^X)_2$, when used terminally; and they refer to an amide group such as -C(O)-$N(R^X)$- or -$N(R^X)$-C(O)- when used internally, wherein R^X and R^Y are defined below. Examples of amido groups include alkylamido (such as alkylcarbonylamino or alkylaminocarbonyl), (heterocycloaliphatic)amido, (heteroaralkyl)amido, (heteroaryl)amido, (heterocycloalkyl)alkylamido, arylamido, aralkylamido, (cycloalkyl)alkylamido, or cycloalkylamido.

[0083] As used herein, an "amino" group refers to -NR^XR^Y, wherein each of R^X and R^Y is independently hydrogen, aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or

(heteroaraliphatic)carbonyl, each of which being defined herein and being optionally substituted. Examples of amino groups include alkylamino, dialkylamino, or arylamino. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR^X-$. R^X has the same meaning as defined above.

[0084] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl" refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl); and tricyclic (e.g., fluorenyl tetrahydrofluorenyl, or tetrahydroanthracenyl, anthracenyl) ring systems in which the monocyclic ring system is aromatic or at least one of the rings in a bicyclic or tricyclic ring system is aromatic. The bicyclic and tricyclic groups include benzofused 2- to 3-membered carbocyclic rings. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents such as aliphatic (e.g., alkyl, alkenyl, or alkynyl); cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); nitro; carboxy; amido; acyl (e.g., aliphaticcarbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphatic-SO_2- or amino-SO_2-); sulfinyl (e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-); sulfanyl (e.g., aliphatic-S-); cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, an aryl can be unsubstituted.

[0085] Non-limiting examples of substituted aryls include haloaryl (e.g., mono-, di- (such as *p,m*-dihaloaryl), or (trihalo)aryl); (carboxy)aryl (e.g., (alkoxycarbonyl)aryl, ((aralkyl)carbonyloxy)aryl, or (alkoxycarbonyl)aryl); (amido)aryl (e.g., (aminocarbonyl)aryl, (((alkylamino)alkyl)aminocarbonyl)aryl, (alkylcarbonyl)aminoaryl, (arylaminocarbonyl)aryl, or (((heteroaryl)amino)carbonyl)aryl); aminoaryl (e.g., ((alkylsulfonyl)amino)aryl or ((dialkyl)amino)aryl); (cyanoalkyl)aryl; (alkoxy)aryl; (sulfamoyl)aryl (e.g., (aminosulfonyl)aryl); (alkylsulfonyl)aryl; (cyano)aryl; (hydroxyalkyl)aryl; ((alkoxy)alkyl)aryl; (hydroxy)aryl, ((carboxy)alkyl)aryl; (((dialkyl)amino)alkyl)aryl; (nitroalkyl)aryl; (((alkylsulfonyl)amino)alkyl)aryl; ((heterocycloaliphatic)carbonyl)aryl; ((alkylsulfonyl)alkyl)aryl; (cyanoalkyl)aryl; (hydroxyalkyl)aryl; (alkylcarbonyl)aryl; alkylaryl; (trihaloalkyl)aryl; *p*-amino-*m*-alkoxycarbonylaryl; *p*-amino-*m*-cyanoaryl; *p*-halo-*m*-aminoaryl; or (*m*-(heterocycloaliphatic)-*o*-(alkyl))aryl.

[0086] As used herein, an "araliphatic" group, such as "aralkyl," refers to an aliphatic group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. "Aliphatic," "alkyl," and "aryl" are defined herein. An example of araliphatic such as an aralkyl group is benzyl.

[0087] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" have been defined above. An example of an aralkyl group is benzyl. An aralkyl is optionally substituted with one or more substituents such as aliphatic (e.g., substituted or unsubstituted alkyl, alkenyl, or alkynyl, including carboxyalkyl, hydroxyalkyl, or haloalkyl such as trifluoromethyl), cycloaliphatic (e.g., substituted or unsubstituted cycloalkyl or cycloalkenyl), (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amido (e.g., aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino), cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0088] As used herein, a "bicyclic ring system" includes 8- to 12- (e.g., 9, 10, or 11) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[0089] As used herein, a "cycloaliphatic" group encompasses a "cycloalkyl" group and a "cycloalkenyl" group, each of which being optionally substituted as set forth below.

[0090] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono- or bicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, adamantyl, azacycloalkyl, or ((aminocarbonyl)cycloalkyl)cycloalkyl. A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, cyclopentenyl, bicyclo[2.2.2]octenyl, or bicyclo[3.3.1]nonenyl. A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents selected

from Group J such as aliphatic (e.g., alkyl, alkenyl, or alkynyl), cycloaliphatic, (cycloaliphatic) aliphatic, heterocycloaliphatic, (heterocycloaliphatic) aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido (e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or ((heteroaraliphatic)carbonylamino), nitro, carboxy (e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy), acyl ((e.g., (cycloaliphatic)carbonyl, (cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl), cyano, halo, hydroxy, mercapto, sulfonyl (e.g., alkyl-SO_2- and aryl-SO_2-), sulfinyl ((e.g., alkyl-S(O)-), sulfanyl (e.g., alkyl-S-), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0091] As used herein, "cyclic moiety" includes cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been defined previously.

[0092] As used herein, the term "heterocycloaliphatic" encompasses a heterocycloalkyl group and a heterocycloalkenyl group, each of which being optionally substituted as set forth below.

[0093] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono- or bicylic (fused or bridged) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl, isoxazolidyl, morpholinyl, thiomorpholyl, octahydrobenzofuryl, octahydrochromenyl, octahydrothiochromenyl, octahydroindolyl, octahydropyrindinyl, decahydroquinolinyl, octahydrobenzo[*b*]thiopheneyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, anad 2,6-dioxa-tricyclo[3.3.1.$0^{3,7}$]nonyl. A monocyclic heterocycloalkyl group can be fused with a phenyl moiety such as tetrahydroisoquinoline. A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicylic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Monocyclic and bicycloheteroaliphatics are numbered according to standard chemical nomenclature.

[0094] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents selected from Group *J* such as aliphatic (e.g., alkyl, alkenyl, or alkynyl), cycloaliphatic, (cycloaliphatic)aliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic,

aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido (e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic) aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic) aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino), nitro, carboxy (e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy), acyl ((e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl), nitro, cyano, halo, hydroxy, mercapto, sulfonyl (e.g., alkylsulfonyl or arylsulfonyl), sulfinyl (e.g., alkylsulfinyl), sulfanyl (e.g., alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl)).

[0095] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system having 4 to 15 ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof) and in which the monocyclic ring system is aromatic or at least one of the rings in the bicyclic or tricyclic ring systems is aromatic. A heteroaryl group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two 4 to 8 membered heterocycloaliphatic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidinyl, pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl,cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1,8-naphthyridyl.

[0096] Without limitation, monocyclic heteroaryls include furyl, thiophenyl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4-H-pranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature.

[0097] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, isoquinolinyl, indolizyl, isoindolyl, indolyl, benzo[*b*]furyl, bexo[*b*]thiophenyl, indazolyl, benzimidazyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature.

[0098] A heteroaryl is optionally substituted with one or more substituents such as aliphatic (e.g., alkyl, alkenyl, or alkynyl); cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic or heterocyclic ring of a bicyclic or tricyclic heteroaryl); carboxy; amido; acyl (e.g., aliphaticcarbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphaticsulfonyl or aminosulfonyl); sulfinyl (e.g., aliphaticsulfinyl); sulfanyl (e.g., aliphaticsulfanyl); nitro; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, a heteroaryl can be unsubstituted.

[0099] Non-limiting examples of substituted heteroaryls include (halo)heteroaryl (e.g., mono- and di-(halo)heteroaryl); (carboxy)heteroaryl (e.g., (alkoxycarbonyl)heteroaryl); cyanoheteroaryl; aminoheteroaryl (e.g., ((alkylsulfonyl)amino)heteroaryl and((dialkyl)amino)heteroaryl); (amido)heteroaryl (e.g., aminocarbonylheteroaryl, ((alkylcarbonyl)amino)heteroaryl, ((((alkyl)amino)alkyl)aminocarbonyl)heteroaryl, (((heteroaryl)amino)carbonyl)heteroaryl, ((heterocycloaliphatic)carbonyl)heteroaryl, or ((alkylcarbonyl)amino)heteroaryl); (cyanoalkyl)heteroaryl; (alkoxy)heteroaryl; (sulfamoyl)heteroaryl (e.g., (aminosulfonyl)heteroaryl); (sulfonyl)heteroaryl ((e.g., (alkylsulfonyl)heteroaryl); (hydroxyalkyl)heteroaryl; (alkoxyalkyl)heteroaryl; (hydroxy)heteroaryl; ((carboxy)alkyl)heteroaryl; (((dialkyl)amino)alkyl)heteroaryl; (heterocycloaliphatic)heteroaryl; (cycloaliphatic)heteroaryl; (nitroalkyl)heteroaryl; (((alkylsulfonyl)amino)alkyl)heteroaryl; ((alkylsulfonyl)alkyl)heteroaryl; (cyanoalkyl)heteroaryl; (acyl)heteroaryl (e.g., (alkylcarbonyl)heteroaryl); (alkyl)heteroaryl; and (haloalkyl)heteroaryl (e.g., trihaloalkylheteroaryl).

[00100] A "heteroaraliphatic" (such as a heteroaralkyl group) as used herein, refers to an aliphatic group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. "Aliphatic," "alkyl," and "heteroaryl" have been defined above.

[00101] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above. A heteroaralkyl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy,

aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00102] As used herein, an "acyl" group refers to a formyl group or R^X-C(O)- (such as alkyl-C(O)-, also referred to as "alkylcarbonyl") wherein R^X and "alkyl" have been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[00103] As used herein, an "aroyl" or "heteroaroyl" refers to an aryl-C(O)- or a heteroaryl-C(O)-. The aryl and heteroaryl portion of the aroyl or heteroaroyl is optionally substituted as previously defined.

[00104] As used herein, an "alkoxy" group refers to an alkyl-O- group wherein "alkyl" has been defined previously.

[00105] As used herein, a "carbamoyl" group refers to a group having the structure -O-CO-NR^XR^Y or -NR^X-CO-O-R^Z wherein R^X and R^Y have been defined above and R^Z can be aliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic.

[00106] As used herein, a "carboxy" group refers to -COOH, -$COOR^X$, -OC(O)H, -$OC(O)R^X$ when used as a terminal group; or -OC(O)- or -C(O)O- when used as an internal group.

[00107] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1-3 halogen. For instance, the term haloalkyl includes the group -CF_3.

[00108] As used herein, a "mercapto" group refers to -SH.

[00109] As used herein, a "sulfo" group refers to -SO_3H or -SO_3R^X when used terminally or -$S(O)_3$- when used internally.

[00110] As used herein, a "sulfamide" group refers to the structure -NR^X-$S(O)_2$-NR^YR^Z when used terminally and -NR^X-$S(O)_2$-NR^Y- when used internally, wherein R^X, R^Y, and R^Z have been defined above.

[00111] As used herein, a "sulfonamide" group refers to the structure -$S(O)_2$-NR^XR^Y or -NR^X-$S(O)_2$-R^Z when used terminally; or -$S(O)_2$-NR^X- or -NR^X -$S(O)_2$- when used internally, wherein R^X, R^Y, and R^Z are defined above.

[00112] As used herein a "sulfanyl" group refers to -S-R^X when used terminally and -S- when used internally, wherein R^X has been defined above. Examples of sulfanyl include aliphatic-S-, cycloaliphatic-S-, aryl-S-, or the like.

[00113] As used herein a "sulfinyl" group refers to -S(O)-R^X when used terminally and -S(O)- when used internally, wherein R^X has been defined above. Exemplary sulfinyl groups

include aliphatic-S(O)-, aryl-S(O)-, (cycloaliphatic(aliphatic)) -S(O)-, cycloalkyl-S(O)-, heterocycloaliphatic-S(O)-, heteroaryl-S(O)-, or the like.

[00114] As used herein, a "sulfonyl" group refers to-$S(O)_2$-R^X when used terminally and -$S(O)_2$- when used internally, wherein R^X has been defined above. Exemplary sulfonyl groups include aliphatic-$S(O)_2$-, aryl-$S(O)_2$-, ((cycloaliphatic(aliphatic))-$S(O)_2$-, cycloaliphatic-$S(O)_2$-, heterocycloaliphatic-$S(O)_2$-, heteroaryl-$S(O)_2$-, (cycloaliphatic(amido(aliphatic)))-$S(O)_2$- or the like.

[00115] As used herein, a "sulfoxy" group refers to -O-SO-R^X or -SO-O-R^X, when used terminally and -O-S(O)- or -S(O)-O- when used internally, wherein R^X has been defined above.

[00116] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine, or iodine.

[00117] As used herein, an "alkoxycarbonyl" group, which is encompassed by "carboxy," used alone or in combination with another group, refers to a group such as alkyl-O-C(O)-.

[00118] As used herein, an "alkoxyalkyl"group refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[00119] As used herein, a "carbonyl" group refer to -C(O)-.

[00120] As used herein, an "oxo" group refers to =O.

[00121] As used herein, an "aminoalkyl" group refers to the structure $(R^X)_2N$-alkyl-.

[00122] As used herein, a "cyanoalkyl" group refers to the structure (NC)-alkyl-.

[00123] As used herein, a "urea" group refers to the structure -NR^X-CO-NR^YR^Z and a "thiourea" group refers to the structure -NR^X-CS-NR^YR^Z when used terminally and -NR^X-CO-NR^Y- or
-NR^X-CS-NR^Y- when used internally, wherein R^X, R^Y, and R^Z have been defined above.

[00124] As used herein, a "guanidine" group refers to the structure -N=C(N(R^XR^Y))N(R^XR^Y) or
-NR^X-C(=NR^X)NR^XR^Y, wherein R^X and R^Y have been defined above.

[00125] As used herein, an "amidino" group refers to the structure -C=(NR^X)N(R^XR^Y), wherein R^X and R^Y have been defined above.

[00126] In general, the term "vicinal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to adjacent carbon atoms.

[00127] In general, the term "geminal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to the same carbon atom.

[00128] The terms "terminally" and "internally" refer to the location of a group within a substituent. A group is terminal when the group is present at the end of the substituent not further bonded to the rest of the chemical structure. Carboxyalkyl, i.e., $R^XO(O)C$-alkyl is an example of a carboxy group used terminally. A group is internal when the group is present in the middle of a substituent to at the end of the substituent bound to the rest of the chemical structure. Alkylcarboxy (e.g., alkyl-C(O)-O- or alkyl-O-C(O)-) and alkylcarboxyaryl (e.g., alkyl-C(O)-O-aryl- or alkyl-O-C(O)-aryl-) are examples of carboxy groups used internally.

[00129] As used herein, a "cyclic" group includes a mono-, bi-, and tri-cyclic ring system, such as cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been defined above.

[00130] As used herein, a "bridged bicyclic ring system" refers to a bicyclic heterocyclicalipahtic ring system or bicyclic cycloaliphatic ring system in which the rings are bridged. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.2.3]nonyl, 2-oxabicyclo[2.2.2]octyl, 1-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.$0^{3,7}$]nonyl. A bridged bicyclic ring system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00131] As used herein, an "aliphatic chain" refers to a branched or straight aliphatic group (e.g., alkyl groups, alkenyl groups, or alkynyl groups). A straight aliphatic chain has the structure $-(CH_2)_v-$, where v is 1-6. A branched aliphatic chain is a straight aliphatic chain that is substituted with one or more aliphatic groups. A branched aliphatic chain has the structure $-(CHQ)_v-$ where Q is hydrogen or an aliphatic group; however, Q shall be an aliphatic group in at least one instance. The term aliphatic chain includes alkyl chains, alkenyl chains, and alkynyl chains, where alkyl, alkenyl, and alkynyl are defined above.

[00132] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds of the invention can

optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables R_1, R_2, and R_3, as well as other variables, encompass specific groups, such as alkyl and aryl. Unless otherwise noted, each of the specific groups for the variables R_1, R_2, and R_3, and other variables contained therein can be optionally substituted with one or more substituents described herein. Each substituent of a specific group is further optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, cycloaliphatic, heterocycloaliphatic, heteroaryl, haloalkyl, and alkyl. For instance, an alkyl group can be substituted with alkylsulfanyl and the alkylsulfanyl can be optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino can be optionally substituted with one to three of halo, cyano, alkoxy, hydroxy, nitro, haloalkyl, and alkyl. When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkxoy groups can form a ring together with the atom(s) to which they are bound.

[00133] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. Combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[00134] The phrase "stable or chemically feasible," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[00135] As used herein, an effective amount is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and

humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, "patient" refers to a mammal, including a human.

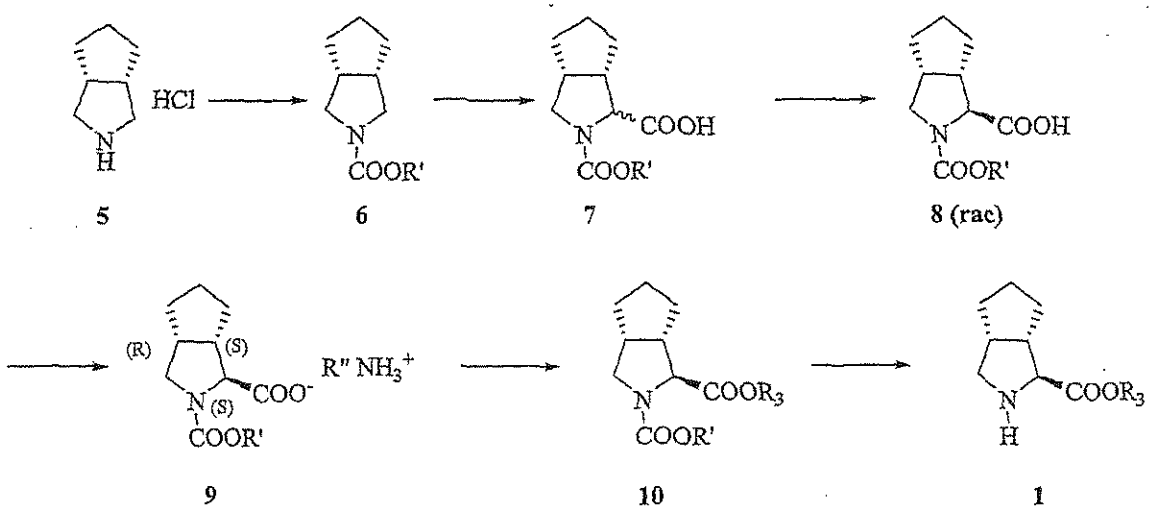
[00136] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[00137] As used herein, EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, HOBt is 1-hydroxybenzotriazole, HOSuc is N-hydroxysuccinimide, THF is tetrahydrofuran, TFA is trifluoroacetic acid, DCM is dichloromethane, DMAP is 4-dimethylaminopyridine, DIPEA is diisopropylethylamine, DMF is dimethylformamide, TFA is trifluoroacetic acid, and CBZ is benzyloxycarbonyl, and TEMPO is 2,2,6,6-tetramethylpiperidinyloxy.

[00138] As used herein, ^{1}H NMR stands for proton nuclear magnetic resonance, and TLC stands for thin layer chromatography.

II. *Processes and Intermediates*

[00139] In one embodiment, the invention provides a process and intermediates for preparing a compound of formula **1** as outlined in Scheme I.



Scheme I

[00140] Referring to Scheme I, 3-azabicyclo[3.3.0]octane of formula **5** (R. Griot, *Helv. Chim. Acta.*, **42**, 67, (1959) is converted to a suitable alkyl carbamate of formula **6** wherein R' is, e.g., *t*-butyl or isobutyl, using known methods. See, e.g., T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley and Sons, Inc. (1999).

[00141] Carboxylation of the N- alkoxycarbonyl-3-azabicyclo[3.3.0]octane of formula **6** is achieved by first forming a 2-anion of formula **6** in the presence of a chelating agent (for formation of similar anions. See, e.g., Daniel. J. Pippel, et. al., *J. Org. Chem.*, 1998, *63*, 2; Donald J. Gallagher et al., *J. Org. Chem.*, 1995, 60(22), 7092-7093; Shawn T. Kerrick et al., *J. Am. Chem. Soc.*, 1991, 113(25), 9708-9710; Donald J. Gallagher et al., *J. Org. Chem.*, 1995, 60(25), 8148-8154; and Peter Beak et al., *J. Am. Chem. Soc.*, 1994, 116(8), 3231-3239. The 2-anion of the alkyl carbamate of formula **6** (not shown in Scheme I) is prepared by treatment of compound of formula **6** with a strong lithium base (e.g., *t*-butyl lithium or *sec*-butyl lithium) in the presence of a complexing agent (e.g., tetramethylethylenediamine, tetraethylethylenediamine, tetramethyl-1,2-cyclohexyldiamine, or 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane) in a suitable aprotic solvent. Suitable aprotic solvents include, e.g., *t*-butylmethyl ether, tetrahydrofuran, and dimethoxyethane. Subsequently, the 2-anion of formula **6** can be treated with carbon dioxide to give a racemic mixture of *trans-/cis*-2-carboxylic acids of formula **7** wherein the *trans-/cis-* ratio is 30 to 70, 40 to 60, 50 to 50, 60 to 40, 80 to 20, 90 to 10, 95 to 5, or greater than 98 to 2.

[00142] In some embodiments, the complexing agent may be optically active, such as, for example, an optical isomer of sparteine. An optically active complexing agent can induce asymetric carboxylation to give a product having an enantiomeric excess (e.e.) of from about 10% to about 95% (see, e.g., Beak et.al., *J. Org. Chem.*, 1995, 60, 8148-8154). The *trans-/cis-* mixture is equilibrated to give a predominantly *trans* acid of formula **8** wherein the

trans-/cis- ratio is 80 to 20, 90 to 10, 95 to 5, or greater than 98 to 2, in the presence of a suitable base. Suitable bases include, e.g., lithium hexamethyldisilazide, lithium di-isopropylamide, or lithium 2,2,6,6-tetramethylpiperidine.

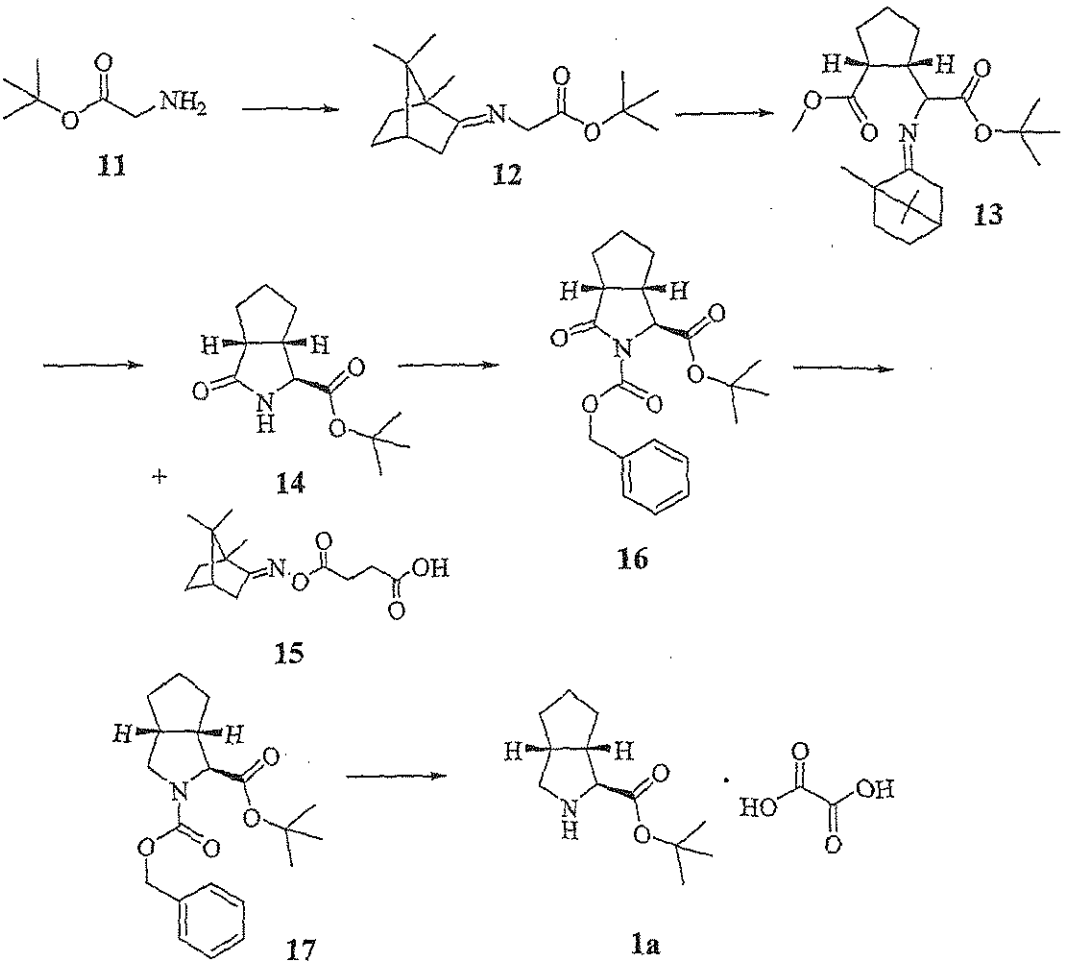
[00143] In another embodiment, the use of 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane as the complexing diamine provides the carboxylic acid of formula **8** with a *trans-/cis-* ratio of isomers of 90 to 10, 95 to 5, or greater than 98 to 2 directly and obviates the equilibration step.

[00144] The racemic mixture of the compound of formula **8** may be resolved to provide a single enantiomer of formula **9**. Known methods of resolving racemic amino acids may be used and include, but are not limited to, crystallization of an optically active amine salt, preparing a 2-carboxylate ester with an optically active alcohol followed by crystallization or chromatographic separation, and preparing an optically active N-alkoxycarbonyl derivative followed by crystallization or chromatography. In one embodiment, the (R) α-aminoethylbenzene or (S) 1-amino-1,2,3,4-tetrahydronaphthalene salt of compound of formula **8** is crystallized to produce the amine salt of formula **9**.

[00145] The free acid of the salt of formula **9**, obtained by extraction of, for example, an aqueous sodium bisulfate solution is esterified with, for example, di-*t*-butyl-dicarbonate (Boc_2O) to give the ester of formula **10**. Removal of the -COOR' protecting group under known conditions, for example, methane sulfonic acid in an organic solvent such as, for example, *t*-butylmethyl ether or tetrahydrofuran, provides the compounds of formula **1**.

[00146] In another embodiment, bicyclic pyrrolidinyl compounds of Formula **3** (as exemplified by compounds **17** shown below) may be prepared as outlined in Scheme II.

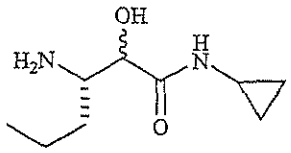
Scheme II



[00147] Referring to Scheme II, the camphor imine of formula **12** is prepared by reaction of glycine t-butyl ester of formula **11** with (1S)-(-)camphor in the presence of a Lewis acid such as, for example, boron trifluoride etherate. Michael addition of the amine of formula **12** to methyl cyclopentenecarboxylate gives an adduct of formula **13**. The single isomer of compound **13** shown is obtained by recrystallization of the crude product from a mixture of isopropanol and water. Removal of the camphor imine with hydroxylamine in the presence of sodium acetate and subsequent cyclization yields the lactam ester of formula **14**. Optionally, the reaction mixture may be treated with succinic anhydride to facilitate recovery of the desired product of formula **14** and the camphor derivative of formula **15**. The lactam of formula **14** is converted to its benzyloxycarbonyl derivative of formula **16** by treatment with a base such as, e.g., sodium hydride, followed by benzylchloroformate. Reduction of the lactam of formula **16** with a hydride reducing agent such as, e.g., borane-dimethylsulfide-piperidine provides the carbamate ester of formula **17**. Removal of the benzyloxycarbonyl protecting group may be achieved under reducing conditions such as, e.g., hydrogen in the presence of a palladium catalyst such as, e.g., palladium hydroxide, to give the desired

bicyclic pyrrolidine ester of formula **17**. Isolation of the ester of formula **17** is optionally achieved through formation of a salt such as, e.g., an oxalate salt of formula **1a**.

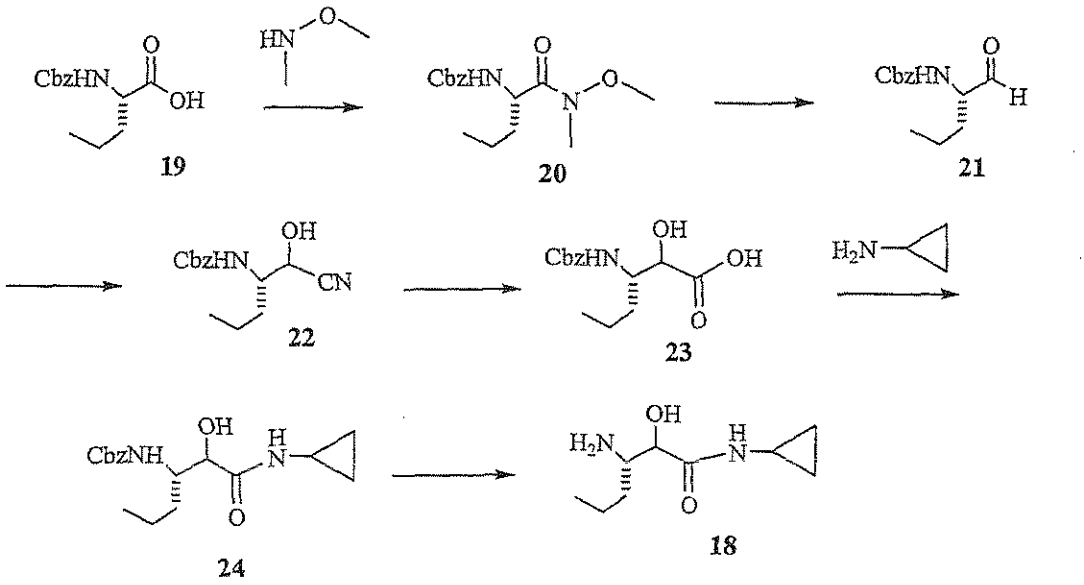
[00148] The invention further provides processes for the preparation of compounds of Formula **2**. One specific example of a compound of Formula **2**, wherein R'_4 is H, R'_5 is *n*-propyl, and R_4 is cyclopropyl, is shown below in formula **18**.



18

[00149] In one aspect, compound **18** can be prepared as outlined in Scheme III.

Scheme III

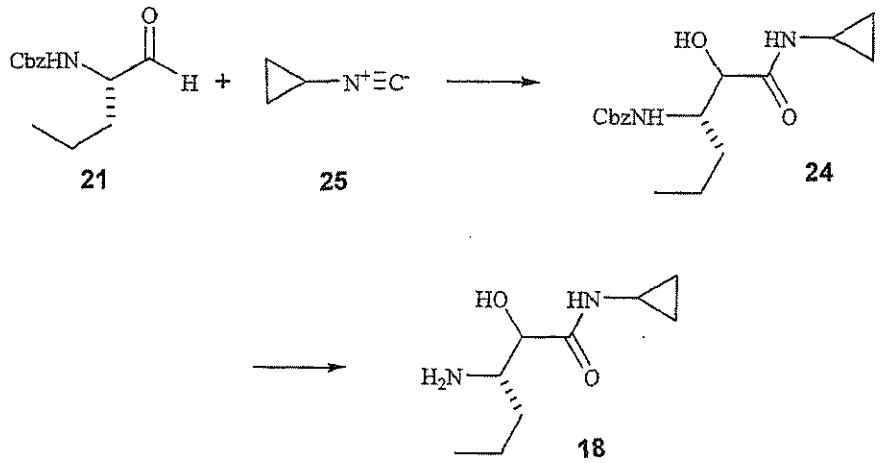


[00150] In Scheme III, the methoxymethylamide of Cbz-norvaline of formula **20** is prepared by reaction of Cbz-norvaline of formula **19** with methoxymethylamine in the presence of a coupling reagent such as, e.g., EDC. Reduction of compound of formula **20** with a hydride reagent such as, e.g., lithium aluminum hydride or diisobutylaluminum hydride at a temperatures between -20 °C and 10 °C provides a norvalinal compound of formula **21**. Preparation of the corresponding cyanohydrin of formula **22** is achieved by reacting compound of formula **21** with an alkali metal cyanide such as, e.g., pottasium cyanide, in the presence of an alkali metal thiosulfite such as, e.g., sodium thiosulfite. Hydrolysis of compound of formula **22** in the presence of HCl in a suitable solvent such as, e.g., dioxane, and at an elevated temperatures of from about 50 °C to 110 °C leads to the corresponding 3-

amino-2-hydroxyhexanoic acid (not shown) which is converted to the Cbz derivative of formula **23** by reaction with Cbz-hydroxysuccinimde. The cyclopropyl amide of of formula **24** is prepared from compound **23** by reaction with cyclopropylamine in the presence of a coupling reagent such as, e.g., EDC. Removal of the Cbz group to give a compound of formula **18** is achieved under known reducing conditions such as, e.g., hydrogen in the presence of a palladium catalyst.

[00151] In another embodiment, as illustrated in Scheme IV below, a cyclopropylamide of Formula **18** is prepared using the Passerini reaction (see, e.g., A. Doemling et al., *Angew. Chem.*, 2000, 112, 3300-3344).

Scheme IV



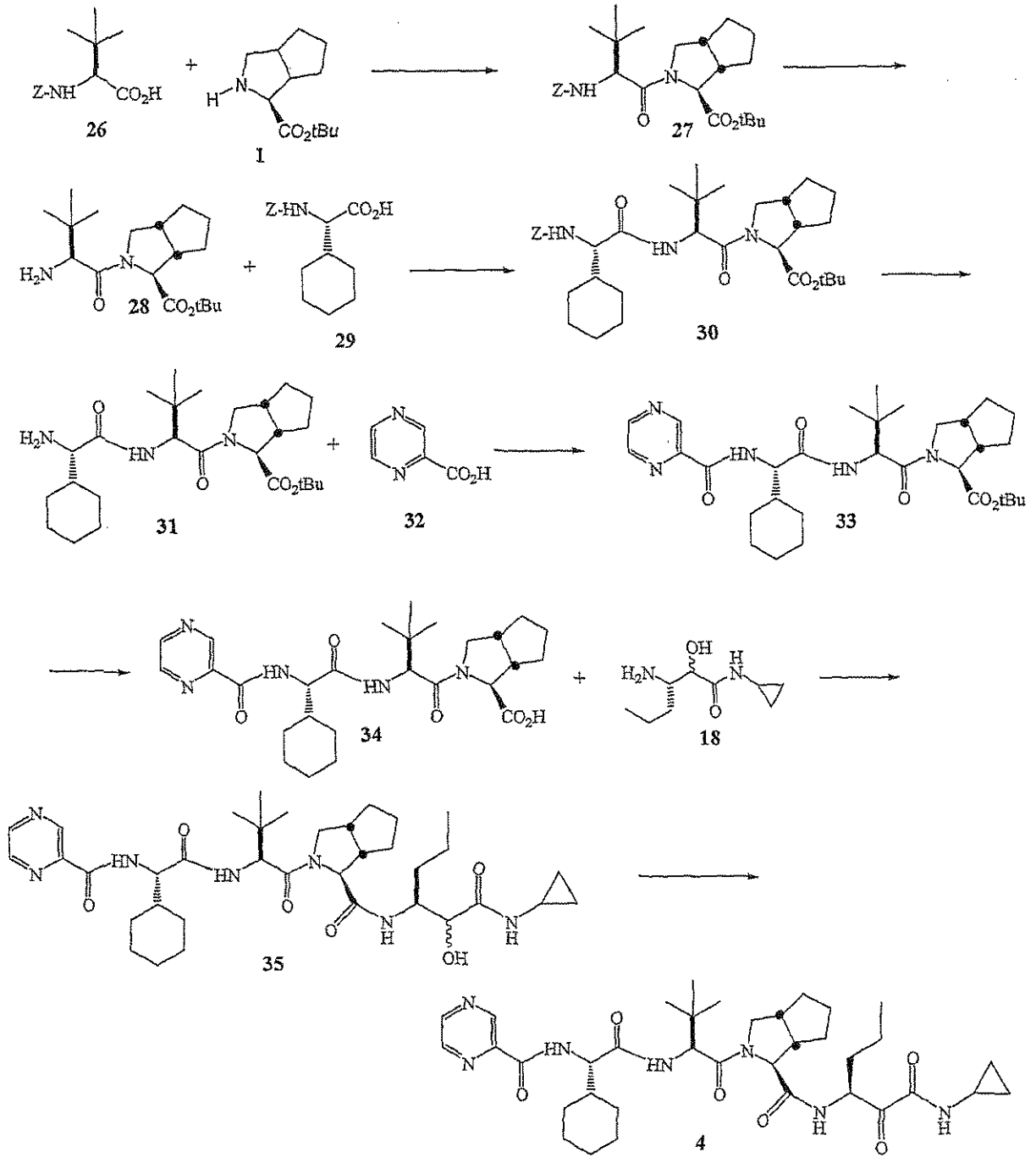
[00152] Refering to Scheme IV, reaction of Cbz-valinal **21** with cyclopropyl isocyanide of formula **25** (available from Oakwood Products, Inc., West Columbia, SC 29172, USA) in the presence of trifluroacetic acid, optionally in the presence of an asymetric catalyst provides the cyclopropylamide of formula **24**. See, e.g., Schreiber, et.al., *Org. Lett.*, 2004, 6, 4231. The intermediate trifluroacetate (not shown) is hydrolyzed during isolation to yield compound **24** directly. Removal of the Cbz protecting group to give the compound of formula **18** is achieved under reducing conditions as previously described.

[00153] In another embodiment, the hydroxy-acid compounds of formula **23** may be prepared according to methods described in U.S. Patent Nos. 6,020,518; 6,087,530 and 6,639,094, each of which is incorporated herein by reference in its entirety.

[00154] Although the processes shown in schemes III and IV above illustrate the synthesis of a specific compound (of formula **18**), the processes in schemes III and IV can be used to produce other compounds of Formula **2**.

[00155] In another embodiment, as illustrated in Scheme V, this invention further provides a process and intermediates for preparing a compound of Formula **4**.

Scheme V



[00156] Referring to Scheme V, a bicyclic aminoester of Formula **1**, wherein R_3 is *t*-butyl, is reacted with a protected amino acid of formula **26** (wherein Z is an amine protecting group and can be removed under acidic, basic or hydrogenating conditions different from those used for removing an R_3 protecting group) in the presence of a coupling reagent, to give an amide-ester of formula **27**. The protecting group Z is removed from the amide-ester of formula **27** to give the amine-ester compound of formula **28**.

[00157] Reaction of the amino-containing compound of formula **28** with the protected amino acid **29** in the presence of a coupling reagent gives a tripeptide of formula **30**.

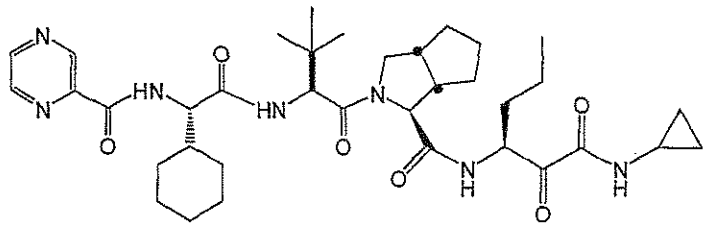
[00158] Removing the protecting group Z in the tripeptide of formula **30** provides a free amino-tripeptide of formula **31**.

[00159] Reaction of the amino-tripeptide of formula **31** with pyrazine-2-carboxylic acid, of formula **32**, in the presence of a coupling reagent yields the amide-tripeptide ester of formula **33**.

[00160] Hydrolysis of the ester of the amide-tripeptide ester of formula **33** provides the amido-tripeptide acid of formula **34**;

[00161] Reacting the amido-tripeptide acid of formula **34** with the amino-hydroxy amide of formula **18** in the presence of a coupling reagent gives the hydroxy-peptide of formula **35**.

[00162] In the final step, oxidation of the hydroxy group of the compound of formula **35** provides the compound of Formula **4**.



4

Oxidation of compound **35** may be achieved with a variety of known oxidizing reagents, such as, for example: chromic acid in acetone; Dess-Martin periodinane (1,1-dihydro-1,1,1-triacetoxy-1,2-benzoiodooxol-3(1H)-one); sodium hypochlorite in the presence of TEMPO and, optionally, an alkali metal halide such as sodium bromide.

[00163] In some embodiments, the configuration of the hydroxy group of **35** is a mixture of R and S isomers in the ratio of from about 90 to 10 to about 10 to 90, typically in a ratio of about 60 to 40 to about 40 to 60.

[00164] In another embodiment, the hydroxy group of compound **35** has the R configuration with an enantiomeric excess of about 90% ee.

[00165] In a further embodiment, the hydroxy group of compound **35** has the S configuration with an enantiomeric excess of about 90% ee.

[00166] Any of the intermediates obtained as described herein, may be used with or without isolation from the reaction mixture. The desired protease inhibitor may be derived by attaching the appropriate RW-, P_2-, P_3-L_2-P_2, or P_4-L_3-P_3-L_2-P_2- moiety. A coupling of an amine with such a moiety may be carried out using the corresponding carboxylic acid, or reactive equivalent thereof, under standard amide bond-forming or coupling conditions. A typical coupling reaction includes a suitable solvent, the amine in a concentration ranging

from about 0.01 to 10M, preferably about 0.1 to about 4.0M, the requisite carboxylic acid, a base and a peptide coupling reagent.

[00167] If an amine is used without isolation, the coupling may be carried out *in situ* in the solvent of the reaction mixture used in the preparation of the amine, or in a different solvent. To this reaction mixture, the requisite carboxylic acid may be added and the reaction maintained at a temperature in the range of about 0 °C to 100 °C, preferably between about 20 °C to about 40 °C. The base and peptide coupling reagent are then added to the mixture, which is maintained at a temperature in the range of about 0 °C to about 60 °C, preferably between about 20 °C to about 40 °C. The base is typically a tertiary amine base, such as triethylamine, di-*iso*-propylethylamine, N-methylmorpholine, DBU, DBN, N-methylimidazole, preferably triethylamine or diisopropylethylamine. The amount of base used is generally up to about 20 equivalents per equivalent of the amine, preferably at least about 3 equivalents of base. Examples of peptide coupling reagents include DCC (dicyclohexylcarbodiimide), DIC (di*iso*propylcarbodiimide), di-*p*-toluoylcarbodiimide, BDP (1-benzotriazole diethylphosphate-1-cyclohexyl-3-(2-morpholinylethyl)carbodiimide), EDC (1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride), cyanuric fluoride, cyanuric chloride, TFFH (tetramethyl fluoroformamidinium hexafluorophosphophosphate), DPPA (diphenylphosphorazidate), BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate), HBTU (O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate), TBTU (O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate), TSTU (O-(N-succinimidyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), HATU (N-[(dimethylamino)-1-H-1,2,3-triazolo[4,5,6]-pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride), PyBOP ((1-H-1,2,3-benzotriazol-1-yloxy)-tris(pyrrolidino)phosphonium tetrafluorophopsphate), BrOP (bromotris(dimethylamino)phosphonium hexafluorophosphate), DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one), or PyBrOP (bromotris(pyrrolidino)phosphonium hexafluorophosphate). EDC, HOAT, BOP-Cl and PyBrOP are preferred peptide coupling reagents. The amount of peptide coupling reagent is in the range of about 1.0 to about 10.0 equivalents. Optional reagents that may be used in the amide bond-forming reaction include DMAP (4-dimethylaminopyridine) or active ester reagents, such as HOBT (1-hydroxybenzotriazole), HOAT (hydroxyazabenzotriazole), HOSu (hydroxysuccinimide), HONB (endo-N-hydroxy-5-norbornene-2,3-dicarboxamide), in amounts ranging from about 1.0 to about 10.0 equivalents.

[00168] Alternatively, one may treat an amine with a reactive equivalent of the R_1 carboxylic acid, such as RW-C(=O)X^1, P_2-C(=O)X^1, P_3-L_2-P_2-C(=O)X^1, or P_4-L_3-P_3-L_2-P_2-C(=O)X^1, wherein C(=O)X^1 is a group that is more reactive than COOH in the coupling reaction. Examples of -C(=O)X^1 groups include groups where X^1 is Cl, F, OC(=O)R (R is, e.g., aliphatic or aryl), -SH, -SR, -SAr, or -SeAr.

[00169] Acid and amine protecting groups as used herein are known in the art (see, e.g., T.W. Greene & P.G.M Wutz, "Protective Groups in Organic Synthesis," 3rd Edition, John Wiley & Sons, Inc. (1999), and the earlier editions of this book. Examples of suitable protecting groups for acids include *t*-butoxy, benzyloxy, allyloxy and methoxymethoxy. Examples of suitable protecting groups for amines include 9-fluorenylmethyl carbamate, *t*-butyl carbamate, benzyl carbamate, trifluoroacetamide and p-toluenesulfonamide. A number of chemical groups are known that may be used as the RW-, P_2-, P_3-L_2-P_2, or P_4-L_3-P_3-L_2-P_2- portion of the protease inhibitor. Examples of such groups are reported in the following publications: WO 97/43310, US 20020016294, WO 01/81325, WO 02/08198, WO 01/77113, WO 02/08187, WO 02/08256, WO 02/08244, WO 03/006490, WO 01/74768, WO 99/50230, WO 98/17679, WO 02/48157, US 20020177725, WO 02/060926, US 20030008828, WO 02/48116, WO 01/64678, WO 01/07407, WO 98/46630, WO 00/59929, WO 99/07733, WO 00/09588, US 20020016442, WO 00/09543, WO 99/07734, US 6,018,020, US 6,265,380, US 6,608,027, US 20020032175, US 20050080017, WO 98/22496, US 5,866,684, WO 02/079234, WO 00/31129, WO 99/38888, WO 99/64442, WO 2004072243, and WO 02/18369, which are incorporated herein by reference in their entireties.

[00170] Although in Scheme V only a single stereoisomer is illustrated for the compound of Formula 4, the present invention is, however, intended to include all steroisomers of Forumula 4 which are depicted in Table I. All these steroisomers can be prepared in the same method by using reagent(s) containing carbon atom(s) of a different steric configuration, e.g.,

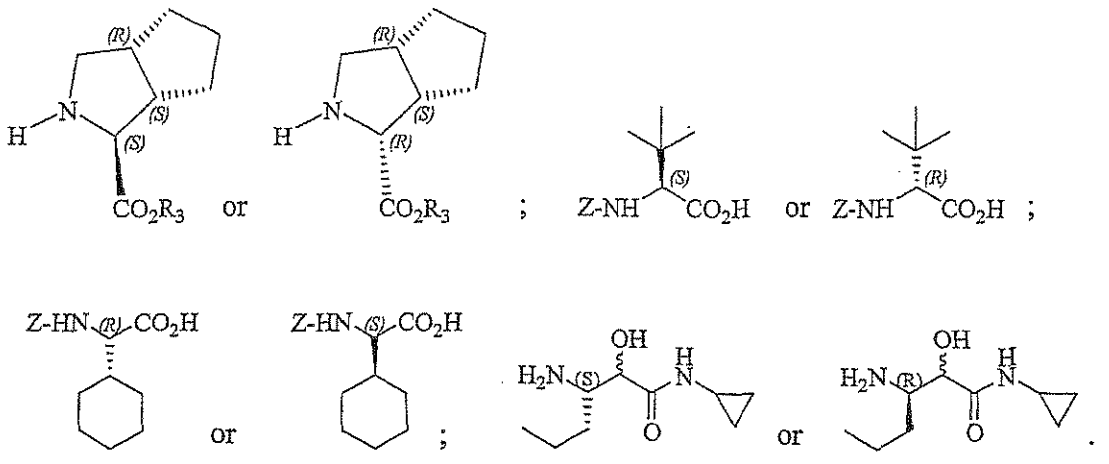
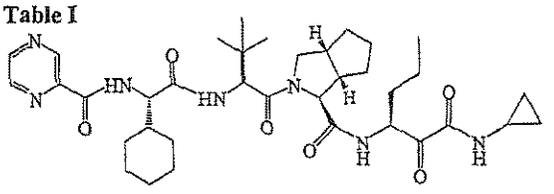
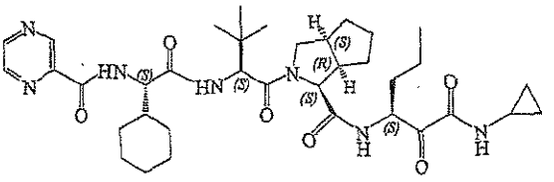
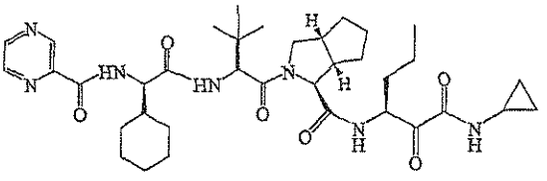
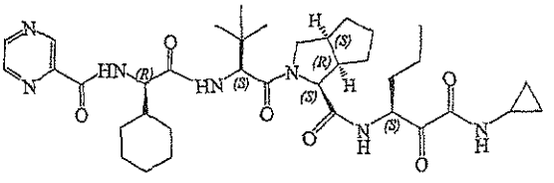


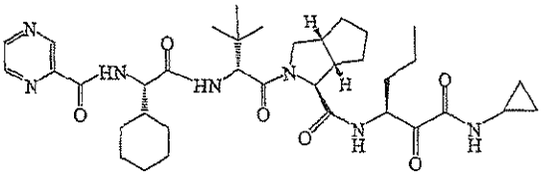
Table I

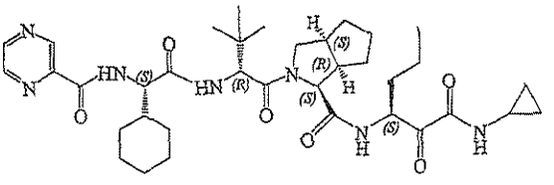


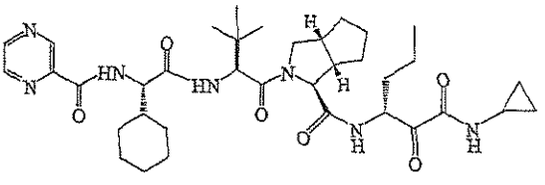


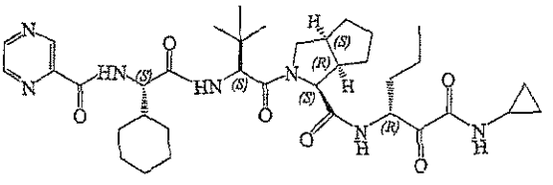


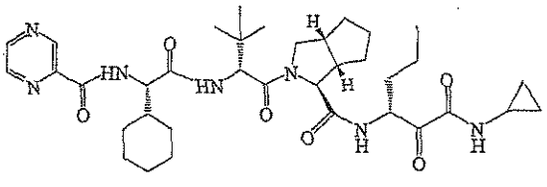


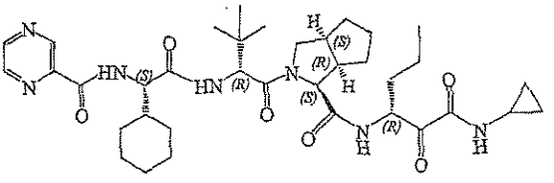


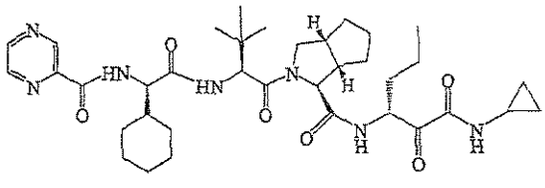


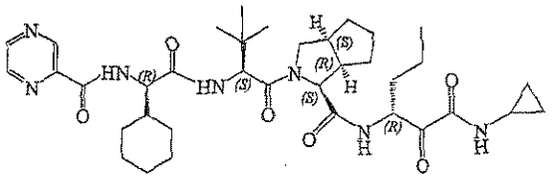


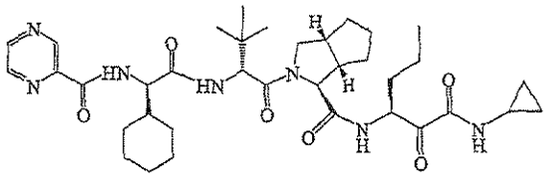


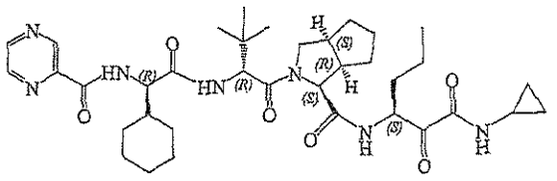


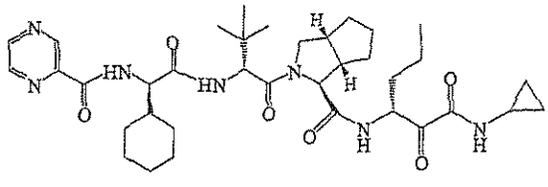


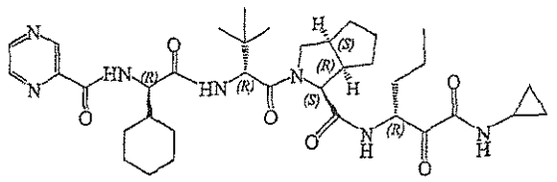


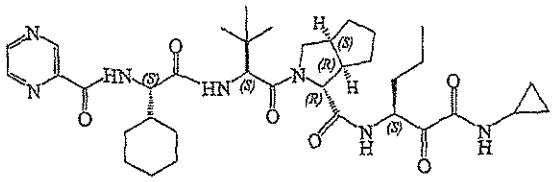


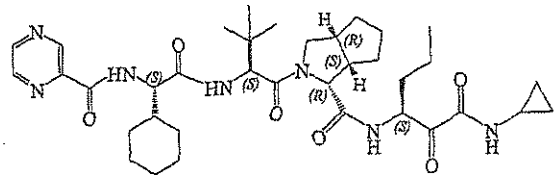


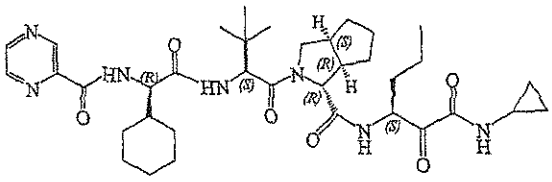


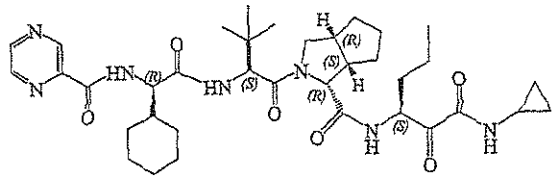


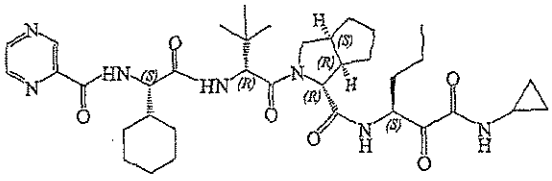


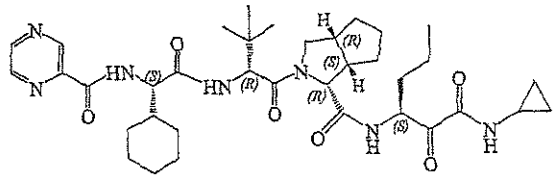


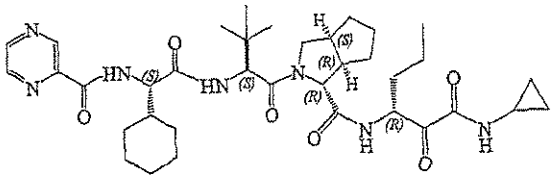


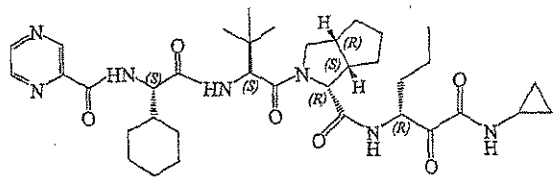


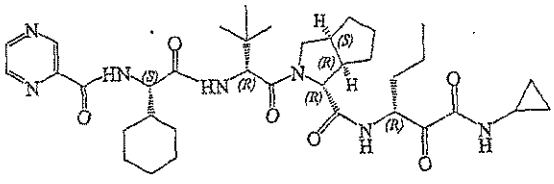


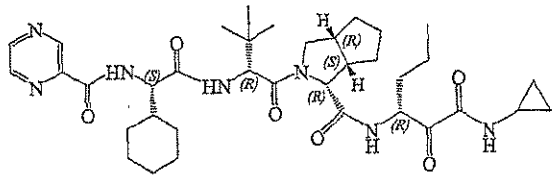


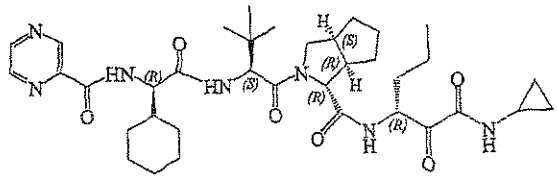


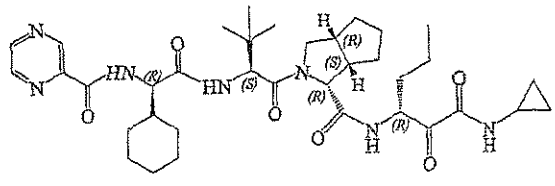


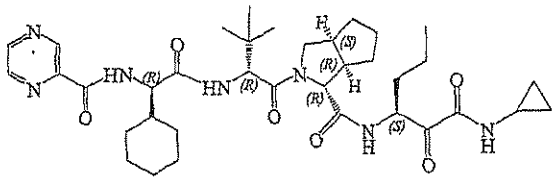


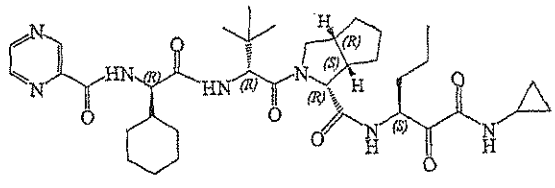


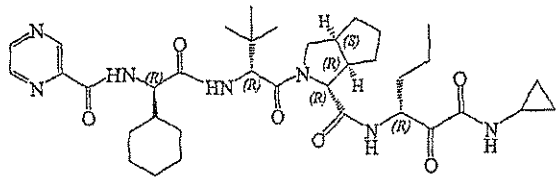


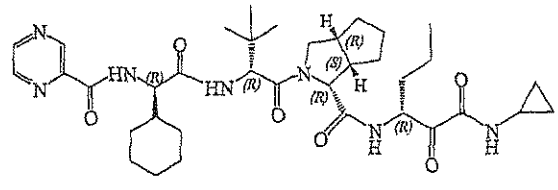


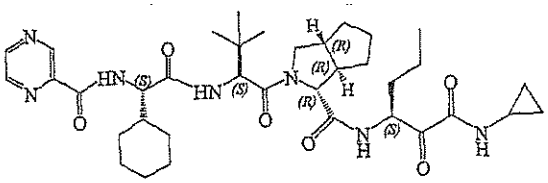


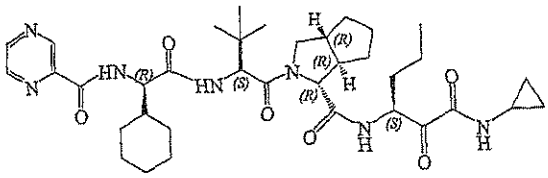


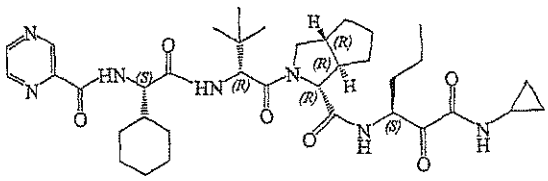


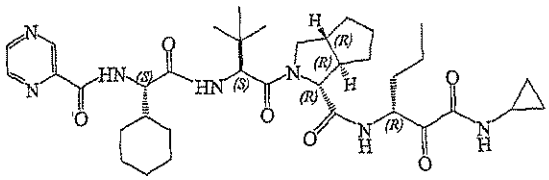


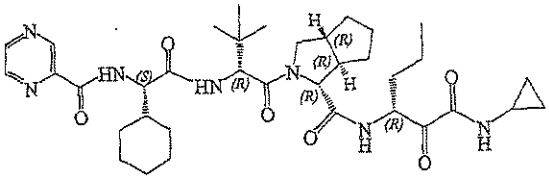


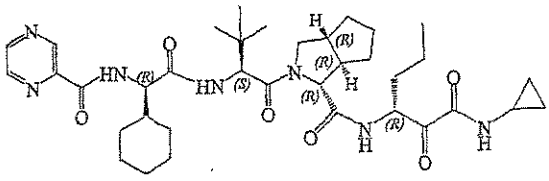


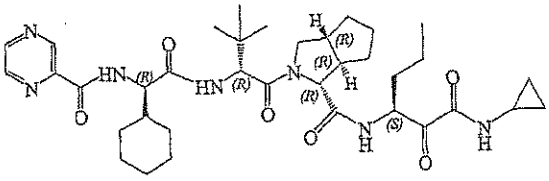


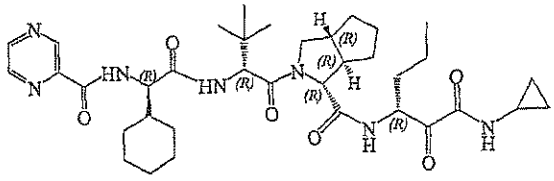


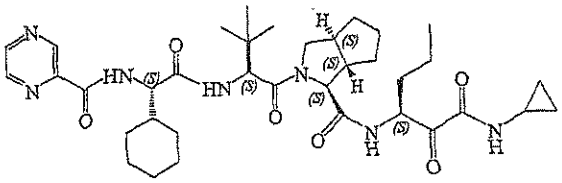


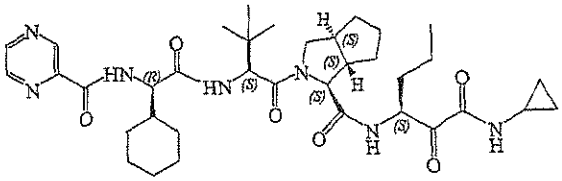


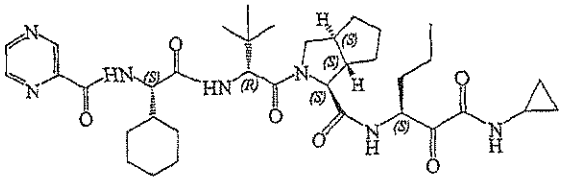


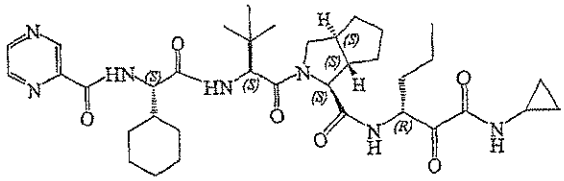


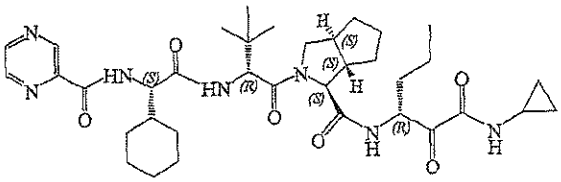


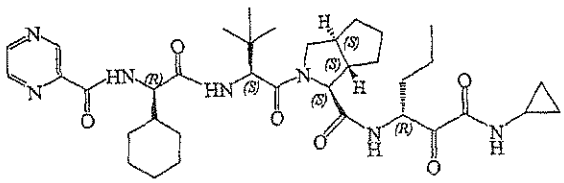


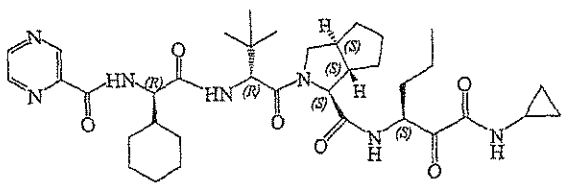


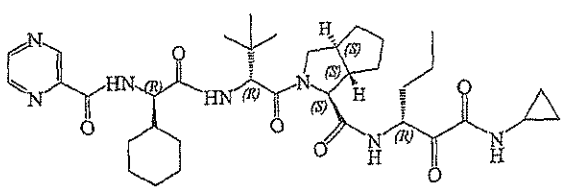


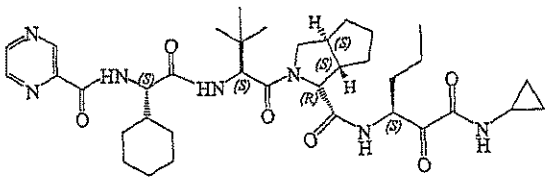


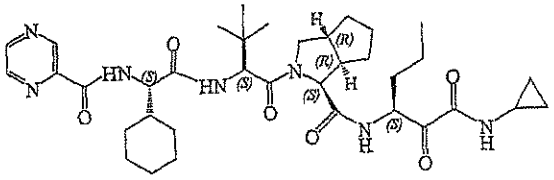


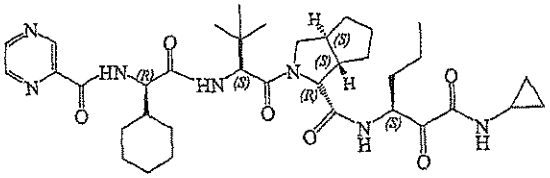


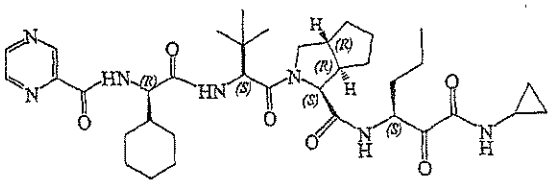


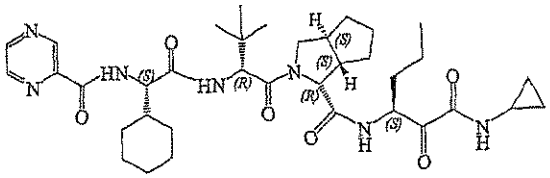


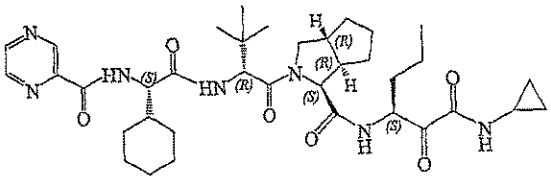


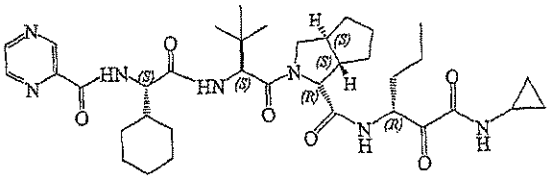


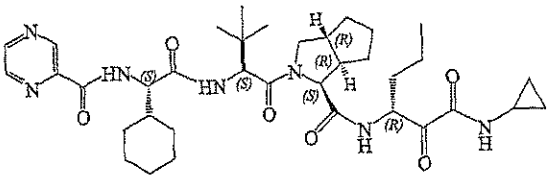


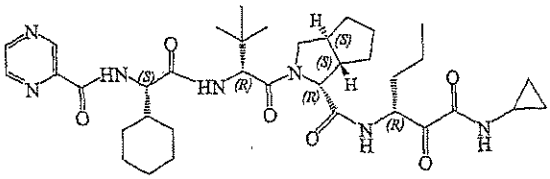


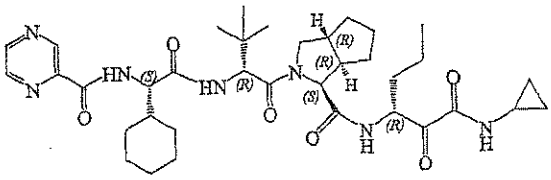


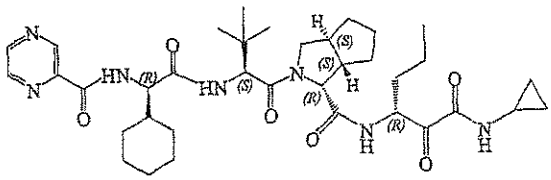


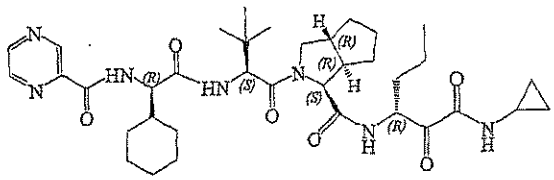


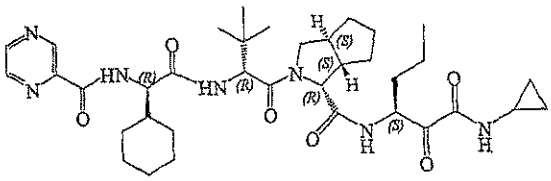


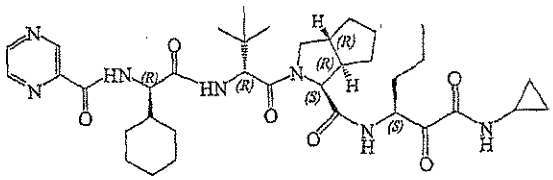


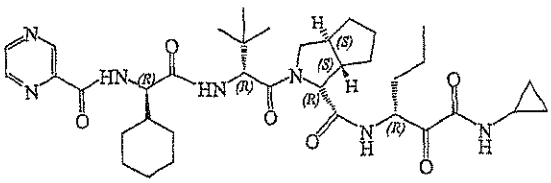


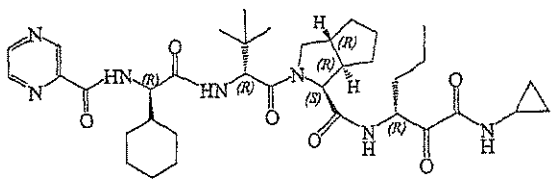








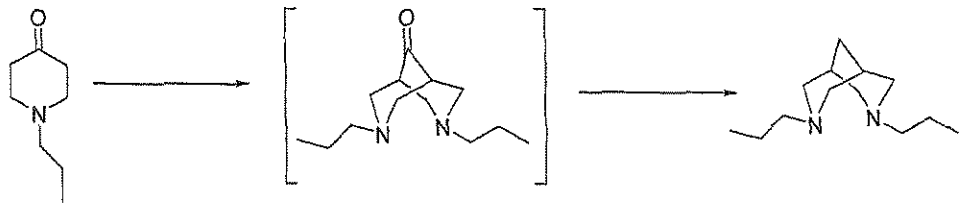




III. Examples

[00171] The following preparative examples are set forth in order that this invention be more fully understood. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Preparation 1: 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane



Method 1

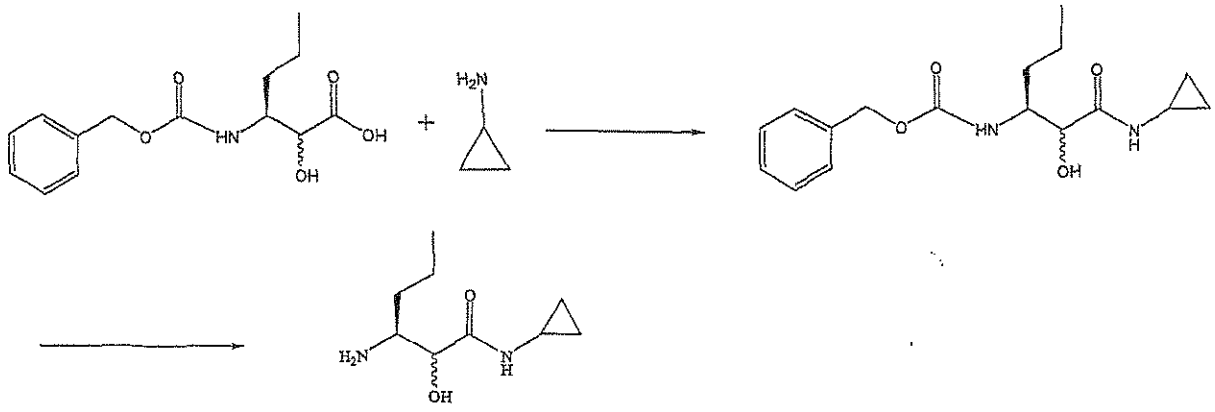
[00172] To a three-neck 5 L flask equipped with a mechanical stirrer, thermocouple, condenser, and addition funnel, under a nitrogen atmosphere, was charged 1-propyl-4-piperidone (100 g, 0.71 mol), paraformaldehyde (50 g, 1.67 mol), and ethyl alcohol (2.0 L) with stirring. Acetic acid (90 mL, 1.56 mol) was charged and the mixture was warmed to 40°C. In a separate flask was dissolved propylamine (64 mL, 0.78 mol) in ethyl alcohol (500 mL). This solution was added to the above mixture over 7-8 hours. The mixture was stirred for an additional 1.5 hours at 40 °C, then cooled to ambient temperature. The mixture was filtered through a pad of Celite®, and the Celite® was rinsed with ethyl alcohol (twice, 100 mL each). The solution was concentrated *in vacuo* and diethyleneglycol (1.0 L) was added. In a separate flask potassium hydroxide (160 g) was dissolved in water (190 mL). The solution was added to the diethyleneglycol mixture, with stirring, then the mixture was warmed to 85 °C. Hydrazine monohydrate (96 mL) was added over 2 hours, and the resultant mixture was stirred at 85 °C for another 1 hour. With nitrogen sparging, the mixture was warmed to 160 °C bath temperature while collecting the distillate in a Dean-Stark trap. The lower aqueous phase was returned to the reaction flask while the upper product phase collected. The process was repeated until the product no longer distilled as an azeotrope with water. The pot temperature varied from 135 to 160 °C during the process. The collected upper-phase fractions were combined and dissolved in heptane (160 mL). The solution was washed with water (twice, 120 mL each), and the combined aqueous phases were extracted with heptane (twice, 100 mL each). The combined organic phases were concentrated to give the title compound (85.3 g, 57% yield).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.60 (dd, J = 10.88, 2.04 Hz, 4H), 2.23 (dd, J = 10.88, 4.58 Hz, 4H), 2.12 (t, J = 7.74 Hz, 4H), 1.91 - 1.84 (m, 2H), 1.44 –1.35 (m, 6H), 0.85 (t, J = 7.25 Hz, 6H)

Method 2

[00173] Under nitrogen atmosphere, acetic acid (260 mL, 4.67 mol) was added to a mixture of 1-propyl-4-piperidone (300 g, 2.12 mol), paraformaldehyde (150 g, 5.00 mol), and ethyl alcohol (6.00 L) in a four-neck 12 L flask equipped with a mechanical stirrer, a thermocouple, and a condenser. The heterogeneous mixture was warmed to 40 °C and a solution of propylamine (192 mL, 2.34 mol) in ethyl alcohol (1.50 L) was added over a period of 7.5 hours. The mixture was maintained at 40 °C for 1.5 hours after the addition was finished. The mixture was cooled to 22 to 25 °C and filtered. The collected solids were washed with ethyl alcohol (twice, 200 mL each) and the combined filtrates concentrated to about 1.0 L under vacuum distillation (90 mmHg, 50 to 55 °C). Diethyleneglycol (2.60 L) was added, followed by a solution of potassium hydroxide (477 g) in water (570 mL). The reaction mixture was heated to 85 °C and hydrazine monohydrate (279 mL) was added over 2 hours. Heating at 85 °C was continued for 1 hour after the addition was finished then the mixture was heated to 155 °C while collecting the distillate which formed two layers. The lower layer was returned periodically to the reaction mixture. Heating at 155-165 °C was continued until the distillation of the upper layer ceased. The upper product layer was diluted with heptane (480 mL) and washed with water (twice, 240 mL each) The combinded aqueous phases were extracted with heptane (twice, 300 mL each). The combined heptane extracts were concentrated to provide the title compound (233 g, 52% yield) as a straw colored liquid.

Preparation 2: (S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide (18)



18

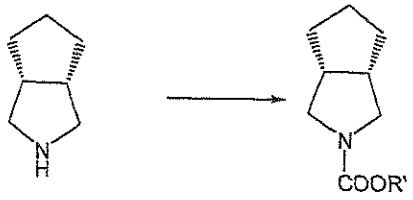
[00174] A 250 mL round bottomed flask equipped with an overhead stirrer, addition funnel, thermocouple, and nitrogen/hydrogen inlet was purged with nitrogen for several minutes. The protected amino-hydroxy acid (10.0 g, 0.035 mol) and N-hydroxysuccinimide (9.0 g, 0.078 mol, 2.2 molar eq.) were added to the flask followed by 105 mL of DMF. The mixture was agitated at 20±5 °C until a clear solution was obtained (approximately 15 minutes). The flask was cooled to -9.8 °C (ice/acetone bath). EDC•HCl (13.6 g, 0.071mol, 2.0 molar eq.) was added to the flask in one portion. The contents of the flask were allowed to stir at -5±5 °C for 3 hours. The contents of the reaction flask were cooled to -10±3 °C and cyclopropyl amine (4.89 g, 0.085 mol, 2.4 molar eq.) was added via an addition funnel while maintaining a temperature range of 5±3 °C. The reaction mixture was allowed to stir at 5±5 °C for 60 minutes then slowly warmed to room temperature and stirred overnight. The reaction mixture was transferred to a larger round bottom flask and quenched with the addition of water (270 mL) at room temperature. The DMF/water layer was extracted with three portions of EtOAc (150 mL) at 35-40 °C, the combined EtOAc extracts were washed with water (twice, 300 mL each), followed by 10% $NaHCO_3$ solution (300 mL), and finally water (300 mL). The EtOAc layer was concentrated at atmospheric pressure and heptane (100 mL) was added. Distillation at 80±5 °C was continued and additional heptane (50 mL) was added to crystallize the product from solution. The mixture was held at 85 °C for 2 hours, slowly cooled to room temperature, and held for 1hour. The product was vacuum filtered and dried at 25 mmHg overnight at 30 °C to give a crude product (12.86 g). An 11.44 g portion of the crude product was placed in a 250 mL round bottom flask, 50 mL of MTBE was added, and the thick slurry was stirred for 3 hours at room temperature. The product was filtered and the cake washed with MTBE (50 mL). The dried product (6.4 g) was sampled for wt% assay (92.2 wt%) and HPLC A% (100 A%).

[00175] A 1.0 L Buchi hydrogenation vessel equipped with an overhead stirrer, ballast tank, thermocouple, and nitrogen/hydrogen inlet was purged with nitrogen for several minutes.

The protected amino-hydroxy amide (49.9 g, 0.156 mol, prepared as descirbed above), and 20% $Pd(OH)_2$ on carbon (2.85 g, 0.002 mol, 50% water by weight) were charged to the vessel followed by 700 mL of MeOH. The mixture was agitated at 40 °C until the starting material dissolved (approximately 15 minutes). The vessel and ballast tank were purged 2 times to 40 psig with nitrogen, vented to atmospheric pressure with nitrogen, and pressurized to 40 psig with hydrogen 2 times, venting to atmosphere each time. The ballast tank was finally pressurized to 400 psig and the vessel was pressurized to 30 psig via the ballast tank. The hydrogenation vessel was held at 40 °C and 30 psig hydrogen (by regulation via ballast tank) for 2 hours. The vessel was vented to atmospheric pressure with nitrogen and the slurry was sampled for HPLC analysis for residual starting material (1.8%; limit = 0.5% both diastereomers). The vessel was re-purged and re-pressurized to 30 psig with hydrogen and held at 40 °C for additional 30 minutes. The vessel was vented to atmospheric pressure with nitrogen and a sample of the slurry was submitted for HPLC analysis for residual amino-amide (1.1%; limit = 0.5% both diastereomers). The vessel was re-purged and re-pressurized with hydrogen and held at 40 °C for an additional 40 min. The vessel was vented to atmospheric pressure and held overnight under a nitrogen atmosphere.

[00176] A sample was submitted for HPLC analysis for residual protected amino-hydroxy amide (none detected; limit ≤ 0.5% both diastereomers). A portion of the product crystallized out of solution during the overnight stir and an additional 300mL of MeOH was added to dissolve the product. The slurry was warmed to 45 °C to assure dissolution, then filtered over a bed of Celite® at 45 °C. The wet filter cake was rinsed with MeOH (250 mL) and the filtrate was distilled at atmospheric pressure to a volume of approximately 150 mL. Ethyl acetate (300 mL) was added and distillation was continued at atmospheric pressure, again to a volume of 150 mL. This procedure was repeated twice more. Heptane (150 mL) was added to the flask at 75 °C and the contents were cooled to room temperature and ultimately to 5 °C in an ice/water bath. The crystallized product was collected, the wet cake was washed with heptane (75 mL) and dried at 40 °C under reduced pressure overnight. The free amino-amide was isolated as an off-white solid (21.2 g, 0.114 mol, 73.1% yield) with an HPLC purity of 98.5 A% and a wt/wt assay of 94.2 wt%.

Example 1: N-*t*-butyloxycarbonyl-3-azabicyclo[3.3.0]octane (6)



5 6

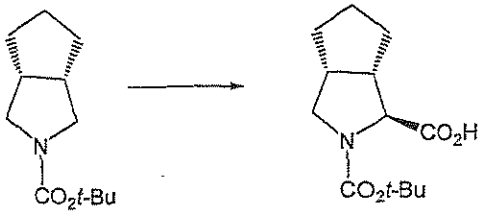
Method 1

[00177] To a 2 L 3-necked round-bottom flask under nitrogen fitted with a mechanical stirrer, a 500 mL addition funnel, and a thermometer was charged 3-azabicyclo[3.3.0]nonane hydrochloride (100 g, 0.677 mol), potassium carbonate (187 g, 1.35 mol), *t*-butyl methyl ether (220 mL) and water (160 mL), with stirring. The mixture was cooled to 14-16 °C. In a separate 500 mL erylenmeyer flask was charged Boc_2O (di-*t*-butyl dicarbonate) (145 g, 0.644 mol) and *t*-butyl methyl ether (190 mL). The mixture was stirred until complete dissolution was obtained. The solution was poured into the addition funnel and added to the above reaction mixture, keeping the reaction temperature below 25 °C. Water (290 mL) was added to dissolve solids, and the mixture was stirred for 10-15 minutes. After separating the lower aqueous phase, the organic phase was washed with 5% aq. $NaHSO_4$ (twice, 145 mL each), then water (145 mL). The organic phase was concentrated and methyl t-butyl ether was added (1.3 L) to give a solution of the title compound in *t*-butyl methyl ether. See, e.g., R.Griot, *Helv. Chim. Acta.*, 42, 67 (1959).

Method 2

[00178] A solution of potassium carbonate (187 g, 1.35 mol) in water (160 mL) was added to a mixture of 3-azabicyclo[3.3.0]octane hydrochloride (100 g, 0.677 mol) and t-butyl methyl ether (220 mL), and the resultant mixture was cooled to 14-16 °C. A solution of Boc_2O (145 g, 0.644 mol) in *t*-butyl methyl ether (190 mL) was added while maintaining a temperature below 35 °C. After the addition, the mixture was stirred for 1 hour then filtered. The solids were washed with MTBE (50 mL). The phases were separated and the organic phase washed with 5% aq. $NaHSO_4$ (twice, 145 mL each) and water (145 mL) and concentrated to 300 mL under vacuum. MTBE (300 mL) was added and the mixture concentrated to remove water to less than 550 ppm. The concentrate was diluted with MTBE (400 mL) to provide a solution of the title compound in MTBE.

Example 2: *rac*-2-(*t*-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid (7)



6 7

Method 1

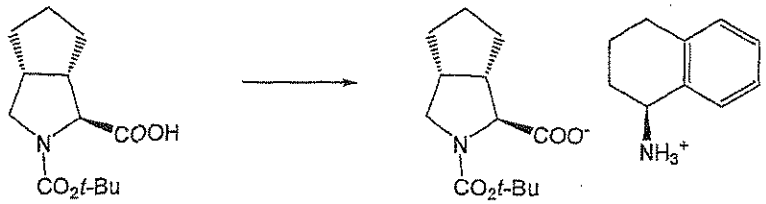
[00179] The solution from Example 1, Method 1, was charged to a 5 L 4-necked flask fitted with a mechanical stirrer, an addition funnel, a ReactIR probe, and a thermometer. 3,7-Dipropyl-3,7-diazabicyclo[3.3.1]nonane (183 g, 0.88 mol) was charged to the flask. Data collection was started on the ReactIR instrument, and the solution was cooled to -72 to -75 °C. *sec*-Butyllithium (600 mL, 1.6 M in cyclohexane) was slowly added to the reaction mixture, keeping the reaction temperature below -69 °C. The addition was monitored with the ReactIR instrument, and the addition was stopped after the absorbance at 1698 cm^{-1} had disappeared and the absorbance at 1654 cm^{-1} ceased to increase for three consectutive scans (2-minute intervals). The solution was agitated for 3 hours at -75 to -72 °C. A 10% mixture of CO_2 in nitrogen was carefully sparged into the reaction mixture, keeping the reaction temperature below -70 °C. The sparge was stopped after the absorbance for CO_2 appeared in the ReactIR spectrum (2350 cm^{-1}). The mixture was warmed to 0-5 °C, and a solution of 30 wt% $NaHSO_4$ (1.4 L) was added. The mixture was warmed to 22-25 °C and stirred for 30 minutes. The aqueous phase was separated and the organic phase washed with water (700 mL). The aqueous phase was decanted and the organic phase concentrated to provide the title compound.

Method 2

[00180] A solution of 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane (183 g, 0.87 mol) in MTBE (300 mL) was added to the solution of N-*t*-butyloxycarbonyl-3-azabicyclo[3.3.0]octane from Example 1, Method 2 in a flask fitted with a mechanical stirrer, an addition funnel, a ReactIR probe, and a thermometer and the mixture was cooled to -75 to -72 °C. A solution of *sec*-butyllithium (510 mL, 1.6 M) was added, keeping the reaction temperature below -70 °C, until the absorbance at 1698 cm^{-1} had disappeared and the absorbance at 1654 cm^{-1} ceased to increase. The solution was stirred for 3 hours at -75 to -72 °C. The reaction mixture was sparged with 10% CO_2 in N_2 keeping the reaction temperature

below -70 °C. The sparge was stopped when the absorbance for CO_2 appears in the ReactIR spectrum (2339 cm^{-1}). The mixture was warmed to 0-5 °C and a solution of 30 wt% $NaHSO_4$ (1.4 L) was added and the mixture was warmed to 22-25 °C then stirred 30 minutes. The phases were separated and the aqueous phase was checked to make sure the pH was lower than 3. The organic phase was washed with water (700 mL) then concentrated to 300 mL. Ethyl acetate (1.7 L) was added and the mixture concentrated to 300 mL twice to give a solution of the title compound in ethyl acetate.

Example 3: (S)-1,2,3,4-tetrahydronaphthalen-1-aminium (1S,3aR,6aS)-2-(*t*-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylate (9a)



8 9a

Method 1

[00181] Ethyl acetate (2.3 L) was added to the residue of Example 2, method 1, and the mixture filtered through a pad of Celite®. (S)-1,2,3,4-tetrahydro-1-naphthylamine (56.7 g, 0.385 mol) was added and the solution was stirred for 3-4 hours at 22-25 °C. The mixture was filtered and the solids were rinsed with ethyl acetate (200 mL). The solids were dried at 20-30 °C under vacuum for 4 hours to give 99.02 g of product (73% yield, 90% ee by chiral HPLC).

[00182] To a 3-necked RBF fitted with a temperature contoller, a mechanical stirrer, a reflux condenser, and a nitrogen bubbler, was charged the (S)-1,2,3,4-tetrahydro-1-naphthylammonium salt (88.98g, 0.22 mol), ethyl acetate (712 mL), and 2-propanol (666 mL). The mixture was warmed to 70-75 °C with stirring. The mixture was stirred for 15-30 minutes, then cooled to -5 to -10 °C over 1 hour. The resultant slurry was filtered and the solids were rinsed with cold ethyl acetate (180 mL). The solids were dried *in vacuo* at 35-40 °C to give 7.37 g of a white solid (83% yield, 98% ee).

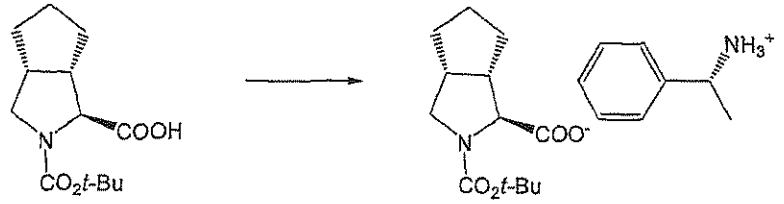
Method 2

[00183] The ethyl acetate solution of racemic N-*t*-butyloxycarbonyl-3-azabicyclo[3.3.0]octane-2-carboxylic acid from Example 2, Method 2, was added to a

solution of (S)-1,2,3,4-tetrahydro-1-naphthylamine (56.7 g, 0.385 mol) in ethyl acetate (300 mL). The mixture was strirred for 3-4 hours at 22-25 °C, then filtered, and the solids washed with ethyl acetate (200 mL). The product was dried at 20-30 °C under vacuum for 4 hours to give the title compound (99.02 g, 36% yield) with a 95 to 5 diasteromer ratio.

[00184] A mixture of the salt as prepared above (89.0 g), ethyl acetate, and 2-propanol was warmed to 70-75 °C until complete dissolution. The mixture was cooled to -5 to -10 °C over two hours and stirred for 3-4 hours. The mixture was filtered and the product dried at 35-40 °C to give the title compound (73.7g, 83% yield, >99.5% ee).

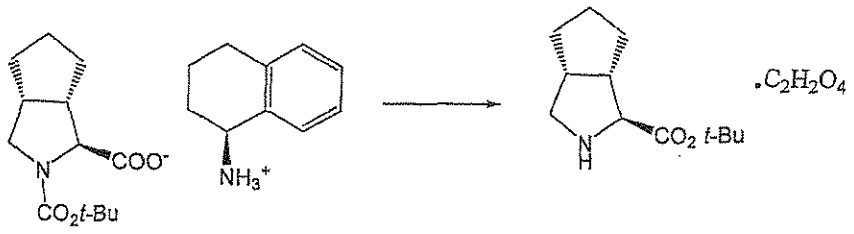
Example 4: (R)-1-phenylethanaminium (1S,3aR,6aS)-2-(*t*-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylate (9b)



8 **9b**

[00185] To a soution of racemic N-*t*-butyloxycarbonyl-3-azabicyclo[3.3.0]octane-2-carboxylic acid (4.66 g) in ethyl acetate (100 mL) was added (R)-α-methylbenzylamine (56.7 g) and the solution was stirred for 16 hr at 22-25 °C. The mixture was filtered and the solids were rinsed with ethyl acetate. The solids were dried at 20-30 °C under vacuum for 4 hours to give 1.47 g of product (43%, 82% ee, 92:8 ratio of exo:endo diastereomers).

Example 5: (1S,3aR,6aS)-*t*-butyl octahydrocyclopenta[c]pyrrole-1-carboxylate, *t*-butylester, oxalate



9a **1**

Method 1

[00186] A mixture of the (S)-1,2,3,4-tetrahydro-1-naphthylammonium salt prepared as in Example 3, Method 1 (81.7 g, 0.203 mol), *t*-butyl methyl ether (400 mL) and 5% $NaHSO_4$-

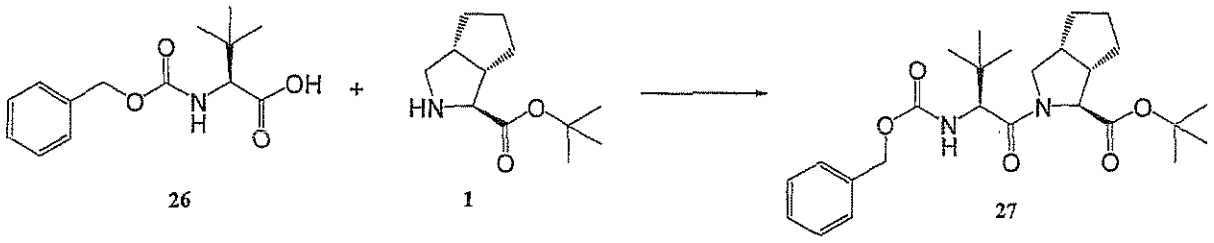
H_2O (867 mL, 0.304 mol) was stirred for 30 minutes until all solids were dissolved. The organic phase was washed with water (334 mL) then concentrated to 259 mL. *t*-Butyl methyl ether (334 mL) was added and the solution was concentrated again to 259 mL. The addition-concentration process was repeated twice more. After the final concentration, *t*-BuOH (158 mL) and dimethylaminopyridine (5.04 g, 41.3 mmol) were added. A solution of Boc_2O (67.6 g, 0.31 mol) in *t*-butylmethyl ether (52.0 mL) was added. After stirring for 5 hours at ambient temperature, *t*-butyl methyl ether (158 mL) and 5% aqueous $NaHSO_4$-H_2O (260 mL) were added and the resultant mixture was stirred. The organic phase was washed with 5% aqueous NaCl (twice, 260 mL each). The organic phase was concentrated to 320 mL, and tetrahydrofuran (320 mL) was added. The organic phase was concentrated again to 320 mL, and tetrahydrofuran (320 mL) was added. After concentrating to 320 mL once more, methane sulfonic acid (80.1 g, 0.62 mol) was added and the solution was stirred at ambient temperature for 4.5 hours. The reaction mixture was added to a 30% aqueous solution of K_2CO_3 (571 mL) and stirred. The aqueous phase was extracted with isopropyl acetate (320 mL). The combined organic phases were concentrated to 320 mL, and isopropyl acetate (320 mL) was added. The organic solution was concentrated again to 320 mL. The organic phase was washed with water (320 mL). Isopropyl acetate (320 mL) was added to the organic phase and the solution was concentrated to 192 mL. Isopropyl acetate (320 mL) was added a second time, and the organic solution was concentrated to 192 mL. A solution of oxalic acid (24.1 g, 267 mmol) in isopropyl acetate (448 mL) was added to the organic solution over 2 hours. The mixture was stirred for 2-4 hours, and the slurry was filtered. The white solids were rinsed with isopropyl acetate (100 mL) and dried at 35-40 °C under vacuum to yield 52.6 g of the title compound (85% yield).

Method 2

[00187] A mixture of (S)-1,2,3,4-tetrahydro-1-naphthylammonium salt as prepared by the method of Example 3, Method 2 (148 g, 0.609 mol), *t*-butyl methyl ether (726 mL) and 5% $NaHSO_4$-H_2O (1.58 L, 0.913 mol) was stirred until all of the solids had dissolved. The phases were separated and the organic phase washed with water (726 mL). The organic phase was concentrated to about 400 mL. *t*-Butyl methyl ether (726 mL) was added and the mixture concentrated to 590 mL. The addition of *t*-butyl methyl ether and concentration was repeated to give a final volume of 350 mL. Dimethylaminopyridine (8.42 g, 68.9 mmol) and *t*-butyl alcohol(260 mL) were added, followed by addition of a solution of Boc_2O (112 g, 0.52 mol) in MTBE (88 mL) over 0.5 hour. The mixture was stirred for 5 hours at 22-25 °C. A solution of 5% sodium bisulfate in water was added and the mixture stirred for 0.5 hour.

The organic phase was washed with 5% sodium chloride (twice, 440 mL each) and concentrated to 270 mL. Tetrahydrofuran (540 mL) was added and the mixture concentrated to 270 mL; this procedure was repeated twice more to give a final volume of 270 mL. Methane sulfonic acid (67 mL) was added over 0.5 hour while maintaining a temperature of lower than 30 °C and the mixture stirred at 22-25 °C for 12 hours. The mixture was added to a 30% aqueous solution of pottassium carbonate (478 mL) while maintaining a temperature of 22-25 °C. The mixture was filtered, the phases separated and the aqueous phase extracted with isopropyl acetate (twice, 540 mL each). The organic phase was concentrated to 270 mL, then twice evaporated with isopropyl acetate (540 ml) to give a final volume of 540 mL. The organic phase was washed with water (twice, 540 mL), then twice evaporated with isopropyl acetate (320 mL) to give a final volume of 320 mL. Additional isopropyl acetate (429 mL) was added followed by addition of a solution of oxalic acid (40.4 g, 0.448 mol) in *t*-butylmethyl ether (321 mL) over 2 hours maintaining a temperature of 22-25 °C. The mixture was stirred for 3 hours at 22-25 °C then filtered. The filter cake was washed with isopropyl acetate (100 mL) and the prouduct dried at 35-40 °C under vacuum to give the title compound as a white solid (88.4g, 81%).

Example 6: (1S,3aR,6aS)-*t*-butyl 2-((S)-2-(benzyloxycarbonylamino)-3,3-dimethylbutanoyl)octahydrocyclopenta[c]pyrrole-1-carboxylate (27)



26 1 27

Method 1

[00188] A 3-L 3-neck round bottomed flask equipped with an overhead stirrer, condenser, thermocouple, and nitrogen outlet was purged with nitrogen for several minutes. In a separate flask, sulfuric acid (46.2 mL, 0.867 mol) was diluted with 442 mL of water. The solution was allowed to cool slightly. Cbz-L-*tert*-Leucine dicyclohexylamine salt (330.0 g, 0.739 mol) was charged to the reaction flask. *t*-Butyl methyl ether (1620 mL) was added to the reactor, and the mixture was stirred to suspend the salt. The acid solution prepared above was added to the reactor over about 10 minutes, keeping the temperature at 20±5 °C. The mixture was stirred at room temperature for approximately 1 hour, then diluted slowly with water (455 mL). Agitation was stopped, and the layers were allowed to settle. The lower

(aqueous) phase was withdrawn to provide 1100 mL colorless solution of pH 1. To the organic phase remaining in the flask was charged additional water (200 mL). The mixture was stirred at room temperature for approximately 1hour. Agitation was stopped, and the layers were allowed to settle. The lower (aqueous) phase was withdrawn to provide 500mL colorless solution of pH 2. The organic phase was heated to about 35 °C, diluted with DMF (300 mL), and concentrated under reduced pressure to the point at which distillation slowed significantly, leaving a concentrate of about 500 mL. The concentrate was transferred without rinsing to a 1-L Schott bottle. The concentrate, a clear colorless solution, weighed 511.6 g. Based on solution assay analysis and the solution weight, the solution contained 187.2 g (0.706 mol) Cbz-L-*tert*-Leucine.

[00189] To a 5-L 4-neck round bottomed flask equipped with an overhead stirrer, thermocouple, addition funnel and nitrogen inlet were charged HOBT•H_2O (103.73 g, 0.678 mol, 1.20 molar eq.), EDC•HCl (129.48 g, 0.675 mol, 1.20 molar eq.) and DMF (480 mL). The slurry was cooled to 0-5 °C. A 36.6 wt% solution of the acid of Cbz-L-tert-Leucine in DMF (491.3 g, 0.745 mol, 1.32 molar eq.) was added over 47 minutes to the reaction mixture while keeping the temperature at 0-5 °C. The reaction mixture was stirred for 1 hour and 27 minutes. A solution of 3-azabicyclo(3.3.0)octane-2-carboxylic acid *t*-butyl ester in isopropyl acetate (28.8 wt%, 414.3 g, 0.564 mol) was added over 53 minutes while keeping the reaction temperature at 0-5.1 °C. The reaction mixture was warmed to 20±5 °C over about 1hour. 4-Methylmorpholine (34.29 g, 0.339 mol, 0.60 molar eq.) was added over 5 minutes. The reaction mixture was agitated for 16 hours then isopropyl acetate (980 mL) was added to the reaction solution. A solution of histamine•2HCl (41.58 g, 0.226 mol, 0.40 molar eq.) in water (53.02 g) was added to the reaction mixture within 4 minutes, followed by 4-methylmorpholine (45.69 g, 0.45 mol, 0.80 molar eq.). The reaction mixture was sampled after 3.5 hours. Water (758 mL) was added, the mixture stirred for about 20 minutes, then allowed to settle for 11 minutes. The phases were separated. The aqueous phase was extracted with isopropyl acetate (716 mL) and the organic phases were combined. 1N aq. HCl was prepared by adding 37 wt% hydrochloric acid (128.3 mL) to water (1435 ml). The organic phase was washed for about 20 minutes with the 1N hydrochloric acid. A 10wt% aq. K_2CO_3 solution was prepared by dissolving K_2CO_3 (171 g, 1.23 mol, 2.19 molar eq.) in water (1540 mL). The organic phase was washed with the 10 wt% aq. K_2CO_3 solution for about 20minutes. The final clear, very slightly yellow organic solution, weighing 1862.1 g, was sampled and submitted for solution assay. Based on the solution assay and the weight of the solution, the solution contained 238.3 g (0.520 mol) of product of the title compound.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.37 ppm (5 H, s), 7.25-7.33 ppm (1 H, m), 5.03 ppm (2 H, s), 4.17 ppm (1 H, d), 3.98 ppm (1 H, d), 3.67-3.75 ppm (2 H, m), 2.62-2.74 ppm (1 H, m), 2.48-2.56 ppm (1 H, m), 1.72-1.89 ppm (2 H, m), 1.60-1.69 ppm (1 H, m), 1.45-1.58 ppm (2 H, m), 1.38 ppm (9 H, s), 1.36-1.42 ppm (1 H, m), 0.97 ppm (9 H, s).

Method 2

[00190] A solution of potassium carbonate (73.3 g) in water (220 mL) was added to a suspension of (1S, 2S,5R) 3-azabicyclo[3.3.0]octane-2-carboxylic, *t*-butylester, oxalate (80.0 g,) in isopropyl acetate (400 mL) while maintaining a temperature of about 20 °C. The mixture was stirred for 0.5 hour, tha phases separated and the organic phase washed with 25% w/w aqueous potassium carbonate (80 mL) to give a slution of the free base. In a separate flask, aqueous sulfuric acid (400 mL, 0.863 M) was added to a suspension of Cbz-*t*-leucine dicyclohexylamine salt (118.4g) in *t*-butylmethyl ether (640 mL) while maintaing a temperature of about 20 °C. The mixture was stirred for 0.5 hour, the phases separated and the organic phase washed with water (200 mL). The phase were separated and N-methylmorpholine (80 mL) was added to the organic phase which was concentrated under reduced pressure at 40 °C to 80 mL to give the free acid as a solution in N-methyl morpholine. This solution was added to a mixture of EDC• HCl (50.8 g) HOBt hydrate (40,6 g) in N-methylmorpholine (280 mL) at 0-10 °C. The mixture was stirred for 1 hour at about 5 °C. The solution of 3-azabicyclo[3.3.0]octane-2-carboxylic, *t*-butylester from above was added at 0-20 °C followed by N-methylmorpholine (32 mL). The mixture was stired for 6 hour then diluted with isopropyl acetate (600 mL) followed by 1N HCl (400 mL). After stirring 0.5 hour, the phases were separated and the organic phase washed with 25% w/w aqueous potassium carbonate (400 mL) and water (80 mL). The mixture was stirred for about 1 hour and the phases separated to give a solution of the title compound in isopropyl acetate.

Method 3

[00191] (1S, 2S,5R) 3-azabicyclo[3.3.0]octane-2-carboxylic, *t*-butylester, oxalate (1.0 eq.) was suspended in isopropyl acetate (6 vol.) and a solution of potassioum carbonate (3.0 eq.) in water (3.5 vol.) was added at 20-25°C. The mixture was stirred for 3 hours then the phases separated. The organic phase was washed with water (2 vol.).

[00192] Cbz-*t*-leucine dicyclohexylamine salt (1.05 eq.) was suspended in isopropyl acetate (6 vol.) and sulfuric acid (1.3 eq.) in water (5 vol.) was added at 20-25°C. The mixture was stirred for 30 minutes, the phases separated, and the organic phase washed twice with water (2.5 vol each).

[00193] The two solutions from above were combined and then cooled to 0-5°C. HOBt hydrate (1.1 eq.) and EDC (1.1 eq.) were suspended in the mixture and the mixture stirred for 6 hours. The mixture was washed with water (5 vol.) and the resulting organic phase treated with L-lysine (1 eq.) and N-methylmorpholine (NMM) (2 eq.) at 20-25°C to destroy excess activated ester. The mixture was then washed with 5% potassium carbonate (5 vol.), 1N hydrochloric acid (5 vol.), 5% potassium carbonate (5 vol.) and twice with water (5 vol. each) to give a solution of the title compound in isopropyl acetate.

Example 7: (1S,3aR,6aS)-*t*-butyl 2-((S)-2-amino-3,3-dimethylbutanoyl)-octahydrocyclopenta[c]pyrrole-1-carboxylate (28)



Method 1

[00194] A 1 L Buchi hydrogenator was purged with nitrogen three times. A 307.8 g portion of a 12.8 wt% solution of (1S,3aR,6aS)-*t*-butyl 2-((S)-2-(benzyloxycarbonylamino)-3,3-dimethylbutanoyl)octahydrocyclopenta[c]pyrrole-1-carboxylate (as prepared by the method of Example 6, Method 1) in isopropyl acetate (39.39 g, 0.086 mol) was charged to the reactor. Isopropyl acetate (100 mL) was added to the reactor. A slurry of 50% water and wet 20% $Pd(OH)_2$/carbon (3.97 g) in isopropyl acetate (168 mL) was prepared and charged to the reactor and agitation was started. The reactor was pressurized to 30 psig with nitrogen gas and vented down to atmospheric pressure. This was repeated twice. The reactor was pressurized to 30 psig with hydrogen and vented down to atmospheric pressure. This was repeated twice. The reactor was pressurized to 30 psig with hydrogen and stirred at ambient temperature for 1 hour. The mixture was filtered using a Buchner funnel with a Whatman # 1 filter paper to remove catalyst. The filter cake was washed with isopropyl acetate (80 mL). The procedure was repeated twice more using 617 g and 290.6 g of the 12.8 wt% solution of the starting Cbz compound. The material from the three hydrogenations were combined and

distilled under reduced pressure (28" Hg). The resultant solution (468.68 g) was assayed for the title compound (23.2%, 98.9 % purity).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.96 ppm (1 H, d), 3.67 ppm (1 H, dd), 3.53 ppm (1 H, dd), 3.19 ppm (1 H, s), 2.66-2.75 ppm (1 H, m), 2.49-2.53 ppm (1 H, m), 1.75-1.92 ppm (2 H, m), 1.66-1.74 ppm (1 H, m), 1.48-1.60 ppm (4 H, m), 1.38 ppm (9 H, s), 1.36-1.42 ppm (1 H, m), 0.91 ppm (9 H, s)

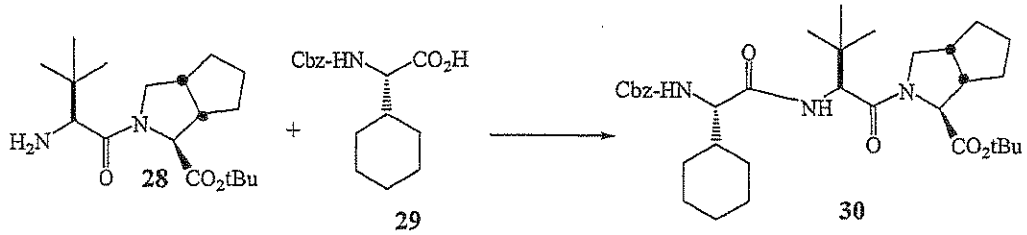
Method 2

[00195] The solution of the Cbz derivative **27** from Example 6, Method 2, was added to 20% $Pd(OH)_2$/water (50%, 12.2 g) in a hydrogenation apparatus. The apparatus was pressurized to 30 psi with hydrogen then stirred for 2 hr at about 20 °C. The mixture was filtered to remove the catalyst, the filter cake washed with isopropyl acetate (160 mL). The combined filtrates were evaporated with about 4 volumes of heptane at 40 °C 2 to 3 times to remove the isopropyl acetate. The resultant slurry was cooled to 0 °C, filtered and the product dried under vacuum to give the title compound (78.8 g, 98.3% purity).

Method 3

[00196] Asolution of (1S,3aR,6aS)-*t*-butyl 2-((S)-2-amino-3,3-dimethylbutanoyl)-octahydrocyclopenta[c]pyrrole-1-carboxylate in isopropyl acetate from Example 6, Method 3, was added to 20% $Pd(OH)_2$ (2 wt% loading, 50% wet) and the mixture was hydrogenated at 2 bar and 20-25 °C for 2 hours. The catalyst was removed by filtration and washed with isopropyl acetate (2 vol.). The filtrate was concentrated to 10 vol. under reduced pressure at 40 °C to give a solution of the title compound in isopropyl acetate.

Example 8: (1S,3aR,6aS)-*t*-butyl 2-((S)-2-((S)-2-(benzyloxycarbonylamino)-2-cyclohexylacetamido)-3,3-dimethylbutanoyl)octahydrocyclopenta[c]pyrrole-1-carboxylate (30)



Method 1

[00197] To a 3 L 3-neck round bottomed flask equipped with an overhead stirrer, thermocouple, addition funnel, nitrogen outlet and ice/water bath was charged HOBt•H_2O (51.74 g; 0.338 mol, 1.05 molar eq.), EDC•HCl (64.8 g; 0.338 mol, 1.05 molar eq.) followed by DMF (197.1 g, 208.8 mL) and agitation was started. The slurry was cooled to 0-5 °C, then a solution of the acid **29** (98.45 g; 0.338 mol, 1.05 molar eq.) in DMF (172.4 g; 182.9 mL) was prepared and charged to the addition funnel. This was added over about 30 minutes to the batch, maintaining the temperature at 0-5 °C. Once addition was complete the reaction mixture was agitated at 0-5 °C for 2 hours. The solution of the amine **28** in isopropyl acetate (450 g solution; containing 104.4 g of acid **29**, 0.322mol) was charged to an addition funnel and added drop wise over 1hour maintaining the temperature at 0-5 °C. Sample analysis indicated incomplete reaction and additional EDC hydrochloride (3.89 g) was added. After 3 hours, analysis of a sample showed 1.8% amine **28** remained. A slurry of HOBT•H_2O (2.59 g; 0.0169 mol), and EDC•HCl (3.24 g; 0.0169 mol) was prepared in DMF (10.44 mL) and cooled to 0-5 °C . A solution of acid **29** (4.92 g; 0.169 mol) in DMF (10.44 mL) was prepared and added to the slurry of EDC•HCl and HOBT in DMF over 30minutes, maintaining the reaction temperature at 0-5 °C. The mixture was stirred for 1 hour at 0-5 °C then added to the original mixture maintaining 0-5 °C. The mixture was stirred for 14 hours at about 25 °C. A solution of histamine•2HCl (11.84 g; 0.064 mol) in water (8.9 mL) was prepared and added to the reaction mixture over 5-10 minutes. A charge of 4-methylmorpholine (13.01 g; 0.129 mol) was added to the batch over about 10 minutes, maintaining the batch temperature at 20±5 °C. The reaction mixture was diluted with isopropyl acetate (443 mL), followed by water (585 mL). A solution of potassium carbonate (57.8 g) in water (585 mL) was added and the mixture was stirred for 0.5 hour. The layers were separated the aqueous layer was extracted twice with isopropyl acetate (twice, 235 mL each). The combined organic phases were washed with 18 % aqueous HCl in water (585 mL), then $NaHCO_3$ (43.25 g) in water (585 mL). The layers were separated to give a light yellow solution of product **30** in isopropyl acetate weighing 1159.3 g (1275 mL) containing 16.0 w/w % **30** in isopropyl acetate.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.74 (1H, d), 7.36 (5H, m), 7.34-7.26 (1H, m), 5.01 (2H, s), 4.51 (1H, d), 4.02 (1H, t), 3.96 (1H, d), 3.73 (1H, m), 3.66 (1H, m), 3.68 (1H, m), 2.53 (1H, m), 1.86-1.76 (2H, m), 1.70-1.30 (10H, m), 1.39 (9H, s), 1.15-0.85 (5H, m), 0.96 (9H, s).

Method 2

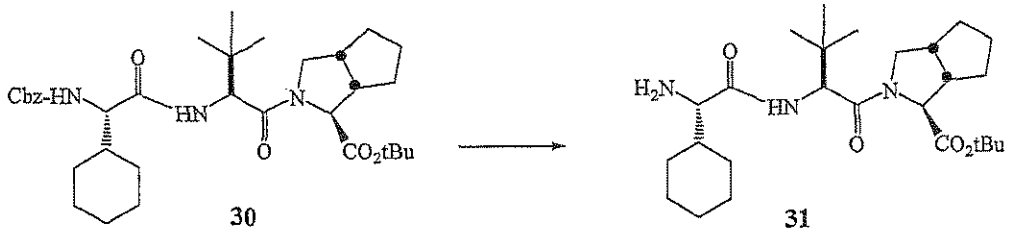
[00198] A solution of Cbz acid **29** (59.62 g) in N-methylpyrrolidone (126 mL) was added to a suspension of EDC.HCL (39.23 g) HOBt hydrate (31.34 g) in N-methylpyrrolidone (221

mL) while maintaining a temperature of about 0 °C. After the addition, the mixture was stirred for 1.5 hours at about 0 °C. A solution of the amine **28** (63.24 g, as prepared in Example 7, Method 2) in isopropyl acetate (632 mL) was added to the mixture maintaining a temperature of about 0 °C. After the addition the mixture was allowed to warm to room temperature and stirred for 5 hours. A solution of potassium carbonate (20.17g) in water (316 mL) was added while maintaining a temperature of about 20 °C. The mixture was vigorously stirred for 0.5 hour. The phases were separated and the organic phase vigorously stirred with potassium carbonate (105.3 g) in water (316 mL). The organic phase was separated and washed with 1N HCl (316 mL), and then water (158 mL) to give a 12.7% w/w solution of the title compound **30** in isopropyl acetate.

Method 3

[00199] To a solution of (1S,3aR,6aS)-*t*-butyl 2-((S)-2-amino-3,3-dimethylbutanoyl)-octahydrocyclopenta[c]pyrrole-1-carboxylate (1 eq) in isopropyl acetate (10 vol) was added NMP (5 vol) followed by EDC (1.15 eq), HOBT hydrate (1.0 eq) and (S)-2-(benzyloxycarbonylamino)-2-cyclohexylacetic acid (**29**, 1.05 eq) and the suspension was stirred at 20-25°C for 4 hr. The mixture was washed with 5% potassium carbonate (5 vol). A mixture of glycine (1 eq), NMM (2 eq) and water (1 vol) was added and the mixture stirred for 4 hr. The mixture was then washed with 5% potassium carbonate (5 vol), 1N hydrochloric acid (5 vol), 5% potassium carbonate (5 vol) and twice with water (5 vol each) to give a solution of the title compound in isopropyl acetate.

Example 9: (1S,3aR,6aS)-*tert*-butyl 2-((S)-2-((S)-2-amino-2-cyclohexylacetamido)-3,3-dimethylbutanoyl)octahydrocyclopenta[c]pyrrole-1-carboxylate (31)



Method 1

[00200] A 60-gallon hasteloy hydrogenating reactor was charged with a solution of the Cbz peptide **30** (15.1 kg) in isopropyl acetate (109 kg). This solution was reduced under vacuum at 50 °C to 68 L. The mixture was then cooled to 25±5 °C and MeOH (15.4 kg) added. This mixture was drained into a container and the reactor was dried. To the dried reactor was charged $Pd(OH)_2/C$ (20%, 1.51 kg). The solution containing the Cbz peptide **30** was added to

the reactor and blanketed with hydrogen (30 psi). The reaction was stirred at 20±5 °C and at 150-220 rpm for 2 hours. After completion, a slurry of activated carbon (0.97 kg) in isopropyl acetate (6.8 kg) was added batch and the mixture stirred for 15 minutes. The mixture was filtered over Celite® (2.0 kg) via Sparkler filter and through a 0.1-um cartridge filter. The reactor was rinsed with isopropyl acetate (33.0 kg) and the rinse was combined with the reaction mixture. The system was rinsed additionally with a mixture of isopropyl acetate (25.6 kg) and MeOH (5.73 kg). The combined organics were reduced under vacuum at 65 °C to 30 L. The solution was cooled to 20-30 °C and heptane added (30.8 kg). Distillation was instituted again and the mixture reduced to 30 L. This procedure was repeated for a total of 4 heptane additions (as above) and solvent reductions (as above). The mixture was cooled to 0-5 °C and the product filtered and washed with heptane (12.6 kg). The wet solid (14.0 kg) was dried under vacuum at 15-20 °C to constant weight to give the title compound (10.17 kg).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.97 (1H, d), 4.49 (1H, d), 3.96 (1H, d), 3.76 (1H, m), 3.67 (1H, m), 3.05 (1H, d), 2.70 (1H, m), 2.53 (1H, m), 1.87-1.77 (2H, m), 1.7-1.3 (10H, m), 1.39 (9H, s), 1.2-0.85 (5H, m), 0.96 (9H, s).

Method 2

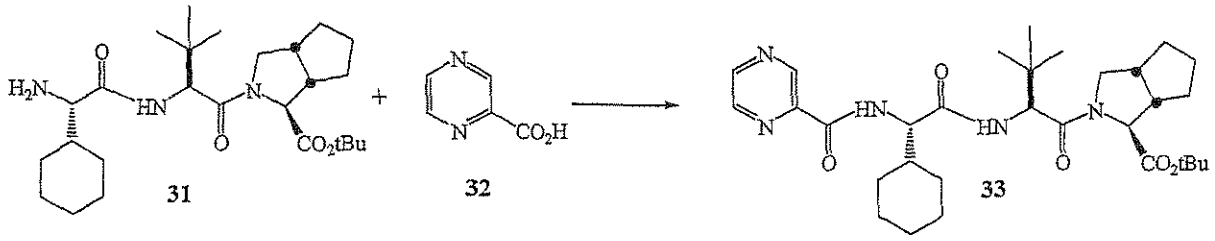
[00201] The solution of compound **30** from Example 8, Method 1, was added to 50% wet 20 wt% $Pd(OH)_2$ on carbon (3.16 g) in a pressure reactor. The reactor was pressurized at 30 psi with hydrogen and the mixture stirred for about 1 hour. The catalyst was filtered, the filter washed with isopropyl acetate and the combined organics distilled to about 65 mL. The mixture was evaporated with heptane (316 mL) several times until analysis indicates <0.5% isopropyl acetate. The resultant slurry is diluted to about 320 mL then warmed to reflux. The solution was slowly cooled to about 5 °C, the suspension stirred for 1 hour then filtered. The filter cake was washed with about 65 mL of heptane and the product dried under vacuum at 30 °C to give the title compound (80.16 g) as a white solid.

Method 3

[00202] The solution of (1S,3aR,6aS)-*t*-butyl 2-((S)-2-((S)-2-(benzyloxycarbonylamino)-2-cyclohexylacetamido)-3,3-dimethylbutanoyl)octahydrocyclopenta[c]pyrrole-1-carboxylate in isopropyl acetate from Example 9, Method 3, was added to 20% $Pd(OH)_2$ (2 wt% loading, 50% wet) and the mixture hydrogenated at 2 bar and 20-25 °C for 2 hour. The catalyst was removed by filtration and washed with isopropyl acetate (1 vol.). The solvent was exchanged by distillation twice with heptane (8.6 vol.) at reflux. The mixture was cooled to 78 °C over 1

hour, then to 22 °C over 2 hours. After 1 hour at 22 °C the suspension was filtered and the cake washed with heptane (3.2 vol.) and the product dried under vacuum at 30 °C with a nitrogen purge to give the title compound.

Example 10: (1S,3aR,6aS)-*t*-butyl 2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)octahydrocyclopenta[c]pyrrole-1-carboxylate (33)



Method 1

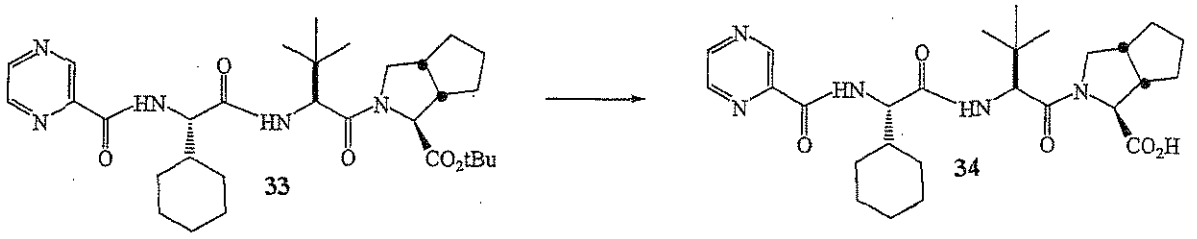
[00203] To a 100mL round bottomed flask was added pyrazine-2-carboxylic acid **32** (1.6070 g, 12.95 mmol) and DMF (4 mL). The slurry was stirred at 20-25 °C. Meanwhile, a solution of CDI was prepared by combining CDI (2.1012 g, 12.96 mmol, 1 molar eq.) and DMF (8.80 g, 9.3 mL) in a 25 mL flask. Mild heating (30 °C) aided in dissolution. The CDI solution was cooled to 20-25 °C and added to the slurry of pyrazine-2-carboxylic acid. Stirring was continued for 1.5 hours to assure complete activation of the acid as carbon dioxide was produced as a byproduct. Meanwhile, the amine **31** (5.0002 g, 10.78 mmol) was dissolved in DMF (14.15 g, 15 mL) with mild warming to 30 °C aided in the dissolution of the material. This solution was cooled to 20-25 °C. The activated pyrazine solution was also cooled to about 15 °C. The solution of compound **31** was added to the activated pyrazine carboxylic acid while maintaining the temperature at 30 °C for about 1 hour. The solution was allowed to cool to 20-25 °C then added to a solution of potassium carbonate (0.25 g) in water (100 mL) at 0 °C. The mixture was filtered and washed with water (four times, 50 mL each). The filter cake was dried under vacuum beginning at 20-25 °C and warmed to 30 °C after 24hours until the cake was constant weight to give the title compound (5.99 g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.19 ppm (1 H, d, J =1.3 Hz), 8.90 ppm (1 H, d, J = 2.5 Hz), 8.76 ppm (1 H, dd, J = 2.4 Hz, 1.5 Hz), 8.50 ppm (1 H, d, J = 9.2 Hz), 8.22 ppm (1 H, d, J = 9.0 Hz), 4.68 ppm (1 H, dd, J = 9.1 Hz, 6.6 Hz), 4.53 ppm (1 H, d, J = 9.0 Hz), 3.96 ppm (1 H, d, J = 4.2 Hz), 3.73 ppm (1 H, dd, J = 10.5 Hz, 7.5 Hz), 3.68 ppm (1 H, dd, J = 10.6 ppm, 3.4 ppm), 2.68-2.74 ppm (1 H, m), 2.52-2.58 ppm (1 H, m), 1.70-1.88 ppm (3 H, m),

1.51-1.69 ppm (7 H, m), 1.31-1.44 ppm (2 H, m), 1.39 ppm (9 H, s), 1.00-1.19 ppm (4 H, m), 0.97 ppm (9 H, s), 0.91-0.97 ppm (1 H, m).

Method 2

[00204] Oxalyl chloride (11.29 mL) was added to a solution of pyrazine-2-carboxylic acid **32** and N-methylmorpholine (59.28 mL) in methylene chloride (150 mL) at about 30 °C. The mixture was stirred for 0.5 hour, then a solution of the amine **31** (50.0 g) in methylene chloride (150 mL) was added at about 30 °C. After 0.5 hour, the mixture was washed with water (250 mL). The aqueous phase was extracted with methylene chloride (100 mL) to give a solution of the title compound in methylene chloride which was used directly in the next step (Example 11, Method 2).

Example 11: (1S)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid (34)



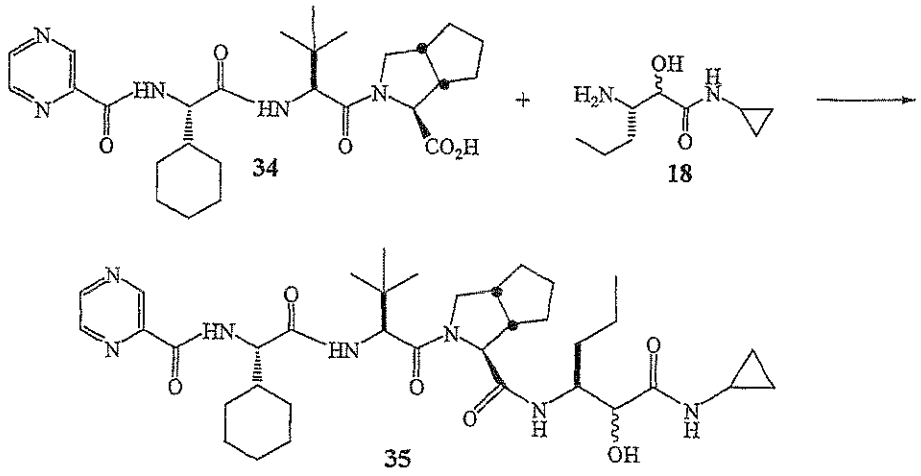
Method 1

[00205] Concentrated HCl (150 g, 0.015 mol, 1.2 molar eq.) was slowly added at 0 °C to a stirred solution of the pyrazinyl peptide **33** (50.0 g) in formic acid (100. 0g). After 3.3 hours, the reaction mixture was diluted with 166.5 g of ice water. Methylene chloride (100 mL) was added and the reaction was stirred for 10 minutes to dissolve the product. The phases were separated and the aqueous layer extracted with methylene chloride (100 mL). The combined organic phases were washed with water (75 mL) then concentrated to about 1/3 volume at 50 °C, 1 atm. Toluene (100 mL) was added at room temperature and the homogeneous solution was evaporated under vacuum at ≤56 °C to about 1/3 volume. The mixture was cooled to 20-25 °C as a precipitate formed. Heptane (75 mL) was slowly added and the slurry stirred for 10-15 minutes. The slurry was filtered and the filter cake was washed with heptane (50 mL). The solids were dried under vacuum at 20-25 °C to give the title compound (15.19 g).

Method 2

[00206] The methylene chloride solution of the starting compound **33** from Example 10, Method 2, was cooled to 0-5 °C then concentrated HCl (200 mL) was added while maintaining a temperature of <10 °C. The mixture was stirred for 3 hours, then diluted with water (200 mL) while maintaining a temperature of < 10 °C. The phases were separated and the aqueous phase extracted with methylene chloride (100 mL). The combined organic phases were washed with water (100 mL) and the aqueous wash phase extracted with methylene chloride. The combined organic extracts were refluxed under an inverse Dean-Stark trap to azeotrope water. The mixture was concentrated by distillation to a minimum volume then diluted with toluene (500 mL) then concentrated by distillation at atmospheric pressure to 250 mL. The mixture was slowly cooled to 20 °C over about 6 hours. The resultant slurry was filtered, the filter cake washed with toluene (100 mL) then dried at about 45 °C in a vacuum oven to provide the title compound (64.7 g) as a pale yellow powder containing about 17 % toluene.

Example 12: (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide (35)



Method 1

[00207] A 500 mL 3-neck round bottomed flask equipped with an overhead stirrer, condenser, thermocouple, and nitrogen outlet was purged with nitrogen for several minutes. The peptide-acid **34** (25.0 g, 0.049 mol), EDC-HCl (10.35 g, 0.054 mol, 1.1 molar eq.), and HOBt-H_2O (8.27 g, 0.054 mol, 1.1 molar eq.) were charged to the flask followed by 175 mL of methylene chloride. The mixture was stirred at room temperature for 1hour then added over 20 minutes to a suspension of hydroxyamide-amine **18** (11.1 g, 0.054 mol, 1.1 molar eq.) in methylene chloride (75 mL) while maintaining a temperature below 10 °C. Upon

complete addition, N-methylmorpholine (5.94 mL, 0.054 mol, 1.1 molar eq.) was added in 2 portions. The mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched by the addition of $NaHCO_3$ (8.0 g) in 200 mL of water. The phases were separated and the organic layer washed with water (175 mL), 0.5 N aq. HCl (200 mL), water (three times, 200 mL each) and saturated NaCl (200 mL) to give a 16% by weight methylene chloride solution of the title compound **35** of 100 A% purity (molar yield 100%).

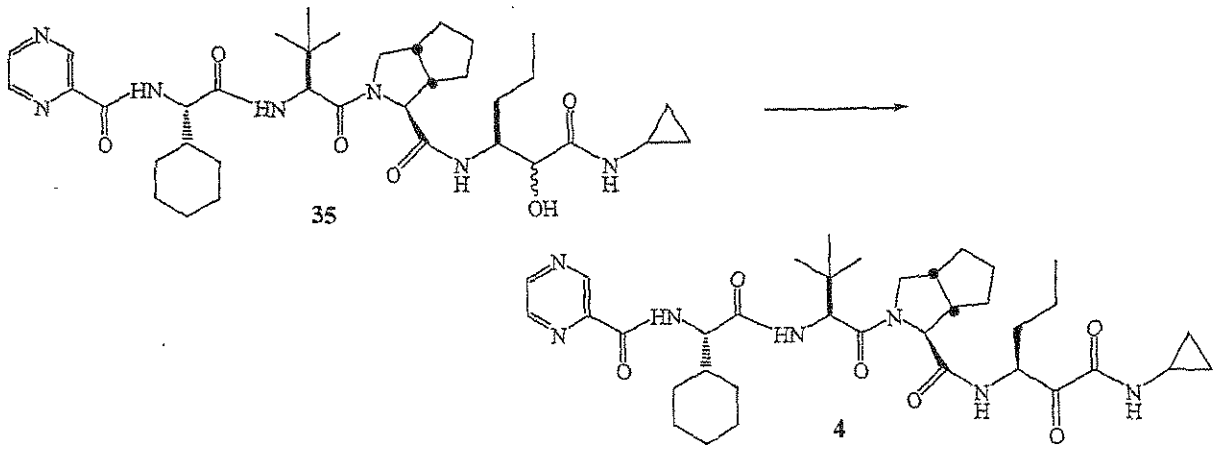
Method 2

[00208] N-methylmorpholine (38.19 mL, 347.3 mmol) was added to a mixture of the peptide-acid **34** (100.0 g, 89.2 wt%, 173.7 mmol), HOBt hydrate (26.79 g, 87.6 wt%, 173.7 mmol), EDCI (36.62 g, 191.04 mmol), and the hydroxyamide-amine **18** in methylene chloride over 30 minutes while maintaining a temperature of 0-5 °C. After the addition, the mixture was warmed to 20 °C and stirred for 5 hours. The mixture was then diluted with water (500 mL) and stirred for about 0.5 hour. The phases were separated and the organic phase washed with 1N HCl (500 mL), 5 wt% aqueous sodium bicarbonate (500 mL) to give a solution of the title compound in methylene chloride, 98.5% AUC purity, 95% solution yield.

Method 3

[00209] Peptide acid **34** (1.00 eq.), EDCI (1.10 eq.), HOBt hydrate (1.00 eq.), and hydroxyamine **18**•HCl (1.05 eq.) were suspended in CH_2Cl_2 (5 vol.) and the mixture was cooled to 0-5 °C. NMM (2.0 eq) was added over 30-60 minutes while maintaining the reaction temperature below 5°C. The reaction mixture was warmed to 20-25 °C over 30 minutes and stirred for additional 5 hours. The reaction was washed with water (5 vol.), 1N HCl (5 vol), and 5 wt% aqueous $NaHCO_3$ (5 vol.) to provide a solution of the title compound in CH_2Cl_2.

Example 13: (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide (4)



Method 1

[00210] A 500 mL 3-neck round bottomed flask equipped with an overhead stirrer, condenser, thermocouple, and nitrogen outlet was purged with nitrogen for several minutes. A methylene chloride solution of the hydroxyamide peptide amide **35** (128.64 g, 16-17wt%, 20.6 g and 30 mmol of **35**) in methylene chloride was added to the reaction flask, followed by the addition of 15% w/w aq. NaBr (13 mL) and 7.5% w/w aq. $NaHCO_3$ (52 mL). The solution was cooled to 5±3 °C in an ice bath. TEMPO (0.7 g) dissolved in methylene chloride (3 mL) was added to the reaction mixture. In a separate Erlenmeyer flask, 10-13% NaOCl solution (23.25 mL, titer = 108 mg/mL, 2.51 g, 33.7 mmol, 1.12 molar eq.) was diluted with water (70 mL). The NaOCl solution was charged to the reaction mixture via addition funnel at a rate that maintained the temperature below 8 °C. The reaction mixture was allowed to stir at 5±3 °C for 1hour. The layers were separated and the organic layer was quenched with 10% (w/w) aq. Na_2SO_3 (100 mL) and washed with water (100 mL). The organic phase was reduced to dryness at reduced pressure and the solid triturated with ethyl acetate (100 mL) and filtered on a Buchner funnel. The solid was submitted for A% analysis (> 99 A%). The isolated wet cake weighed 16.6 g and the molar yield was 80% (wet). The wet cake was not dried as it was not deemed necessary for use-test purposes.

Method 2

[00211] TEMPO (1.09 g, 6.95 mmol) was added to the methylene chloride solution of **35** from Example 12, Method 2, followed by a solution of sodium bicarbonate (21.89 g, 260.5 mmol) in water (400 mL) and the mixture cooled to 0-5 °C. A solution of sodium hypochlorite (122.17 g, 11.64 wt%, 191.04 mmol) was added over 2 hours while maintaining a temperature of 0-5 °C. The mixture was stirred for 1 hour at 0-5 °C, then the phases separated. The organic phase was washed with water (500 mL), 1 wt% aqueous sodium

bisulfite (500 mL) and water (500 mL), then polish filtered. The mixture was distilled at 38-42 °C, 710 mm Hg, to a volume of about 320 mL. Ethyl acetate (44 mL) was added followed immediately by 1.5 g of seed crystals of **4** and the mixture was stirred for 15 minutes at 38-42 °C. Ethyl acetate (800 mL) was added over 3 hours while maintaining a temperature of 38-42 °C. The mixture was then distilled at 38-42 °C, 200-250 mm Hg, to a volume of about 400 mL. Additional ethyl acetate (200 mL) was added over 0.5 hour. The resultant slurry was cooled over 1 hour to 20-25 °C and stirred an additional hour at the same temperature. The mixture was filtered and the filter cake washed with ethyl acetate (twice, 300 mL each) and dried under vacuum with a nitrogen bleed at 45-55 °C to give the title compound **4** as a white solid (102.4 g, 99.7% AUC purity, 85% yield) from the hydroxyamide peptide amide **35.**

Method 3

[00212] TEMPO (0.06 eq) was added to the CH_2Cl_2 solution of **35** from Example 12, method 3, and the solution was stirred at 20-25 °C until all TEMPO dissolved. To this solution was added a solution of $NaHCO_3$ (1.5 eq.) in water (4 vol.). The resulting biphasic mixture was cooled to 0-5 °C. While maintaining the reaction temperature at 0-5 °C, a 10-13 wt% NaOCl solution (1.10 eq.) was added over 2-3 hours and the mixture stirred for additional one hour. The layers were separated and the organic layer was washed at 0-5 °C with H_2O (5 vol.), 1 wt% Na_2SO_3 (5 vol.), and H_2O (5 vol.). Glacial acetic acid (0.12 eq.) was added to the solution of compound **4** in CH_2Cl_2 to stabilize compound **4**.

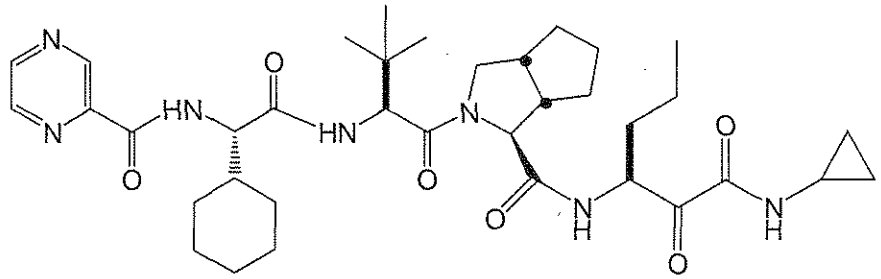
Example 14: Recrystallization of Compound of Formula 4.

[00213] The solution of Compound **4** from Example 13, Method 3, was filtered through Celite, and the filtrate solution was reduced to 3.1-3.3 volumes by vacuum distillation at lower than 20 °C. After distillation, the solution was brought to 38-42 °C before EtOAc (0.80 vol.) was added, followed by the addition of Compound **4** seed (1.5 wt% relative to **34**, Example 12). The resulting mixture was stirred for 15 minutes at 38-42 °C. EtOAc (8 vol.) was added over 3 hours to this mixture while maintaining a temperature of 38-42 °C. The total volume of the slurry was then reduced to 3.9-4.1 volumes by vacuum distillation at 38-42 °C. To this mixture was added EtOAc (2 vol.) over 30 minutes while maintaining the batch temperature at 38-42 °C. The resulting slurry was then cooled to 20-25 °C over 1 hour and stirred at 20-25 °C for additional 1 hour. The slurry was filtered. The filter cake was washed with EtOAc (twice, 3 vol. each) and dried under vacuum with a nitrogen bleed at 45-55 °C for 6 hours.

[00214] To the dried filter cake was added 2.2-2.4 volumes of CH_2Cl_2 to a total volume of 3.1-3.3 volumes. The mixture was brought to 38-42 °C to give a homogeneous solution. EtOAc (0.80 vol) was added, followed by the addition of Compound **4** seed (1.5 wt% relative to **34**, Example 12). The resulting mixture was stirred for 15 minutes at 38-42 °C. EtOAc (8 vol.) was added over 3 hours to this mixture while maintaining a temperature of 38-42 °C. The total volume of the slurry was then reduced to 3.9-4.1 volumes by vacuum distillation at 38-42°C. EtOAc (2 vol.) was added over 30 minutes to this mixture while maintaining the batch temperature at 38-42°C. The resulting slurry was then cooled to 20-25 °C over 1 hour and stirred at 20-25 °C for additional one hour. The slurry was filtered and the filter cake was washed with EtOAc (twice, 3 vol. each) and dried under vacuum with a nitrogen bleed at 45-55 °C for 12 hour to give purified Compound **4**.

What is claimed is:

1. A process of purifying the compound of Formula **4**, comprising:



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a) dissolving the compound of Formula **4** in an organic solvent to obtain a solution of the compound of Formula **4**,

b) adding an acid to the solution of the compound of Formula **4**, and

c) concencentrating the solution of the compound of Formula **4** to obtain the compound in a solid form.

2. The process of claim 1, wherein the organic solvent is methylene chloride, and the acid is acetic acid.