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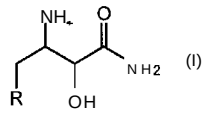
(54) **Title:** PROCESS AND INTERMEDIATES FOR THE PREPARATION OF 3-AMINO-4-CYCLOBUTYL-2-HYDROXY-BUTANAMIDE AND SALTS THEREOF



(I)

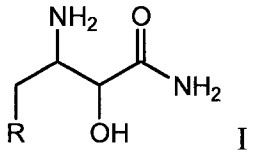
(57) **Abstract:** The present invention relates to synthetic processes useful in the preparation of a compound of Formula (I), and salts thereof. Compounds of Formula (I) and salts thereof have application in the preparation of inhibitors of the hepatitis C virus, such as (lR,5S)-N-[3-amino- 1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(l ,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl- 1-oxobutyl]-6, 6-dimethyl-3-azabicyclo[3. 1.0]hexan-2(S)-carboxamide. The present invention also encompasses intermediates useful in the disclosed synthetic processes and the methods of their preparation.

TITLE OF THE APPLICATION

PROCESS AND INTERMEDIATES FOR THE PREPARATION OF 3-AMΓNO-4-CYCLOBUTYL-2-HYDROXYBUT ANAMIDE AND SALTS THEREOF

FIELD OF THE INVENTION

The present invention relates to synthetic processes useful in the preparation compounds, having the structure of Formula I:




I

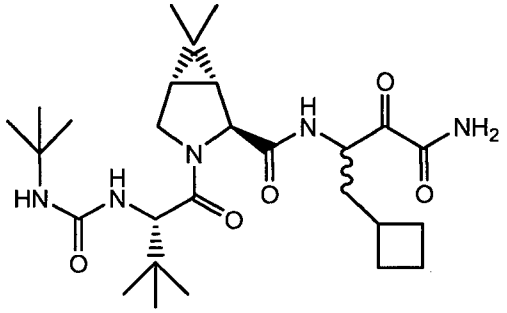
and related compounds and salts thereof. Such compounds and salts have application in the preparation of inhibitors of the hepatitis C virus, such as (lR,5S)-N-[3-amino-l-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(l ,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-l-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide. The present invention also encompasses intermediates useful in the disclosed synthetic processes and the methods of their preparation.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Current treatments for HCV infection include immunotherapy with recombinant interferon-a alone or in combination with the nucleoside analog ribavirin.

U.S. Patent No. 7,012,066 describes compounds that are useful as HCV NS3 inhibitors and useful in the treatment of HCV and conditions caused by HCV infection. U.S. Patents Nos. 7,728,165, 7,723,531, 7,595,419, 7,569,705, 7,528,263, 7,326,795, 7,309,717, and 6,992,220; U.S. Patent Application Publications Nos. US201 1/0034705, US20 10/0256393, US20 10/0 145069, US2010/0145013, US2010/01 13821, US2009/0326244 US2008/0254128, and US2008/0193518; and International Patent Application Publication WO2009/073380 describe processes for preparing such compounds.

The compound of Formula I is an intermediate used in the preparation of the HCV protease inhibitor (lR,5S)-N-[3-amino-l-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(l,l-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-l-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide, which has the following structure of Formula II:



II.

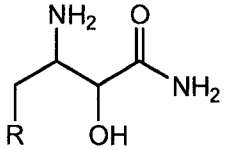
The compound of Formula II and other related compounds are disclosed and claimed in U.S. Patent No. 7,012,066, as compounds useful for treating HCV, specifically as potent inhibitors of intermolecular cleavage at the NS3/4A site. Compound of Formula I are useful as intermediates for preparation of the compound of Formula II, and of other related compounds, and there is a continuing need for improved chemical processes for preparing compounds and intermediates of compounds that are potent inhibitors of intermolecular cleavage at the HCV NS3/4A site. This disclosure addresses this need.

## SUMMARY OF THE INVENTION

The present invention relates to chemical processes and intermediates useful in the synthesis of the compound of Formula I, and related compounds, that are useful as intermediates in the preparation of compounds that are potent inhibitors of intermolecular cleavage at the HCV NS3/4A site.

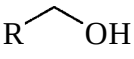
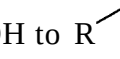
The chemical processes of the present invention afford advantages over previously known procedures and include a more efficient, high-yielding and cost-effective route to the compound of Formula I and salts thereof. Specifically, the chemical processes of the present invention offer shorter synthetic routes with higher overall yields, up to 46-51% overall, compared to the previously reported processes, including the processes disclosed in WO2004/1 13272 (26.4% overall yield), WO2008/082486 (30.5-33.3% overall yield) and WO2009/085858 (32% overall yield). In addition, the chemical processes of this invention afford operational advantages on an industrial scale, including improved efficiency and reduced costs.

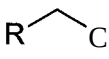
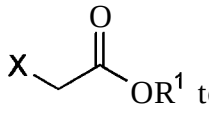
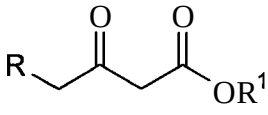
More particularly, the present application relates to processes and intermediates for preparing a compound of Formula I,



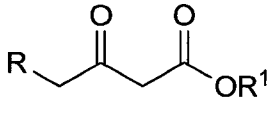
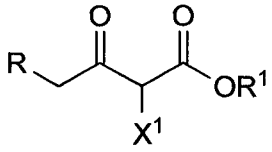
I

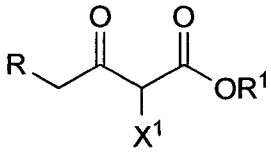
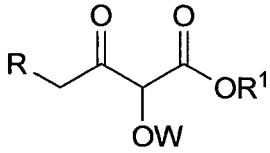
or salt thereof, wherein R is selected from the group consisting of $C_{3-8}$cycloalkyl and Ci.ioalkyl, said process comprising one or more of the following steps:

(1) converting  to  ;

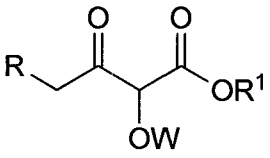
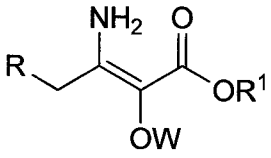
(2) coupling  with  to form  ,

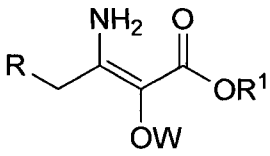
where $R^1$ is selected from the group consisting of Ci_8alkyl and benzyl, and X is a halogen;

(3) halogenating  to form  , where $X^1$ is a halogen;

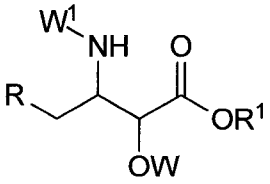
(4) reacting  with WOH to form  , where W is a protecting group;

(5) conducting an enamine formation reaction to convert

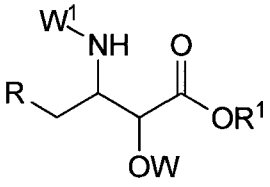
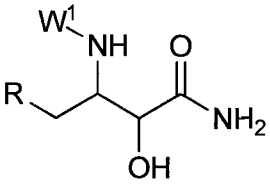
 to  ;

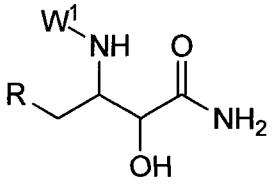
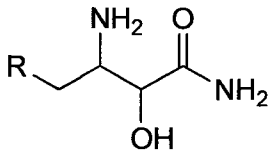


(6) reducing in the presence of $W^1$ to form

 , where $W^1$ is a protecting group;

(7) performing aminolysis and deprotecting the protected hydroxyl

 to form  ; and

(8) deprotecting the protected amine of  to form  .

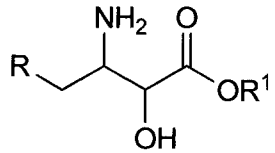
In embodiments, the compound of Formula I may be present as an amorphous compound, or as a salt thereof.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention includes chemical processes useful in the synthesis of the compound of Formula I, above, and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts and/or hydrates are useful as intermediates for the preparation of compounds that are HCV protease inhibitors *(e.g.*, HCV NS3 protease inhibitors).

In a first embodiment of the invention, R is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In aspects of this embodiment, R is cyclobutyl. In all aspects of this embodiment, all other groups are as provided in the general process above.

In a second embodiment of the invention, step (8) further comprises adding an acid to  to form a salt. In aspects of this embodiment, the acid is selected from the group consisting of ammonium sulfate, ammonium nitrate, ammonium chloride, trifluoroacetic acid, $H2SO_4$, HCl, ¾P0 $_4$, citric acid, methanesulfonyl acid, *p*-toluenesulfonic acid, and p-toluenesulfonic acid pyridinium salt. In particular instances of this aspect, the acid is selected from the group consisting of trifluoroacetic acid, ¾S0 $_4$, HCl and H3PO4; in specific instances, the acid is selected from the group consisting of trifluoroacetic acid and HCl. In all

aspects and instances of this second embodiment, all other groups are as provided in the general formula above or in the first embodiment.

In a third embodiment of the invention, the process further comprises step (9) recrystallizing the product of step (8). In aspects of this embodiment, step (9) comprises recrystallizing the product of step (8) from water and acetonitrile. In all aspects of this third embodiment, all other groups are as provided in the general process above or in either or both of the first or second embodiments.

In a fourth embodiment of the invention, step (1) comprises: (a) reacting **R**⌒**OH** with a reagent selected from alkyl sulfonyl chlorides, aryl sulfonyl chlorides and halogenating agents to form **R**⌒$L_5$ wherein L is a leaving group selected from the group consisting of methanesulfonyloxy, ethanesulfonyloxy, chloromethanesulfonyloxy, /?-toluenesulfonyloxy, benzensulfonyloxy, trifluoromethanesulfonyloxy and halogens, and (b) further reacting **R**⌒**L** with at least one cyanating reagent to form **R**⌒**CN.**

In a first aspect of this fourth embodiment, L is selected from the group consisting of methanesulfonyloxy, ethanesulfonyloxy, chloromethanesulfonyloxy, /?-toluenesulfonyloxy, benzensulfonyloxy, trifluoromethanesulfonyloxy, CI, Br and I.

In a second aspect of this fourth embodiment, step (l)(a) comprises reacting **R**⌒**OH** with a sulfonyl chloride selected from the group consisting of methanesulfonyl chloride, ethanesulfonyl chloride, chloromethanesulfonyl chloride, p-toluenesulfonyl chloride, benzensulfonyl chloride and trifluoromethanesulfonyl chloride, to form R⌒L, where L is selected from the group consisting of methanesulfonyloxy, ethanesulfonyloxy, chloromethanesulfonyloxy, j^-toluenesulfonyloxy, benzensulfonyloxy and trifluoromethanesulfonyloxy.

In a first instance of this second aspect, step (l)(a) comprises reacting **R**⌒**OH** with a halogenating agent selected from the group consisting of $Cl_2$, $Br_2$, $1_2$, $PC1_3$, $PBr_3$, $PI_3$, $PC1_5$, $PBr_5$, $PI_5$, $POCl_3$, $POBr_3$, $POI_3$, $SOCl_2$, $SOBr_2$, $SOI_2$, N-chlorosuccinimide, N-bromosuccinimide, N-iodosuccinimide, HC1, HBr, HI, **PPI13,** $CC1_4$, $CBr_4$, **CI4,** to form **R**⌒**L**; and in specific instances, the halogenating agent is selected from the group consisting of $POCl_3$ and $SOCl_2$.

In a second instance of this second aspect, the reaction of step (l)(a) is conducted in an organic solvent, such as dichloromethane, ethyl acetate, isopropyl acetate, methyl *tert*-butyl

ether, tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentyl methyl ether, toluene, acetonitrile, N,N-dimethylformaide, N,N-dimethylacetamide, N-methylpyrrolidone or N-ethylpyrrolidone.

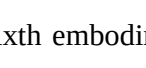
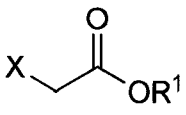
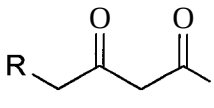
In a third instance of this second aspect, the reaction of step (l)(a) is conducted in the presence of an organic trialkylamine, such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, tributylamine or trimethylamine.

In a third aspect of this fourth embodiment, the cyanating agent of step (l)(b) is selected from the group consisting of HCN, NaCN, KCN, $Cu(CN)_2$ and $Zn(CN)_2$. In particular instances of this aspect, the cyanating agent is selected from the group consisting of HCN, NaCN, KCN and $Zn(CN)_2$; and in specific instances, the cyanating agent is NaCN or KCN.

In a fourth aspect of this fourth embodiment, the cyanation reaction of step (l)(b) is conducted in an organic solvent such as dimethylsulfoxide, methyl *tert*-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentyl methyl ether, toluene, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or N-ethylpyrrolidone.

In all aspects and instances of this fourth embodiment, all other groups are as provided in the general process above or in any or all of the first through third embodiments.

In a fifth embodiment of the invention, in step (2), $R^1$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl and benzyl. In aspects of this embodiment, $R^1$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, *tert*-butyl and benzyl; in specific instances, $R^1$ is ethyl. In all aspects and instances of this fifth embodiment, all other groups are as provided in the general formula above or in any or all of the first through fourth embodiments.

In a sixth embodiment of the invention, step (2) comprises reacting  with  in the presence of zinc dust and an activating agent to form  , wherein said activating agent is selected from the group consisting of $(CH_3)_3SiCl$, $CH_3SO_3H$ and HC1.

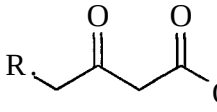
In a first aspect of this sixth embodiment, step (2) further comprises removing dimer impurities by use of an inorganic salt. In particular instances of these aspects, the inorganic salt is $Na_2S_2O_5$.

In a second aspect of this sixth embodiment, step (2) is conducted in a solvent such as tetrahydrofuran, 2-methyl-tetrahydrofuran, cyclopentyl methyl ether or diisopropyl ether.

In a third aspect of this sixth embodiment, step (2) is conducted in the presence of an organic and inorganic acid, such as chlorotrimethylsilane, hydrogen chloride, methanesulfonic acid, sulfuric acid or acetic acid.

In all aspects and instances of this sixth embodiment, all other groups are as provided in the general formula above or in any or all of the first through fifth embodiments.

In a seventh embodiment of the invention, step (3) comprises reacting



with a halogenating agent selected from the group consisting of N-iodosuccinimide, $SO_2Cl_2$, N-chlorosuccinimide, l,3-dichloro-5,5-dimethylhydantoin, trichloroisocyanuric acid, N-bromosuccinimide, bromine and l,3-dibromo-5,5-dimethylhydantoin.

In a first aspect of this seventh embodiment, the halogenating agent is selected from the group consisting of $SO_2Cl_2$, N-chlorosuccinimide, l,3-dichloro-5,5-dimethylhydantoin, and N-bromosuccinimide. In particular instances of this aspect, the halogenating agent is $SO_2Cl_2$.

In a second aspect of this seventh embodiment, the reaction of step (3) is conducted in an organic solvent such as methyl *tert*-butyl ether, dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentyl methyl ether or acetonitrile.

In all aspects and instances of this seventh embodiment, all other groups are as provided in the general formula above or in any or all of the first through sixth embodiments.

In an eighth embodiment of the invention, X and $X^1$ are independently selected from the group consisting of F, CI, Br, and I. In aspects of this embodiment, X and $X^1$ are independently selected from the group consisting of CI, Br, and I. In a particular aspect, X is Br and $X^1$ is CI. In all aspects of this eighth embodiment, all other groups are as provided in the general formula above or in any or all of the first through seventh embodiments.

In a ninth embodiment of the invention, in step (4), W is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, *p*-methoxybenzoyl, />-toluoyl, benzoyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, silyl and tosyl groups.

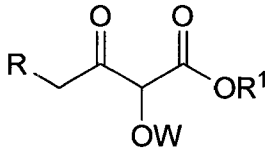
In a first aspect of this ninth embodiment, W is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, />-methoxybenzoyl, *p*-toluoyl and benzoyl. In a particular aspect, W is />-methoxybenzoyl.

In a second aspect of this ninth embodiment, the reaction of step (4) is conducted in an organic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, N-ethylpyrrolidone or acetonitrile.

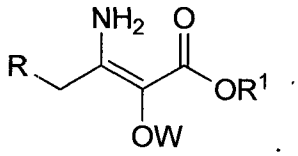
In a third aspect of this ninth embodiment, the reaction of step (4) is conducted in the presence of an organic trialkyl amine such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, tributylamine or trimethylamine; or in the presence of an inorganic base such as sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium phosphate, potassium phosphate, sodium hydroxide or potassium hydroxide.

In all aspects of this ninth embodiment, all other groups are as provided in the general formula above or in any or all of the first through eighth embodiments.

In a tenth embodiment of the invention, the enamine formation reaction of



step (5) comprises reacting with an ammonia-containing compound selected from the group consisting of $NH_4OAc$, $NH_4Cl$, $NH_3$, ammonium sulfate, ammonium formate and ammonium glycolate to form



.

In a first aspect of this tenth embodiment, the ammonia-containing compound is $NH_4OAc$.

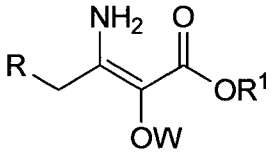
In a second aspect of this tenth embodiment, the enamine formation reaction of step (5) is conducted in an organic solvent or combination of two or more organic solvents such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, sec-butanol, tetrahydrofuran, methyl *tert*-butyl ether, acetonitrile or any solvent that can effectively remove water via azeotropic distillation.

In all aspects of this tenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through ninth embodiments.

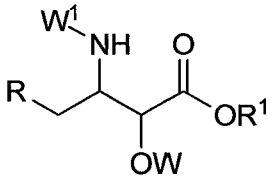
In an eleventh embodiment of the invention, in step (6), $W^1$ is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, p-methoxybenzoyl, /?-toluoyl, benzoyl, benzyl, /?-methoxybenzyl, 3,4-dimethoxybenzyl, silyl and tosyl groups. In aspects of this embodiment, $W^1$ is selected from the group consisting of benzyloxycarbonyl,

*tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and p-methoxybenzyl. In particular instances of these aspects, $W^1$ is *tert*-butyloxycarbonyl. In all aspects of this eleventh embodiment, all other groups are as provided in the general formula above or in any or all of the first through tenth embodiments.

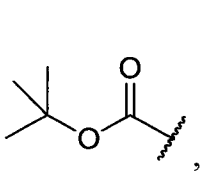
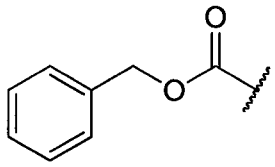
In a twelfth embodiment of the invention, step (6) comprises reacting



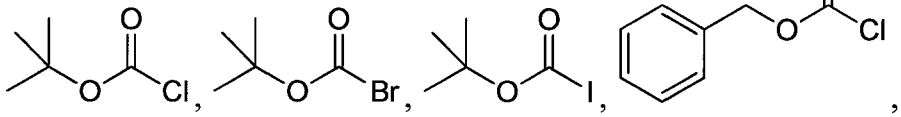
with a reducing agent in the presence of a protecting reagent to form



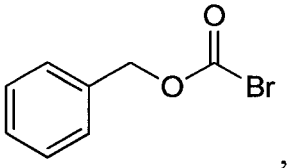
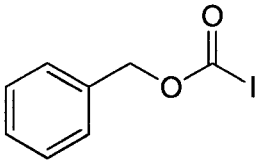
, wherein $W^1$ is a protecting group selected from the group consisting of

and ($Ci_{-6}$alkyl)CO-; the protecting reagent is selected from the group consisting of



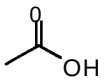
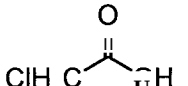
,

, ($C_{1-6}$alkyl)COCl, ($Ci_{-6}$alkyl)COBr and ($C]_{-6}$alkyl)COI; and the reducing agent is selected from the group consisting of $NaBH_4$, $KBH_4$, $LiBH_4$, $Zn(BH_4)_2$, $KBH(OAc)_3$, $NaBH(OAc)_3$, $LiBH(OAc)_3$, $Zn(BH(OAc)_3)_2$, $KBH_3(CN)$, $NaBH_3(CN)$, $LiBH_3(CN)$, $Zn(BH_3(CN))_2$, **$BH_3NH3$,** $BH_3C(CH_3)_3NH_2$, $BH_3N(CH_2CH_3)_2H$, $BH_3$-tetrahydrofuran, $BH_3S(CH_3)_2$ and $BH_3$-pyridine.

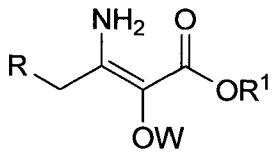
In a first aspect of this twelfth embodiment, step (6) further comprises treating the reaction mixture with an amine followed by treating with a base. In particular instances of these aspects, the amine is selected from $NR^a_3$, where each $R^a$ is independently selected from the group consisting of H and $Ci_{-6}$alkyl, where each $Ci_{-6}$alkyl is substituted by 0, 1 or 2 independently selected substituents selected from the group consisting of OH and COOH.

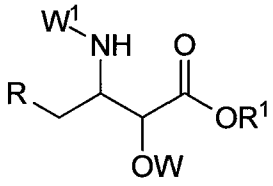
In a second aspect of this twelfth embodiment, the reducing agent is selected from the group consisting of $NaBH_4$ and $NaBH_3(CN)$.

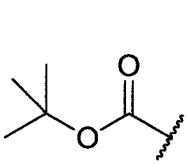
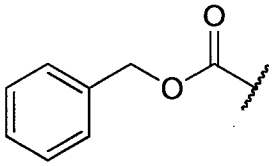
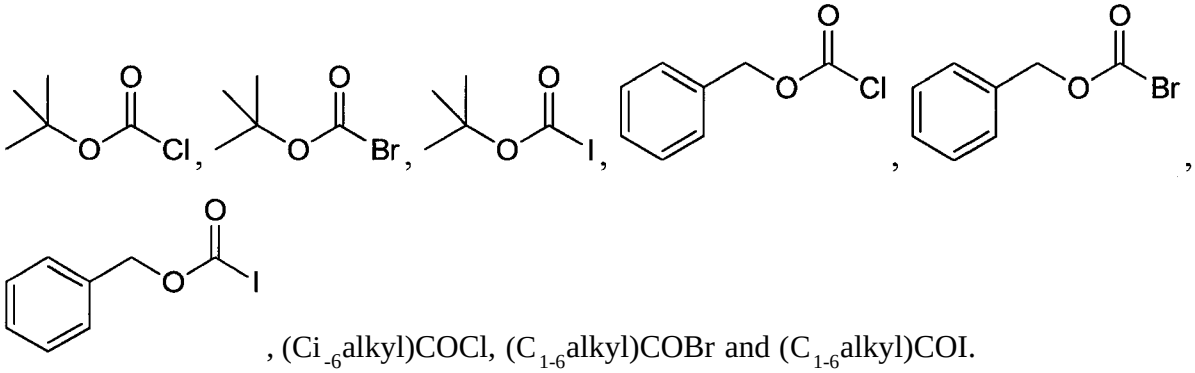
In a third aspect of this twelfth embodiment, step (6) is conducted in the presence of an acid selected from the group consisting of HC1, HBr, *HI,*  ,  ,  , ,  , $(C_{1-6}alkyl)S0_3H$, trifluoroacetic acid, />-toluenesulfonic acid, $ArS0_3H$, $CF_3S0_3H$, glycolic acid, tartaric acid, citric acid, malonic acid, propionic acid, oxalic acid, trifluoroacetic acid, sulfamic acid, salicylic acid and succinic acid; wherein Ar is one or more rings selected from the group consisting of: a) 5- or 6-membered saturated or unsaturated monocyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, and c) 11- to 15-membered saturated or unsaturated tricyclic rings with 0, 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, wherein Ar is substituted with 0 to 4 independently selected substituents $R^{Ar}$ or oxo; wherein each $R^{Ar}$ is independently selected from the group consisting of H, halogen atoms, -OH, $Ci_{-6}$alkoxy, $C_{1-6}$alkyl, -CN, $-CF_3$, $-OCF_3$, -C(0)OH, $-C(0)CH_3$, $C_{3-8}$cycloalkyl, $C_{3-8}$cycloalkoxy, $C_{1-6}$haloalkyl, $-NH_2$, $-NH(C_{1-6}alkyl)$ and $-N(C]_{-6}alkyl)(Ci_{-6}alkyl)$. In particular instances of this aspect, the reducing agent is selected from the group consisting of $NaBH_4$ and $NaBH_3(CN)$, and the acid is selected from the group consisting of $CH_3S0_3H$ and glycolic acid.

In a fourth aspect of this twelfth embodiment, the reduction reaction of step (6) is conducted in an organic solvent or combination of two or more organic solvents such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, sec-butanol, tetrahydrofuran, methyl *ter*t-butyl ether, acetonitrile, cyclopentyl methyl ether, ethyl acetate or isopropyl acetate.

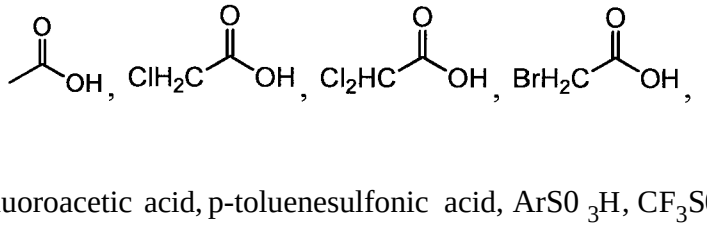
In all aspects and instances of this twelfth embodiment, all other groups are as provided in the general formula above or in any or all of the first through eleventh embodiments.

In a thirteenth embodiment of the invention, step (6) comprises (a) reacting  with a reducing agent and an acid; and (b) further reacting the product of step (6)(a) with at least one protecting reagent in the presence of a base to form



; wherein the reducing agent is selected from the group consisting of $NaBH_4$, $KBH_4$, $LiBH_4$, $Zn(BH_4)_2$, $KBH(OAc)_3$, $NaBH(OAc)_3$, $LiBH(OAc)_3$, $Zn(BH(OAc)_3)_2$, $KBH_3(CN)$, $NaBH_3(CN)$, $LiBH_3(CN)$, $Zn(BH_3(CN))_2$, $BH_3NH_3$, $BH_3C(CH_3)_3NH_2$, $BH_3N(CH_2CH_3)_2H$, $BH_3$-tetrahydrofuran, $BH_3S(CH_3)_2$ and $BH_3$-pyridine; $W^1$ is a protecting group selected from the group consisting of  ,  and $(Ci_{-6}alkyl)CO$-; and the protecting reagent is selected from the group consisting of  , $(Ci_{-6}alkyl)COCl$, $(C_{1-6}alkyl)COBr$ and $(C_{1-6}alkyl)COI$.

In a first aspect of this thirteenth embodiment, the reducing agent is selected from the group consisting of $NaBH_4$ and NaB¾(CN).

In a second aspect of this thirteenth embodiment, the acid is selected from the group consisting of HCl, HBr, HI,  , $(C_{1-6}alkyl)S0_3H$, trifluoroacetic acid, p-toluenesulfonic acid, $ArS0_3H$, $CF_3S0_3H$, glycolic acid, tartaric acid, citric acid, malonic acid, propionic acid, oxalic acid, sulfamic acid, salicylic acid and succinic acid; wherein Ar is one or more rings selected from the group consisting of a) 5- or 6-membered saturated or unsaturated monocyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, and c) 11- to 15-membered saturated or unsaturated tricyclic rings with 0, 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, wherein Ar is substituted with 0 to 4

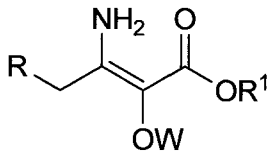
independently selected substituents $R^{Ar}$ or oxo; wherein each $R^{Ar}$ is independently selected from the group consisting of H, halogen atoms, -OH, $C_{1-6}$alkoxy, $C_{1-6}$alkyl, -CN, $-CF_3$, $-OCF_3$, -C(0)OH, -C(0)$CH_3$, $C_{3-8}$cycloalkyl, $C_{3-8}$cycloalkoxy, $C_{1-6}$haloalkyl, $-NH_2$, -NH($C_{1-6}$alkyl) and -N($C_{1-6}$alkyl)(Ci-**6alkyl).** In instances of this aspect, the reducing agent is selected from the group consisting of $NaBH_4$ and $NaBH_3(CN)$, and the acid is selected from the group consisting of $CH_3S0_3H$ and glycolic acid.

In a third aspect of this thirteenth embodiment, the base is selected from the group consisting of NaOH, $NaHC0_3$, $Na_2C0_3$, KOH, $K_2C0_3$, $K_3P0_4$ and $(C_{1-6}alkyl)_3N$. In instances of this aspect, the base is NaOH or $K_3P0_4$.

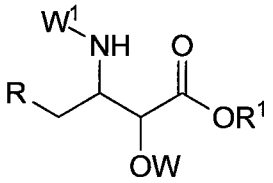
In a fourth aspect of this thirteenth embodiment, step (6)(b) further comprises treating the reaction mixture with an amine followed by treating with a base. In instances of this aspect, the amine is selected from $NR^a_3$, where each $R^a$ is independently selected from the group consisting of H and $C_{1-6}$alkyl, where each $C_{1-6}$alkyl is substituted by 0, 1 or 2 independently selected substituents selected from the group consisting of OH and COOH. In particular instances, the amine is selected from the group consisting of diethanolamine and glycine; in still more particular instances, the amine is glycine.

In all aspects and instances of this thirteenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through twelfth embodiments.

In a fourteenth embodiment of the invention, step (6) comprises reacting

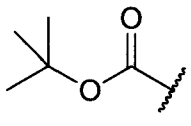


with a reducing agent in the presence of$W^1$ to form



;

wherein $W^1$ is a protecting group selected from the group consisting of



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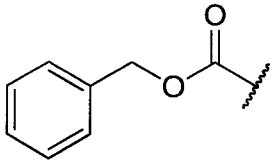
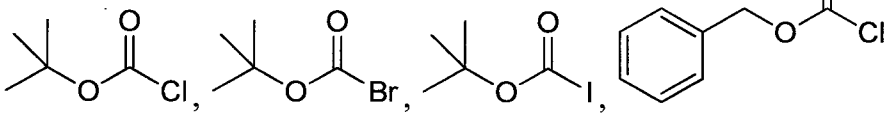


and ($Ci_{-6}$alkyl)CO-; the protecting reagent is selected from the group consisting of



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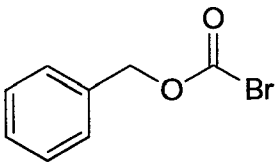
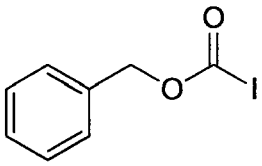
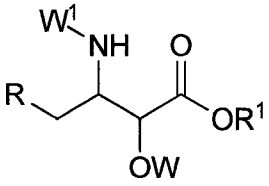
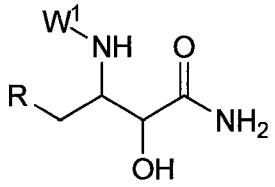



, , $(C_{1-6}alkyl)COCl$, $(Ci_{-6}alkyl)COBr$ and $(C_{1-6}alkyl)COI$; and the reducing agent is a transition metal catalyst and hydrogen gas, where the transition metal catalyst is selected from the group consisting of Pd/C, Ru/C, $Ru0_2$, Rh/C, Pt/C, $Pt/Al_20_3$, $Pt0_2$, $Pd(OH)_2$, PdO, Ir/C, $Ir0_2$ and $Ir/CaC0_3$. In aspects of this embodiment, the transition metal is $Ir/CaC0_3$. In all aspects of this fourteenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through thirteenth embodiments.

In a fifteenth embodiment of the invention, the reaction of step (7) comprises reacting  with ammonia to form  .

In a first aspect of this fifteenth embodiment, the reaction of step (7) is conducted in conducted in an organic solvent such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol or sec-butanol. In particular instances of this first aspect, the solvent is methanol.

In a second aspect of this fifteenth embodiment, the ammonia is provided in the form of gaseous ammonia. In particular instances of this aspect, the gaseous ammonia is provided at a pressure in a range of from 5 psi to 500 psi, in particular in a range of from 10 to 200 psi, more particularly in a range of from 20 to 150 psi.

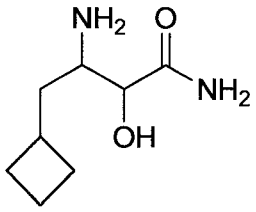
In a second aspect of this fifteenth embodiment, the ammonia is provided in solution. In a first instance of this aspect, the ammonia is provided as a solution in methanol. In a second instance of this aspect, the ammonia is provided at a solution concentration in a range of from 1M to 10M, particularly 2M to 9M, more particularly 4M to 8M.

In a third aspect of this fifteenth embodiment, the reaction of step (7) is conducted in the presence with of a catalyst. In particular instances of this aspect, the catalyst is selected from the group consisting of $CaCl_2$, $MgCl_2$, $ZnCl_2$ and $CeCl_2$, and in more particular instances, the catalyst is $CaCl_2$.

In all aspects and instances of this fifteenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through fourteenth embodiments.

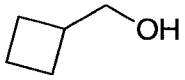
In a sixteenth embodiment of the invention, the reaction of step (8) is conducted in an organic solvent such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol or sec-butanol, methyl *tert*-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentyl methyl ether, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or N-ethylpyrrolidone. In this sixteenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through fifteenth embodiments.

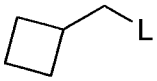
A seventeenth embodiment of the invention relates to processes for preparing a compound of Formula la:



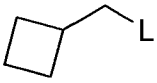

Ia

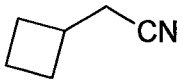
or a salt thereof, said process comprising:

(l)(a) reacting 

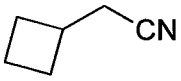
with methanesulfonyl chloride to form 

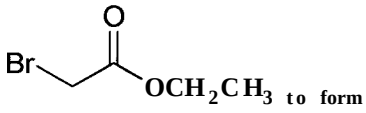
, wherein L is methanesulfonyloxy, and

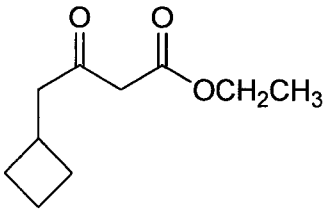
(1)(b) further reacting 

with NaCN to form 

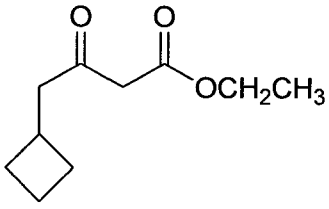
;

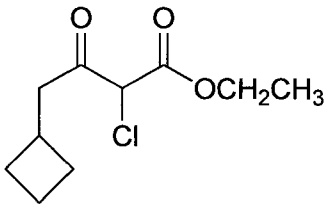
(2) coupling 

with 

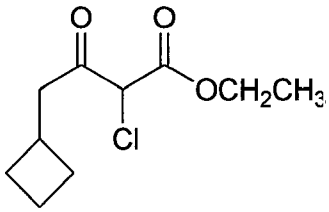
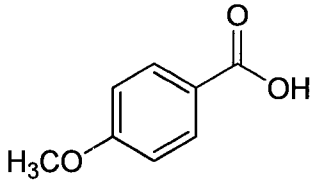
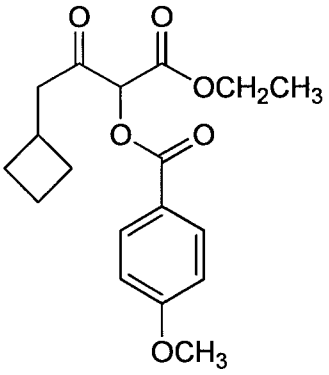
to form 

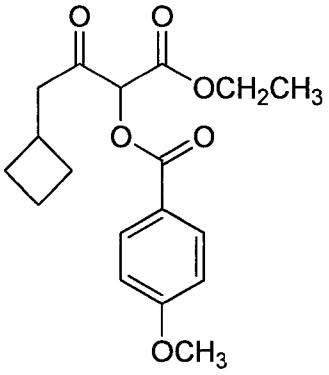
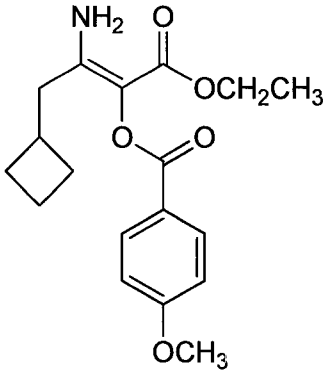
;

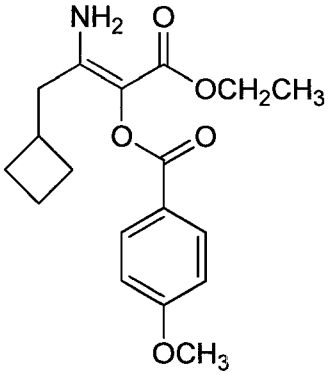
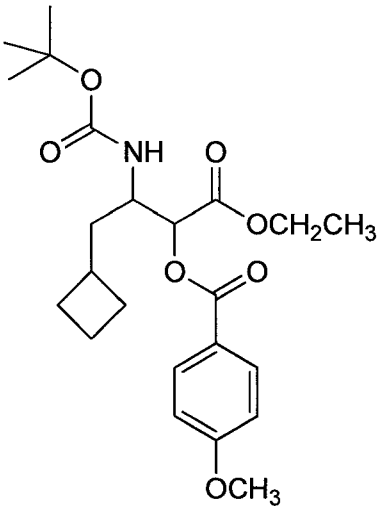
(3) halogenating 

to form 

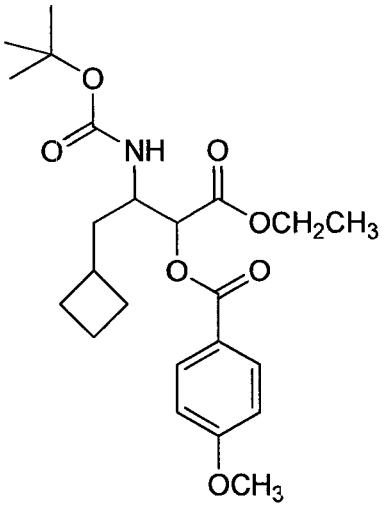
;

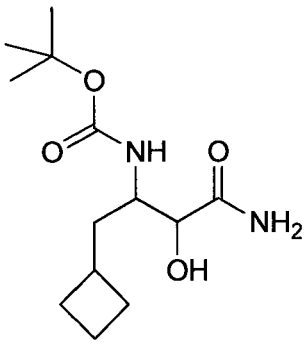
(4) reacting  with  to form  ;

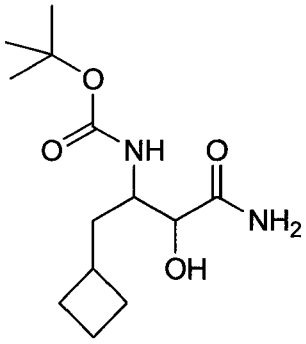
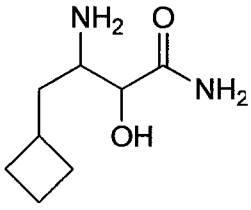
(5) conducting an enamine formation reaction by reacting  with $NH_4OAc$ to form  ;

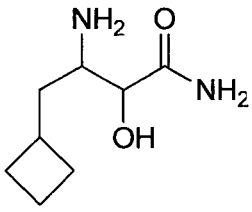
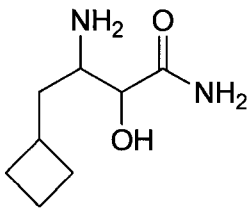
(6) reducing  to form  ;

(7) performing aminolysis and deprotecting the protected hydroxyl



to form  ; and

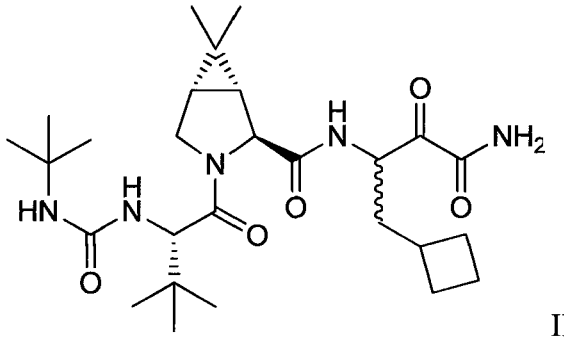
(8) deprotecting the protected amine of  to form  .

In a first aspect of this seventeenth embodiment, step (8) further comprises adding an acid selected from the group consisting of ammonium, trifluoroacetic acid, $H_2S0_4$, HCl, $H_3P0_4$, citric acid, methanesulfonyl acid, j>-toluenesulfonic acid, and ju-toluenesulfonic acid pyridinium salt to form an acid salt of  . In instances of this first aspect, step (8) comprises adding HCl to form an HCl salt of  .

In a second aspect of this seventeenth embodiment, the processes further comprise recrystallizing the product of step (8) from water and acetonitrile.

In all aspects of this seventeenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through sixteenth embodiments.

An eighteenth embodiment of the invention relates to processes for preparing a compound of Formula II,



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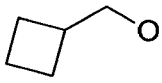
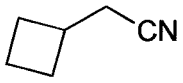
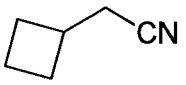
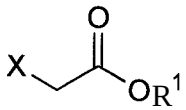
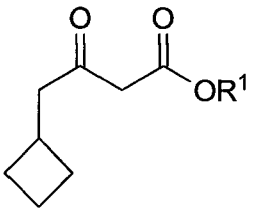
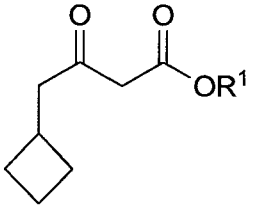
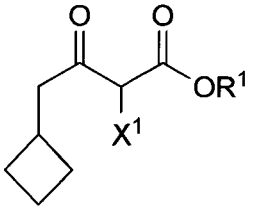
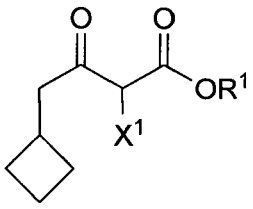
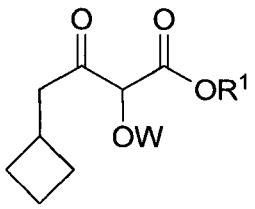
or a pharmaceutically acceptable salt or hydrate thereof, said process comprising:

(1) converting  to  ;

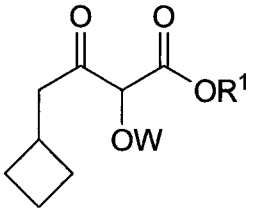
(2) coupling  with  to form  ,

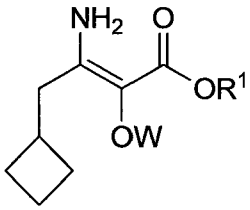
where $R^1$ is selected from the group consisting of $C_{1-8}$alkyl and benzyl, and X is a halogen;

(3) halogenating  to form  , where $X^1$ is a halogen;

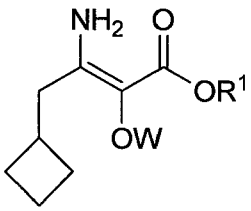
(4) reacting  with WOH to form  ,

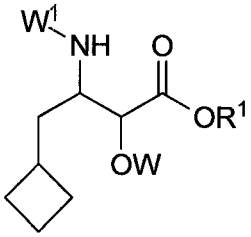
where W is a protecting group;

(5) conducting an enamine formation reaction to convert 

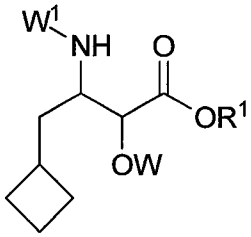

to 

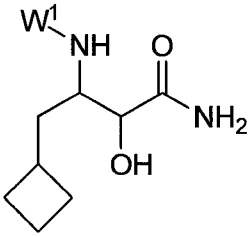
;

(6) reducing 

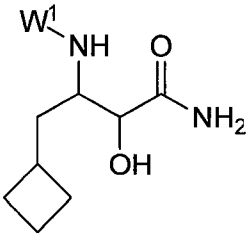
to form 

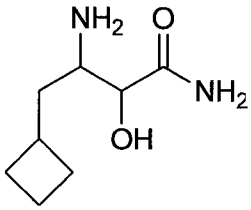
, where $W^1$ is a protecting group;

(7) performing aminolysis and deprotecting the protected hydroxyl 

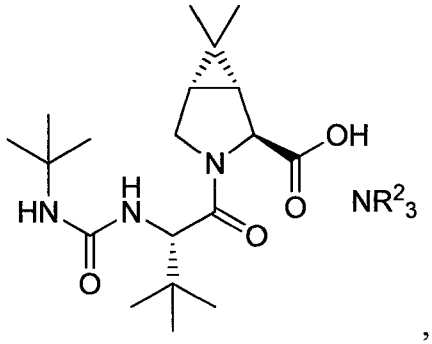
to form 

;

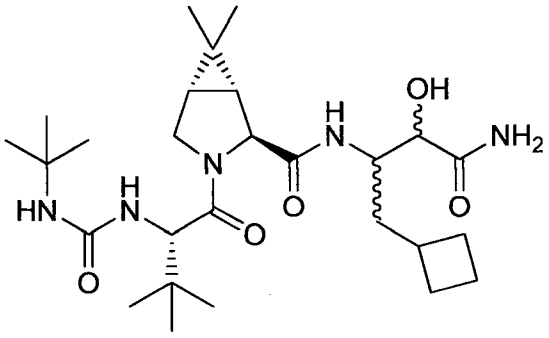
(8) deprotecting the protected amine of 

to form 

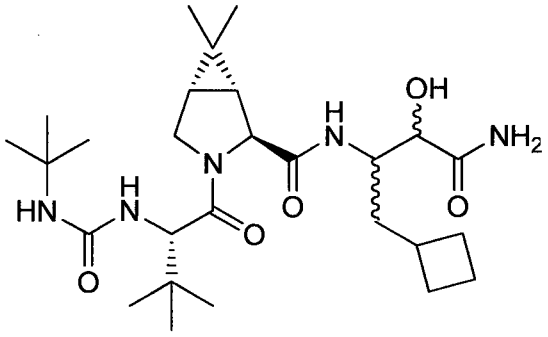
, adding an acid to form an acid salt and optionally recrystallizing the acid salt;



(9) coupling the acid salt of step (8) with , wherein $R^2$ is selected from the group consisting of $C_{1-6}$alkyl, $C_{1-6}$cycloalkyl and $C_{1-6}$alkyl$C_{1-6}$cycloalkyl, in the presence of a peptide coupling agent to form

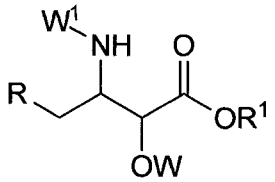


; and

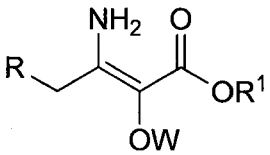


(10) oxidizing to form the compound of Formula II. In all aspects of this eighteenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through seventeenth embodiments.

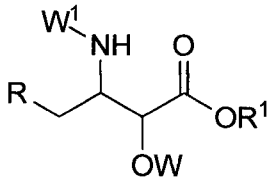
A nineteenth embodiment of the invention relates to processes for preparing



, the processes comprising reducing



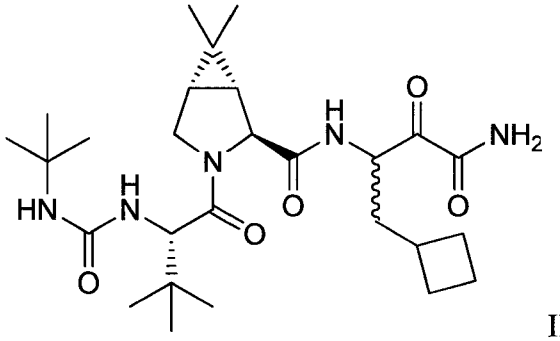
in the presence of



$W^1$ to form , wherein R is selected from the group consisting of

$C_{3-8}$cycloalkyl and Ci-ioalkyl; $R^1$ is selected from the group consisting of $C_{1-8}$alkyl and benzyl; W is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxy-carbonyl, pivaloyl, acetyl, />-methoxybenzoyl, p-toluoyl, benzoyl, benzyl, carbamate, j?-methoxybenzyl, 3,4-dimethoxybenzyl, silyl and tosyl groups; and $W^1$ is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, di-*tert*-butyl dicarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, *p*-methoxybenzoyl, *p*-toluoyl, benzoyl, benzyl, carbamate, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, silyl and tosyl groups. In all aspects of this nineteenth embodiment, all other groups are as provided in the general formula above or in any or all of the first through eighteenth embodiments.

A twentieth embodiment of the invention relates to processes for preparing a compound of Formula II,



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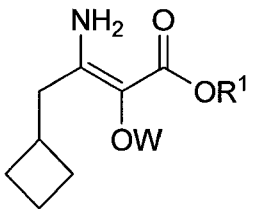
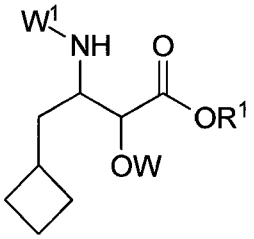
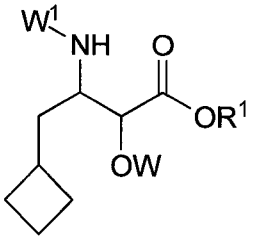
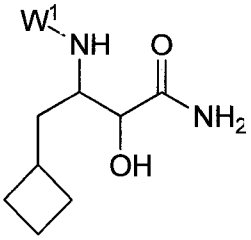
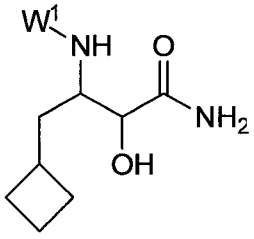
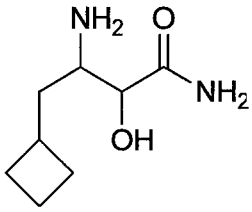
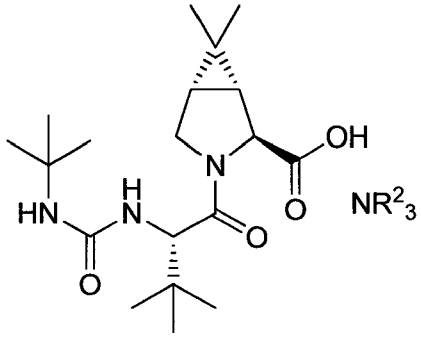
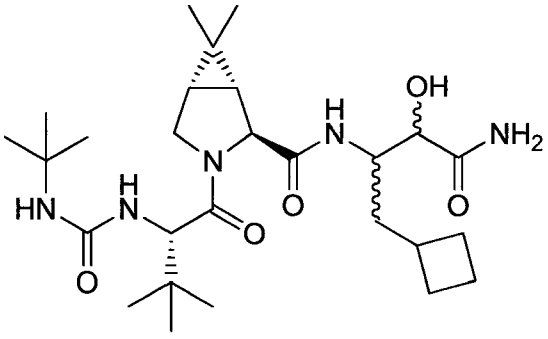
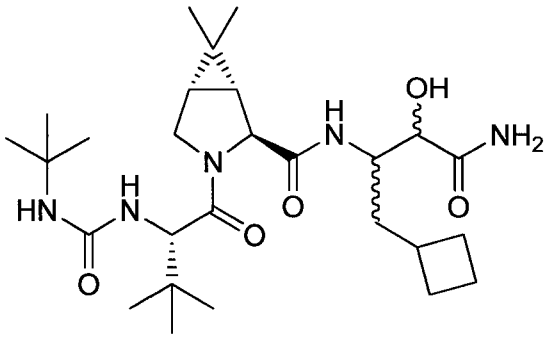
or a pharmaceutically acceptable salt or hydrate thereof, the processes comprising:

(1) reducing  to form  , where $W^1$ is a protecting group;

(2) performing aminolysis and deprotecting the protected hydroxyl  to form  ;

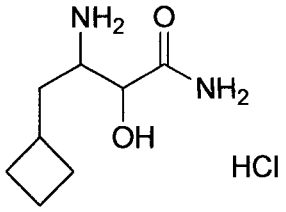
(3) deprotecting the protected amine of  to form  , adding an acid to form an acid salt and optionally recrystallizing the acid salt;

(4) coupling the acid salt of step (8) with  , wherein $R^2$ is selected from the group consisting of $C_{1-6}$alkyl, $C_{1-6}$cycloalkyl and $C_{1-6}$alkyl$C_{1-6}$cycloalkyl, in the presence of a peptide coupling agent to form  ; and

(5) oxidizing  to form the compound of Formula II. In all aspects of this twentieth embodiment, all other groups are as

provided in the general formula above or in any or all of the first through nineteenth embodiments.

In a twenty-first embodiment of the invention, the compound of Formula I or Formula la is



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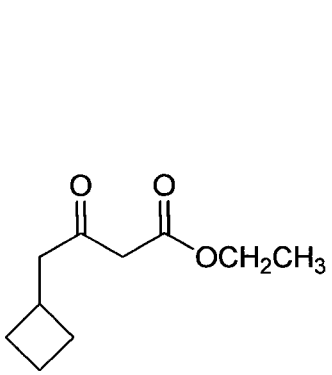
A twenty-second embodiment of the invention relates to compounds selected from the group consisting of:



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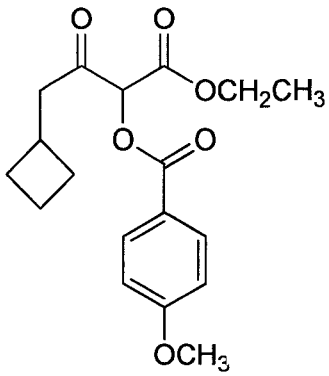

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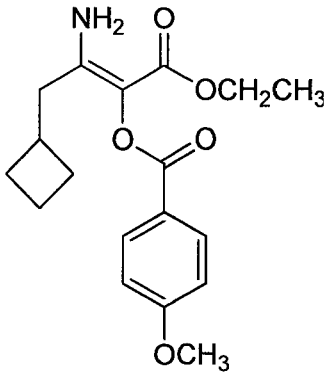
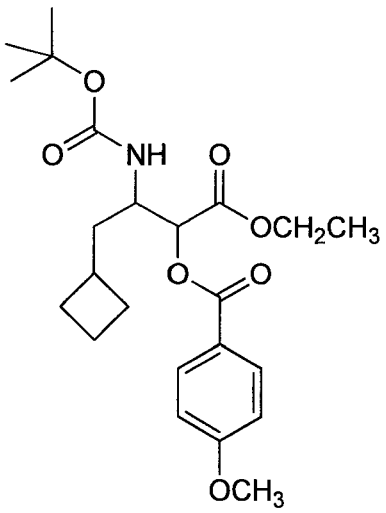


and



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In a twenty-third embodiment of the invention, a compound of the invention is prepared by process according to any one of the general process above and/or any one of the first through twentieth embodiments and/or is selected from the twenty-first embodiment, the twenty-second embodiment or the exemplary species depicted in the Examples shown below.

Additional embodiments are directed to each individual step of the processes of the above embodiments alone and to combinations of an individual step with one or more process steps that may be upstream (earlier) or downstream (later).

In the embodiments of processes for preparing the compounds and salts provided above, it is to be understood that each embodiment or instance of an embodiment may be combined with one or more other embodiments and/or instances, to the extent that the combination is consistent with the description of the embodiments and instances. It is further to be understood that the embodiments of compositions and methods provided are understood to include all embodiments of the compounds and/or salts, including such embodiments as result from combinations of embodiments. Further, each of the embodiments described above, variables R, $R^1$, $R^a$, R^, $R^2$, X, $X^1$, W, $W^1$, L, Ar and reagents, including the cyanating agents, halogenating agents, activating agents, ammonia-containing compounds, reducing agents, acids, and transition metals are selected independently from each other.

As used above, and throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "$Ci._6$alkyl" (or "Ci-C6alkyl") refers to all of the hexyl and pentyl isomers as well as n-, iso-, sec- and *tert*-butyl, n- and isopropyl, ethyl and methyl. Alkyl groups may be substituted as indicated, by substituents that may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, carboxy and -C(0)0-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, *tert*-butyl, n-pentyl, heptyl, nonyl, decyl, fluoromethyl, trifluoromethyl and cyclopropylmethyl.

The term "cycloalkyl" refers to any cyclic ring of an alkane or alkene having a number of carbon atoms in the specified range. Thus, for example, "$c_{3_8}$cycloalkyl" (or "Cs-Cgcycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl groups may be substituted as indicated.

The term "alkoxy" refers to an "alkyl-O-" group. The term "cycloalkoxy" refers to a "cycloalkyl-O-" group. Alkoxy and cycloalkoxy groups may be substituted as indicated.

The term "halogen" means fluorine (F), chlorine (CI), bromine (Br), and iodine (I). Preferred are fluorine, chlorine and bromine, and more preferred are chlorine and

bromine. Similarly, "halo" means fluoro, chloro, bromo, and iodo groups. Preferred are fluoro, chloro and bromo, and more preferred are chloro and bromo.

Unless otherwise specifically noted as only "substituted" or "unsubstituted", a particular group is unsubstituted. Preferably, the substituents are selected from the group which includes, but is not limited to, halo, $Ci_{-20}$alkyl, $-CF_3$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $-N0_2$, oxo, -CN, $-N_3$, -OH, $-0(C_{1-6}$alkyl), $C_{3-10}$cycloalkyl, $C_{2-6}$alkenyl, $C_{2-6}$ alkynyl, $(C_{0-6}$alkyl) $S(O)_{0-2}$-, aryl-$S(O)_{0.2}$-, $(C_{0-6}$alkyl$)S(O)_{0-2}(C_{0-6}$alkyl)-, $(C_{0-6}$ alkyl$)C(0)NH$-, $H_2N$-C(NH)-, $-0(C_{1-6}$alkyl$)CF_3$, $(C_{0-6}$alkyl$)C(O)$-, $(C_{0-6}$alkyl$)OC(O)$-, $(C_{0-6}$alkyl$)O(C_{1-6}$ alkyl)-, $(C_{0-6}$alkyl$)C(O)_{1-2}(C_{0-6}$alkyl)-, $(C_{0-6}$alkyl$)OC(O)NH$-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle and halo-heterocyclylalkyl.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a cycloalkyl ring described as a "$C_{3-8}$cycloalkyl" means the ring can contain 3, 4, 5, 6, 7 or 8 atoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range.

In addition, the term "or," as used herein, denotes alternatives that may, where appropriate, be combined; that is, the term "or" includes each listed alternative separately as well as their combination.

Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom provided such substitution is chemically allowed and results in a stable compound. A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described.

As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

The compounds prepared via the present invention may be chiral as a result of asymmetric centers, chiral axes, or chiral planes as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and may occur as single optical isomers or as mixtures of any number of the possible optical isomers, including racemates, racemic mixtures, diastereomers, diastereomeric mixtures, enantiomers, and enantiomeric mixtures. In certain instances, the compounds disclosed may exist as tautomers and all tautomeric forms are intended to be encompassed by the scope of the

invention, even though only one tautomeric structure is depicted. That is, for the purposes of the present invention, a reference to a compound of Formula I is a reference to the compound ***per se,*** or to any one of its tautomers ***per se,*** or to mixtures of two or more tautomers.

Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxiliary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

The compounds of the present invention may be in the form of salts, including pharmaceutically acceptable salts, and reference to compounds and to structures includes reference to salts of the compounds or structures. By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof. The term "pharmaceutically acceptable salts" describes salts that possess the effectiveness of the parent compound and that are not biologically or otherwise undesirable ***(e.g.,*** are neither toxic nor otherwise deleterious to the recipient thereof). The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, ***N,N***'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, ***N***-ethyl-morpholine, ***N***-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic and trifluoroacetic acids and the like. Particularly

preferred are citric, fumaric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The compounds afforded by the instant invention are useful intermediates in the production of HCV NS3 inhibitor compounds.

The following schemes and examples are illustrative of the processes encompassed by the present invention. As will be readily apparent to those in the field, the substituents and substitution patterns on the substrates exemplified herein may be modified without undue experimentation by the choice of readily available starting materials, reagents, and conventional procedures or variations.

The illustrative examples below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound in place of multiple substituents allowed under the definitions of Formula I defined above.

The processes of the instant invention are useful in the preparation of compounds of Formula I. The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. The following reaction schemes and examples serve only to illustrate the invention and its practice.

## EXAMPLES

The following listing defines the abbreviations used herein, both above and in the Examples below.

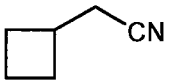
**ABBREVIATIONS**

| | |
|---|---|
| (aq.) | Aqueous |
| $^{13}$C NMR | Carbon-13 nuclear magnetic resonance spectrum |
| $CaCl_2$ | Calcium chloride |
| $CaC0_3$ | Calcium carbonate |

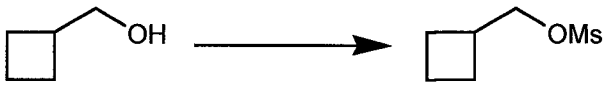
| | |
|---|---|
| $CDC1_3$ | Trichloro($H^2$)methane |
| $CH_3C(0)ONH_4$ | Ammonium acetate (also $NH_4OAc$) |
| $CH_3CN$ | Acetonitrile |
| DCM | Dichloromethane |
| DMSO | Dimethylsulfoxide |
| Et | Ethyl or $CH_3CH_2$ |
| EtOAc | Ethyl acetate |
| EtOH | Ethanol or ethyl alcohol |
| eq. | Equivalents |
| GC | Gas chromatography |
| $^1H$ NMR | Proton nuclear magnetic resonance spectrum |
| $H_2$ | Hydrogen gas |
| $H_20$ | Water |
| ¾S0 4 | Sulfuric acid |
| HC1 | Hydrochloric acid |
| Hg | Mercury |
| IPA | Isopropyl alcohol |
| /PrOAc | Isopropyl acetate |
| Ir | Iridium |
| $K_3P0_4$ | Potassium phosphate tribasic |
| KF | Karl Fischer titration |
| kg | Kilogram |
| L | Liter |
| M | Molar |
| Me | Methyl or $CH_3$ |
| MeOH | Methanol or methyl alcohol |
| MHz | Megahertz |
| mL | Milliliters |
| mol | Moles |
| Ms | Methanesulfonyl or mesyl group |
| MsCl | Methanesulfonyl chloride or mesyl chloride |
| MTBE | Methyl *tert*-butyl ether |
| N | Normal |

| | |
|---|---|
| $N_2$ | Nitrogen atmosphere |
| $Na_2S_20_5$ | Sodium metabisulfite |
| $NaBH_4$ | Sodium borohydride |
| NaCl | Sodium chloride |
| NaCN | Sodium cyanide |
| $NaHC0_3$ | Sodium bicarbonate |
| NaOH | Sodium hydroxide |
| $NH_3$ | Ammonia |
| $NH_4$ | Ammonium (+) |
| ppm | Parts per million |
| psig | Pounds per square inch |
| RB flask | Round-bottom flask |
| RT | Room temperature, approximately 25°C |
| $S0_2C1_2$ | Sulfuryl chloride |
| TEA | Triethylamine |
| THF | Tetrahydrofuran |
| Tosyl | p-Toluenesulfonyl group |

***Example 1: Cyclobutylacetonitrile***




Step 1: Cyclobutylmethyl methanesulfonate




A 50-L jacket vessel was charged with DCM (20 L) (KF 34 ppm), and cyclobutylmethyl alcohol (5.0 kg, 58.0 mol) followed by TEA (8850 mL, 63.5 mol). The reaction mixture was cooled to approximately -10°C, and MsCl (4735 mL, 60.8 mol) was added via an addition funnel dropwise over approximately 3 hours, while the temperature was maintained below -5°C. The reaction resulted in a yellow slurry after 70 minutes of aging. $H_20$ (8 L) was added to give a clear solution, which was agitated for 15 minutes. Then, the organic layer was separated. $H_20$ (8 L) was charged to the organic layer. The mixture was agitated for 20 minutes, and then the organic layer was separated. Brine (10% solution, 4 L) was charged to the organic layer. The mixture was agitated for 20 minutes, and then the organic layer was

separated. The organic phase was concentrated by vacuum distillation at approximately 30°C to 40°C and 28 inches Hg, resulting in a light brown residue (10.0 kg crude, approximately 9.5 kg product assumed, 58.0 mol, approximately 100% yield). A portion of the material was purified by distillation for characterization.

$^1$H NMR ($CDCl_3$, 400 MHz): δ 4.18 (d, J = 6.8 Hz, 2H), 3.00 (s, 3H), 2.71 (m, 1H), 2.11 (m, 2H), 2.00-1.80 (m, 4H).

Step 2: Cyclobutylacetonitrile


A 100-L RB flask was set up with a mechanical stirrer, a thermocouple, an addition funnel, a $N_2$ inlet, and a condenser that is connected to a scrubber (11 L bleach and 5 L 2N NaOH). DMSO (30.3 L) (KF approximately 680 ppm) and NaCN (3030 g, 61.8 mol) were charged to the flask. The mixture was heated to approximately 75°C by steam to dissolve most chunks of NaCN, resulting in a turbid solution. The product of Step 1 (9476 g, 57.7 mol) in DMSO (4 L) was added dropwise in 1 hour, 40 minutes while the temperature was maintained below approximately 87°C. The reaction was aged at approximately 85°C for 3 hours and cooled down to RT. $H_20$ (24 L) and MTBE (24 L) were charged. The mixture was agitated, and the organic layer was separated. The aqueous layer was extracted with MTBE (18 L), and the combined organic layer was agitated with $H_20$ (12 L) and separated. The organic layer was washed with 10% brine (4 L and 2 L), and concentrated by vacuum distillation at approximately 45°C and approximately 20 inches Hg, giving a light brown liquid (7.235 kg crude, 73.3% by GC assay, 5.30 kg product assay, 55.7 mol, 96.5% for two steps).

$^1$H NMR ($CDCI_3$, 400 MHz): δ 2.65 (m, 1H), 2.41 (d, J = 5.2 Hz , 2H), 2.18 (t, J = 6.8 Hz, 2H), 2.00-1.80 (m, 4H).

***Example 2: Ethyl 4-cyclobutyl-3-oxobutanoate***

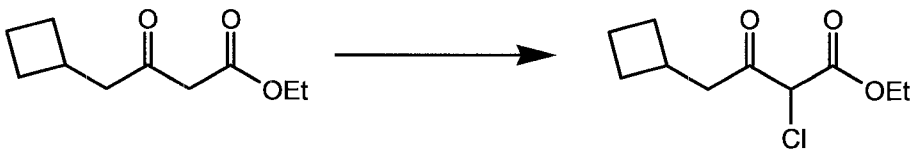

THF (20 L) and zinc dust (2.75 kg, 42.0 mol) were charged under $N_2$ to a 50-L jacketed vessel with a thermocouple, an addition funnel and a condenser. The mixture was stirred, and chlorotrimethylsilane (0.571 kg, 5.26 mol) was added at RT. The mixture was heated at 67°C for 30 minutes. Cyclobutylacetonitrile (2.5 kg, 26.3 mol, product of Example 1) was added at 67°C. Ethyl bromoacetate (6.108 kg, 36.6 mol) was added to the mixture at approximately 67°C to 70°C for over 3 hours. After the addition, the mixture was heated at

approximately 70°C for 1 hour and then cooled to approximately 0°C to 5°C. 10% $H_2S0_{4\,(aq.)}$ (35 L, 33.9 mol, approximately 1.3 eq.) was added slowly. The mixture was aged at RT for 1 hour. The organic layer was separated and subsequently washed with 10% aqueous citric acid (15 L, 7.88 mol, 0.3 eq.), 10% aqueous $Na_2S_20_5$ (25 L), 10% $Na_2S_20_{5\,(aq.)}$ (10 L), and 10% brine (10 L). The organic layer was concentrated *in vacuo* to afford the crude product (4.08 kg assay, 22.15 mol) in 84% yield. A part of the material was purified by distillation for characterization (with NMR in $CDC1_3$, approximately 10-15% enol-form of the compound was observed, major keto-form as shown.)

$^1$H NMR ($CDC1_3$, 400 MHz): δ 4.19 (q, J = 7.1 Hz, 2 H), 3.38 (s, 2 H), 2.75-2.65 (m, 1H), 2.65-2.63 (m, 2 H), 2.19-2.08 (m, 2 H), 1.95-1.79 (m, 2 H), 1.73-1.60 (m, 2 H), 1.27 (t, J = 7.1 Hz, 3 H).

$^{13}$C NMR ($CDC1_3$, 400 MHz): δ 202.2, 167.2, 61.3, 50.0, 49.3, 31.1, 28.4, 18.7, 14.1.

***Example 3: Ethyl 2-chloro-4-cyclobutyl-3-oxobutanoate***

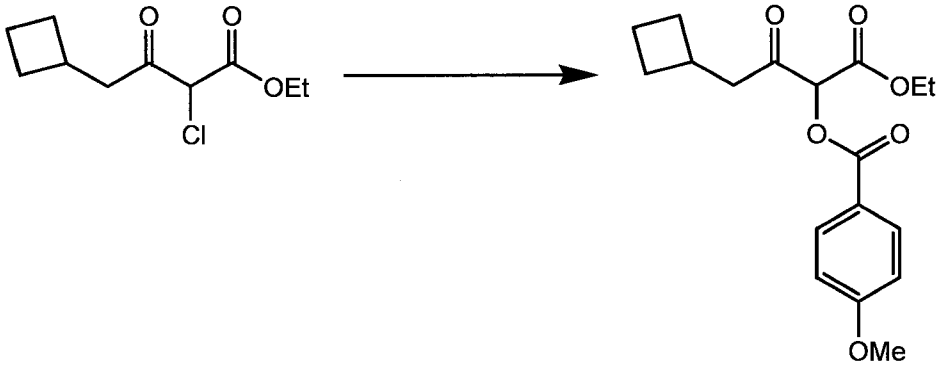



Methyl t-butyl ether (30.2 L), and the crude product of Example 2 (3.78 kg assay, 20.52 mol) were charged to a 100-L RB flask with an overhead stirrer, an addition funnel, a thermometer, and an acid scrubber (with 2N NaOH at RT under $N_2$). Sulfuryl chloride (2.98 kg, 22.06 mol) was added at approximately 20°C to 23°C over 1.5 hours. After addition, the mixture was cooled to approximately 5°C and then quenched with 1M $K_3P0_{4\,(aq.)}$ (23.6 L). The organic layer was separated and concentrated under vacuum to afford the crude chloride (4.487 kg, assume 100% yield, 20.52 mol), which was used in the next reaction without purification. A part of the material was purified by distillation for characterization (with NMR in $CDC1_3$, approximately 10% enol-form of the compound was observed, major keto-form was shown below).

$^1$H NMR ($CDCI_3$, 400 MHz): δ 4.73 (s, 1 H), 4.29 (q, J = 7.1 Hz, 2 H), 2.89-2.79 (m, 2 H), 2.79-2.69 (m, 1 H), 2.20-2.07 (m, 2 H), 1.98-1.78 (m, 2 H), 17.3-1.61 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H).

$^{13}$C NMR ($CDC1_3$, 400 MHz): δ 198.1, 165.0, 63.1, 60.9, 45.7, 31.0, 28.3, 18.7, 13.9.

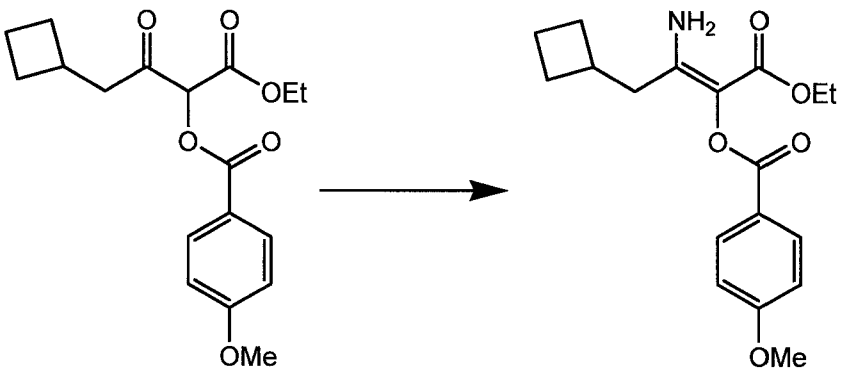
***Example 4: 4-Cyclobutyl-1-ethoxy-1,3-dioxobutan-2-yl 4-methoxybenzoate***




The crude chloride product of Example 3 (4.487 kg assumed, 20.52 mol) and N,N-dimethylformamide (11.2 L) were charged to a 50-L jacketed vessel with a thermocouple and a condenser at RT under $N_2$. p-Methoxybenzoic acid (3.75 kg, 24.62 mol) and TEA (2.285 kg, 22.57 mol) were added to the mixture. The mixture was heated at 55°C for 14 hours. The mixture was cooled to approximately 10°C, diluted with methyl *tert*-butyl ether (24 L), quenched with ¾ 0 (24 L). The organic layer was separated and subsequently washed with IN $NaHC0_3$ (20 L), then $H_20$ (18 L) with NaCl (0.90 kg) and $NaHC0_3$ (0.45 kg). The organic layer was separated and concentrated *in vacuo* to afford the product (6.07 kg, 18.15 mol) in 88% assay yield. A part of the material was purified by distillation for characterization.

H NMR ($CDCI_3$, 400 MHz): δ 8.09 (dt, J = 2.1, 9.0 Hz, 2 H), 6.96 (dt, J = 2.1, 9.0 Hz, 2 H), 5.66 (s, 1 H), 4.31 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 2.86 (dd, J = 5.7, 7.6 Hz, 2 H, 2.83-2.74 (m, 1 H), 2.23-2.12 (m, 2H), 1.98-1.80 (m, 2 H), 1.74-1.65 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H).

***Example 5: (2E)-3-Amino-4-cyclobutyl-1-ethoxy-1-oxobut-2-en-2-yl 4-methoxybenzoate***



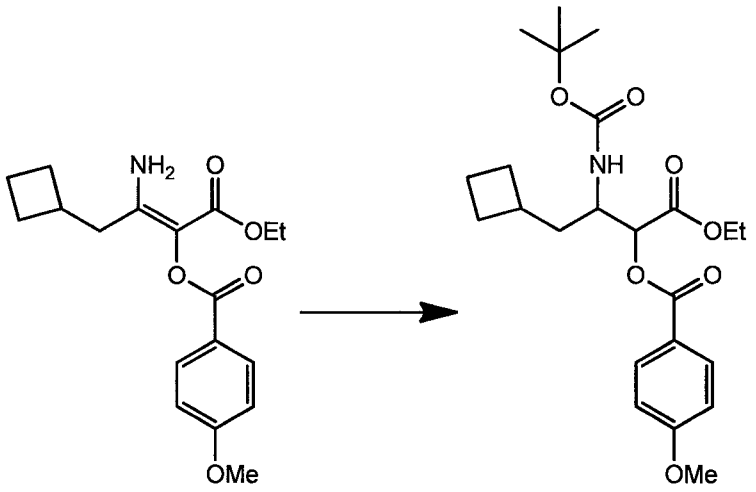

The crude product of Example 4 (5.97 kg, 17.85 mol), 1-propanol (12 L), and EtOH (12 L) were charged to a 100-L RB flask with an overhead stirrer and a thermometer at RT under $N_2$. $NH_4OAc$ (4.82 kg, 62.5 mol) was added to the mixture. The mixture was heated at 50°C for 1 hour. The mixture was concentrated *in vacuo* to remove $H_20$ azeotropically with

continuous addition of 1-propanol (total approximately 24 L). The mixture was solvent-switched to $_i$PrOAc (24 L) under vacuum. The mixture was quenched with 2M $K_3P0_{4\,(aq\cdot)}$ (17.85 L). The organic layer was separated and washed with 15% brine (18 L) twice. The organic layer was concentrated *in vacuo* to afford crude enamine product (5.95 kg, assume 100% yield, 17.85 mol).

$^1$H NMR ($CDC1_3$, 400 MHz): δ 8.12 (d, $J$ = 8.0 Hz, 2H), 6.98 (d, $J$ = 8.0 Hz, 2H), 6.02 (s, 2H), 4.15 (q, $J$ = 8 Hz, 2H), 3.89 (s, 3H), 2.60-2.53 (m, 1H), 2.33 (s, 2H), 2.13-2.06 (m, 2H), 1.91-169 (m, 4H), 1.20 (t, $J$ = 8 Hz, 3H).

$^{13}$C NMR ($CDC1_3$, 400 MHz): δ 165.7, 167.6, 163.6, 153.9, 132.1, 122.2, 113.9, 113.7, 112.5, 59.6, 44.5, 37.8, 33.9, 28.5, 28.4, 18.5, 14.4.

***Example 6A: 3-[(tert-Butoxycarbonyl)amino]-4-cyclobutyl-l-ethoxy-l-oxobut-2-yl 4-methoxybenzoate***

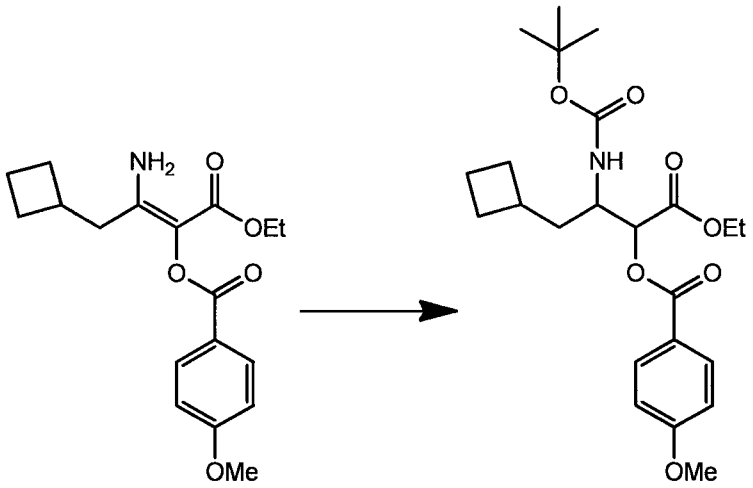



The crude product of Example 5 (5.92 kg, 17.75 mol) and MeOH (23.7 L) were charged to a 100-L RB flask with an overhead stirrer, a thermocouple, and an addition funnel at RT under $N_2$. Di-*tert*-butyl dicarbonate (5.81 kg, 26.6 mol) and sodium cyanoborohydride (1.171 kg, 18.64 mol) were charged to the mixture. A solution of glycolic acid (1.485 kg, 19.53 mol) in MeOH (3.55 L) was added to the mixture dropwise at a rate to maintain the temperature at approximately 15°C to 22°C. The mixture was aged at approximately 20°C for approximately 8-10 hours. EtOAc (3.49 L, 35.5 mol) and a solution of glycine (0.866 kg, 11.4 mol) in $H_20$ (11 L) were added to the mixture at RT. Then, 2M $K_3P0_{4\,(aq\cdot)}$ solution (17.75 L) was added. The mixture was aged for 20 minutes. The mixture was extracted with methyl *tert*-butyl ether (28 L). The organic layer was separated and washed subsequently with 2M $K_3P0_{4(aq.)}$ solution (17.75 L), 10% brine (17.75 L, twice). The organic layer was concentrated under vacuum to afford the desired two diastereoisomers in almost 1:1 ratio (7.30 kg, 16.76 mol) in 94% assay yield.

$^1$H NMR **($CDCI_3$,** 400 MHz): δ 8.02 (d, $J$ = 8.0 Hz, 2H), 6.94 (d, $J$ = 8.0 Hz, 1H), 6.93 (d, $J$ = 8.0 Hz, 1H), 5.30 (d, $J$ = 4.0 Hz, 0.5H), 5.17 (d, $J$ = 4.0 Hz, 0.5H), 4.80 (d, $J$ = 8.0

Hz, 0.5H), 4.63 (d, ***J*** = 8.0 Hz, 0.5H), 4.27-4.18 (m, 3H), 3.86 (s, 3H), 2.50-2.30 (m, 1H), 2.15-2.00 (m, 2H), 1.89-1.60 (m, 6H), 1.43 -1.42 (m, 9H), 1.27 (t, ***J*** = 8.0 Hz, 3H).

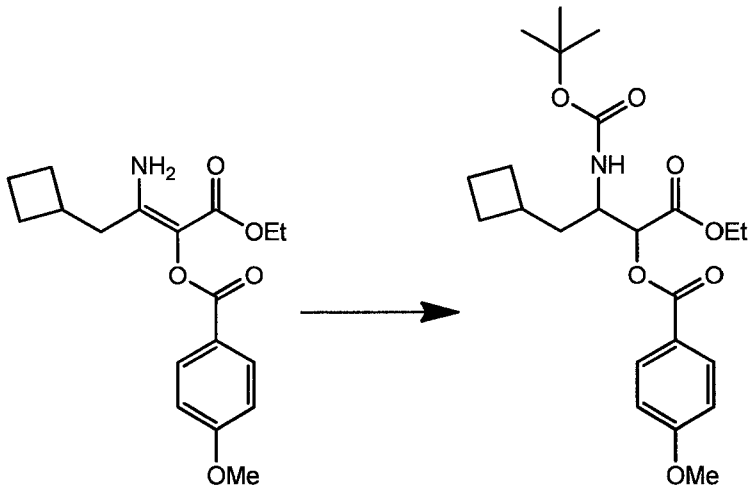
***Example 6B: 3-[(tert-Butoxycarbonyl)amino]-4-cyclobutyl-l-ethoxy-l-oxobut-2-yl 4-methoxybenzoate (First alternate procedure)***




The crude product of Example 5 (19.2 g, 58.0 mmol) and MeOH (100 mL) were charged to an autoclave with a thermocouple at RT. Di-*tert*-butyl dicarbonate (19.0 g, 87.0 mmol) and 5% Ir/CaC0 $_3$ (10.0 g) were charged to the mixture. The mixture was heated to 40°C under sealed conditions, where $H_2$ was transferred until the internal pressure became approximately 200 psig. The mixture was heated at 40°C at approximately 200 psig for 20 hours. The reaction mixture was cooled to RT and filtered to remove the solid to afford a clear solution. EtOAc (5.7 mL, 58 mmol) and a solution of glycine (2.8 g, 38 mmol) in $H_2$0 (37 mL) were added to the mixture at RT. Then, 2M $K_3P0_{4\,(aq.)}$ solution (58 mL) was added. The mixture was aged for 20 minutes. The mixture was extracted with methyl *tert*-butyl ether (130 mL). The organic layer was separated and washed subsequently with 2M $K_3P0_{4\,(aq.)}$ solution (58 mL), 10% brine (58 mL, twice). The organic layer was concentrated under vacuum to afford the desired two diastereoisomers in almost 1:1 ratio (23 g, 52 mmol) in a 90% assay yield.

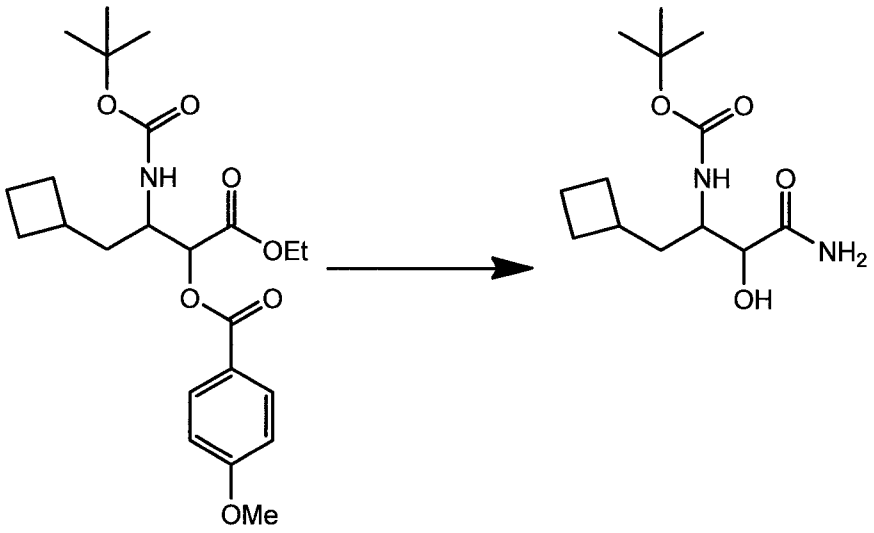
H NMR ($CDC1_3$, 400 MHz): δ 8.02 (d, ***J*** = 8.0 Hz, 2H), 6.94 (d, ***J*** = 8.0 Hz, 1H), 6.93 (d, ***J*** = 8.0 Hz, 1H), 5.30 (d, ***J*** = 4.0 Hz, 0.5H), 5.17 (d, ***J*** = 4.0 Hz, 0.5H), 4.80 (d, ***J*** = 8.0 Hz, 0.5H), 4.63 (d, ***J*** = 8.0 Hz, 0.5H), 4.27-4.18 (m, 3H), 3.86 (s, 3H), 2.50-2.30 (m, 1H), 2.15-2.00 (m, 2H), 1.89-1.60 (m, 6H), 1.43 -1.42 (m, 9H), 1.27 (t, ***J*** = 8.0 Hz, 3H).

***Example 6C: 3-[(tert-Butoxycarbonyl)amino]-4-cyclobutyl-l-ethoxy-l-oxobut-2-yl 4-methoxybenzoate (Second alternate procedure)***




$NaBH_4$ (0.23 g, 6 mmol) and THF (5 mL) were charged to a 100-ml RB flask. The mixture was cooled to -10°C. Methanesulfonic acid (0.78 mL, 12 mmol) was charged slowly into the mixture at less than -8°C and the mixture was agitated for 15 minutes. A 0.3M solution of the crude product of Example 5 (1 g, 3 mmol) in THF was charged slowly into the mixture at below -8°C. The mixture was agitated for 16 hours. $H_20$ (1 ml) was charged slowly into the mixture at 0°C, and the mixture was warmed to RT. Di-*tert*-butyl dicarbonate (1.31 g, 6 mmol) and 2M aqueous NaOH (3.75 ml) were charged into the mixture. The mixture was agitated for 2 hours at RT. An assay of the reaction mixture gave the product (1.23 g, 94%).

***Example 7A: Ethyl 3-f(tert-buyoxycarbonyl)aminoJ-4-cyclobutyl-2-hydroxybutanoate***



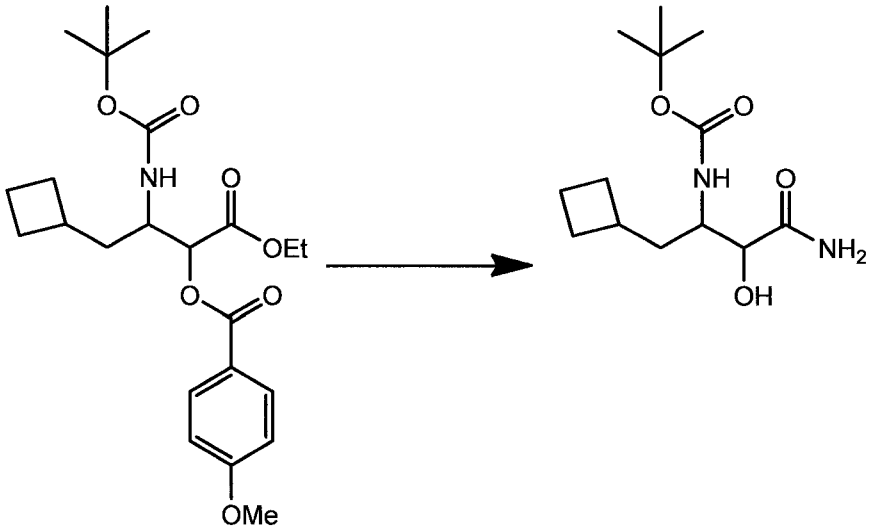

The crude product of Example 6A (6.0 kg, 13.78 mol) and MeOH (24 L) were charged into a 10-gallon autoclave at RT. The mixture was heated to 70°C under sealed conditions, where $NH_4$ was transferred until the internal pressure became approximately 80 psig.

The mixture was heated at 70°C at approximately 80 psig for 22 hours. The mixture was cooled to RT. $NH_4$ was vented at RT. DMSO (5.4 L) was added to the mixture, and the mixture was aged at RT for 1 hour. The mixture was transferred into a 100-L RB flask with an overhead stirrer and a thermometer. The autoclave was rinsed with MeOH, and the mixture and rinse liquid were combined. This combined mixture was concentrated to remove MeOH under vacuum. Then, the flask was rinsed with DMSO (2.6 L) to wash the walls. Total DMSO volume was 8.0 L. The mixture was heated to 70°C to dissolve the solid to afford a clear solution, which was cooled to RT slowly to afford a slurry. ¾ 0 (32.0 L) was charged for approximately 1.5 hours at 20°C to 27°C. After addition of $H_20$, the mixture was aged at RT overnight and then cooled to 0°C to 5°C for 4 more hours. The mixture was filtered to collect the solid, which was washed with cold $H_20$ (12 L). The solid was dried at 40°C in a vacuum oven with $N_2$ sweep (approximately 150 torr) to afford the crude product 5.63 kg (3.75 kg).

H NMR (DMSO-$d_6$, 400 MHz): δ 7.20-7.15 (m, 2H), 7.25 (d, ***J*** = 12.0 Hz, 0.5H), 5.92 (**d, *J*** = 12.0 Hz, 0.44H), 5.52-5.44 (m, 1H), 3.83-3.81 (m, 0.5H), 3.74-3.62 (m, 1.5H), 2.29-2.22 (m, 1H), 2.03-1.92 (m, 2H), 1.83-1.70 (m, 2H), 1.62-1.24 (m, 13H).

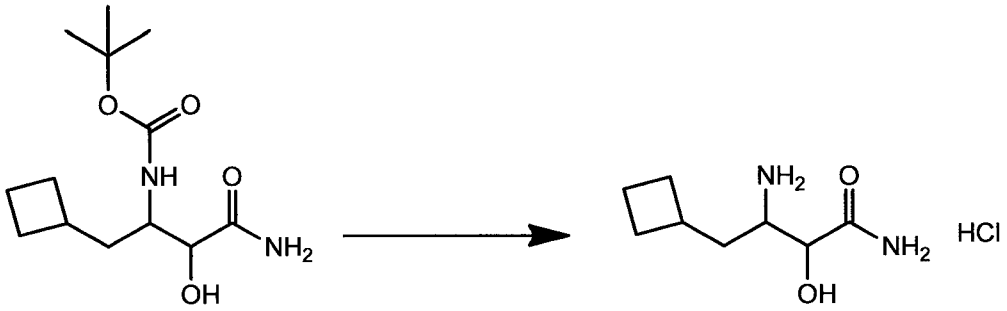
$^{13}$C NMR (DMSO-$d_6$, 400 MHz) δ 175.2, 174.6, 155.5, 155.4, 78.0, 77.9, 74.4, 72.7, 51.9, 51.8, 38.8, 35.8, 33.3, 33.2, 33.0, 28.8, 28.7, 28.6, 28.5, 28.4, 28.2, 18.6, 18.5.

***Example 7B: Ethyl 3-[(tert-buyoxycarbonyl)amino]-4-cyclobutyl-2-hydroxybutanoate***




The crude product of Example 6A (6.0 g, 84 wt%, 11.57 mmol) and $CaCl_2$ (1.413 g, 12.73 mmol) and 7N $NH_3$ in MeOH (60 mL, 420 mmol) were charged into a 40 mL vial. The mixture was aged at approximately 33°C for 3 hours. The mixture was concentrated under reduced pressure to afford the product (7.8 g crude, assume 100% yield) as a tan solid.

***Example 8: Ethyl 3-amino-4-cyclobutyl-2-hydroxybutanoate hydrochloride***

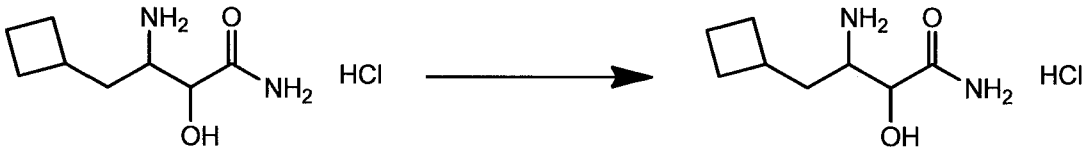



IPA (13.8 L) was charged into a 100-L RB flask with a mechanical stirrer, dry and clean with a thermometer and an addition funnel, followed by addition of the product of Example 7 (3.46 kg assay, 12.70 mol). HCI in IPA (5-6 M 13.8 L, 69 mol) was slowly added into the reaction mixture. The reaction mixture was heated at 50°C for 4 hours. The mixture was cooled to RT. Then, MTBE (28 L) was added to the mixture over 30 minutes. The reaction mixture was cooled to 0°C to 5°C by MeOH/ice bath for 1.5 hour. The mixture was filtered to collect the solid, which was washed with MTBE (7 L) twice. The wet cake was dried under vacuum with $N_2$ and sweep overnight to afford the product as an off-white solid (2.15 kg, 10.30 mol) in 76.6% overall yield for Examples 5-8.

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ 8.20-7.95 (m, 3H), 7.54-7.44 (m, 2H), 6.46 (d, ***J*** = 4.0 Hz, 0.5H), 6.26 (d, ***J*** = 8.0 Hz, 0.5H), 4.22 (s, 0.5H), 3.98 (s, 0.5H), 3.26 (s, 0.5H), 3.10 (d, ***J*** = 4.0 Hz, 0.5H), 2.45-2.36 (m, 1H), 2.00-1.96 (m, 2H), 1.81-1.39 (m, 6H).

$^{13}$C NMR (DMSO-$d_6$, 400 MHz) δ 174.1, 173.6, 71.2, 69.8, 51.7, 51.5, 36.0, 34.6, 31.7, 31.5, 28.0, 27.8, 27.7, 18.3, 18.1.

***Example 9: Ethyl 3-amino-4-cyclobutyl-2-hydroxybutanoate hydrochloride (Recrystallization)***



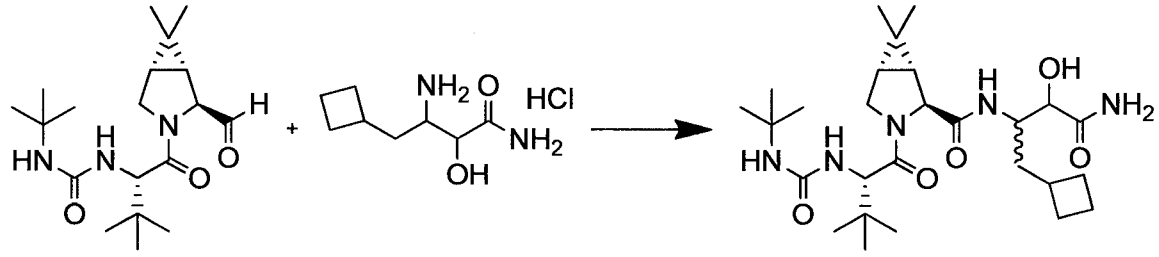

$H_20$ (3.0 L), $CH_3CN$ (6 L) and the product of Example 8 (2.00 kg, 9.58 mol) were charged to a 100-L RB flask with an overhead stirrer, a thermocouple and a condenser at RT under $N_2$. The mixture was heated to 65°C to get a clear solution. The mixture was cooled to 50°C to get a thin slurry. $CH_3CN$ (6.0 L) was added at 50°C for over 1 hour. The mixture was cooled to 40°C. $CH_3CN$ (9.0 L) was added at 40°C for over 1 hour. The mixture was cooled to 30°C. $CH_3CN$ (18 L) was added at 30°C. The mixture was cooled to approximately 0°C to 5°C and stirred for 1 hour before filtration. The mixture was filtered, washed with $CH_3CN$ (4 L)

twice, and dried with $N_2$ stream to afford the recrystallized product as a white solid (1.887 kg, 9.04 mol, 94% isolated yield).

$^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 8.20-7.95 (m, 3H), 7.54-7.44 (m, 2H), 6.46 (d, ***J*** = 4.0 Hz, 0.5H), 6.26 (d, ***J*** = 8.0 Hz, 0.5H), 4.22 (s, 0.5H), 3.98 (s, 0.5H), 3.26 (s, 0.5H), 3.10 (**d, *J*** = 4.0 Hz, 0.5H), 2.45-2.36 (m, 1H), 2.00-1.96 (m, 2H), 1.81-1.39 (m, 6H).

$^{13}C$ NMR (DMSO-$d_6$, 400 MHz): δ 174.1, 173.6, 71.2, 69.8, 51.7, 51.5, 36.0, 34.6, 31.7, 31.5, 28.0, 27.8, 27.7, 18.3, 18.1.

***Example 10: (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-[N-(ttrt-butylcarbamoyl)-3-methyl-I^valyl]-6,6-dimethyl-3-azabicyclo[3AM]hexane-2-carboxamide***

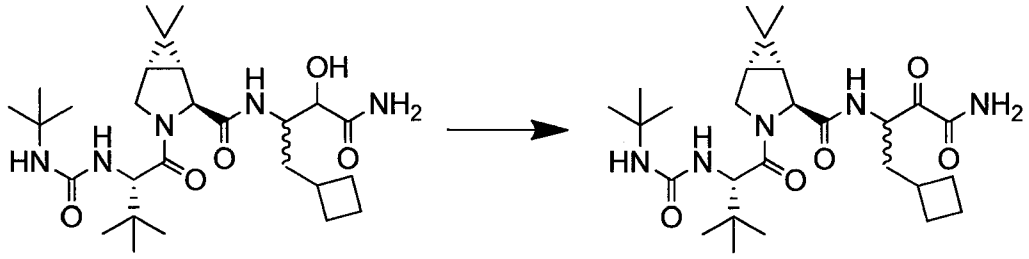



Hydroxybenzotiazole (HOBT, 4.83 g, 31.5 mmol), water (4.5 mL), (1R,2S,5S)-N-(4-amino- 1-cyclobutyl-3 -hydroxy-4-oxobutan-2-yl)-3- [N-(tertbutylcarbamoyl)-3 -methylvalyl] -6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (30 g, 60.6 mmol), HCl salt product of Example 9 (13.79 g, 66.1 mmol), ethyl acetate (120 mL) and ***N***-methyl-2-pyrrolidone (NMP, 30 mL) were added at 19°C to a three-necked 500mL RB flask equipped with an overhead stirrer and a thermocouple. ***N***-methylmorpholine (13.3 mL, 121 mmol) was added to the mixture at 19°C. l-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 15.0 g, 78.0 mmol) was added to the mixture at 21°C. Ethyl acetate (30 mL) was then added to the mixture at 18°C.

The mixture was agitated at approximately 20°C to 24°C for about 16 hours. After the reaction was complete, ethyl acetate (120 mL) was added at 23°C. The mixture was washed with 10% aqueous potassium carbonate solution (180 mL) twice at approximately 20°C to 24°C. Then, the organic layer was washed with 3.3% aqueous HCl (180 mL) twice at approximately 12°C to 18°C. The organic layer then was washed with 10% aqueous potassium carbonate solution (180 mL) and water (180 mL). The organic layer was concentrated to approximately 100 mL volume and was added to heptane (900 mL) dropwise at approximately -10°C to -5°C to precipitate the product. The mixture was filtered and washed with heptane. The solid was dried *in vacuo* at approximately 50°C to 60°C overnight. 31.3 g of the product compound was obtained as a white solid in 99% yield.

The above procedure is in accordance with the processes disclosed in U.S. Patent Application Publication No. US2010/519485 Al, the disclosures of which are herein incorporated by reference. It will be appreciated that the processes disclosed therein can be modified without undue experimentation to prepare specifically desired materials. The results of $^{1}H$ NMR and $^{13}C$ NMR for the above procedure were consistent with those reported in U.S. Patent Application Publication No. US2010/519485 Al.

***Example 11: (lR,5S)-N-[3-Amino-l-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(l,l-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-l-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide***



Acetic acid (27.0 mL, 472 mmol) and MTBE (240 mL) at RT were added to a three-necked 1L RB flask equipped with an overhead stirrer, a thermocouple and a chiller. The mixture was cooled to approximately 14°C, then the product from Example 10 (30.0 g, 57.5 mmol) was charged at approximately 14°C. The mixture was cooled to approximately 11°C. 2,2,6,6-Tetramethylpiperidin-l-yl)oxyl (TEMPO, 9.97 g, 63.8 mmol) was added to the mixture. A pre-mixed solution containing 40% aqueous sodium permanganate (17.02 g, 48.0 mmol) and water (99 mL) at approximately 12°C to 14°C was added to the reaction mixture over about 2 hours. The mixture was agitated at approximately 12°C until completion.

After the reaction was complete, the mixture was cooled to approximately 1°C. Water (30 mL) was added, then aqueous layer was separated. The organic layer was then washed with water (150 mL) at approximately 0°C to 10°C, and then washed with a pre-mixed solution of sodium ascorbate (30.0 g, 151 mmol) in water (150 mL) and concentrated HCl (12.42 mL, 151 mmol) at approximately 5°C to 15°C. The mixture was agitated at approximately 5°C to 10°C for 2 hours; then aqueous layer was separated. The organic layer was further washed with 2.5 N HCl (120 mL) at approximately 0°C to 10°C and with water (150 mL) at approximately 0°C to 10°C four times. The organic layer (approximately 170 mL) was then added dropwise to heptane (720 mL) at approximately -20°C to -15°C to precipitate the product. The mixture was then warmed to -5°C and filtered to collect the solid. The solid was washed

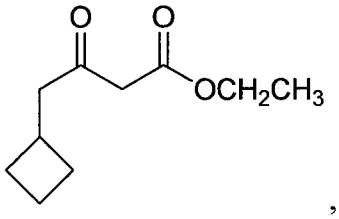
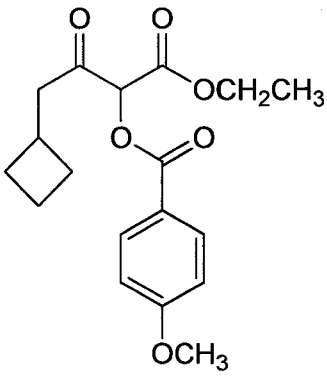
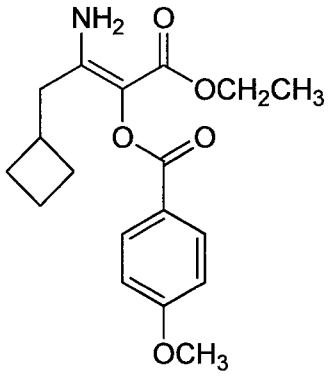
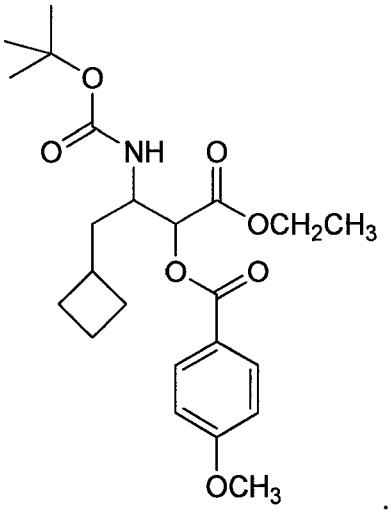
with heptane, dried in a vacuum oven with nitrogen sweep at room temperature to afford 27.1 g of desired product of Formula II as a white solid in 91% yield.

The above procedure is in accordance with the processes disclosed in U.S. Provisional Patent Application No.6 1/482,592 (unpublished), the disclosures of which are herein incorporated by reference. It will be appreciated that the processes disclosed therein can be modified without undue experimentation to prepare specifically desired materials. The results of $^{1}H$ NMR and $^{13}C$ NMR for the above procedure were consistent with those reported in U.S. Provisional Patent Application No.61/482,592 (unpublished).

It will be appreciated that various of the above-discussed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. It will also be appreciated that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art that are also intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of:


,

,

and

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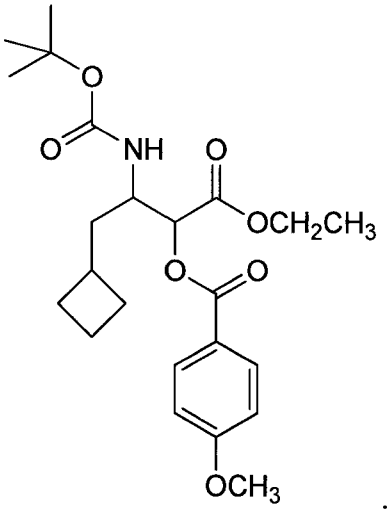
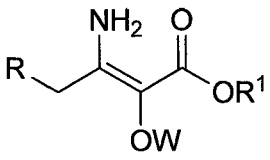
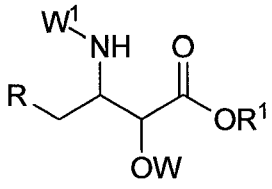
2. The compound of claim 1, wherein the compound is

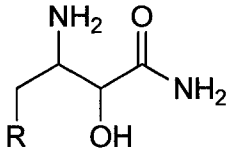

.

3. A process for preparing the compound of claim 2, said process comprising



reducing  in the presence of $W^1$ to form , wherein R is selected from the group consisting of $C_{3-8}$cycloalkyl and d-ioalkyl; $R^1$ is selected from the group consisting of $C_{1-8}$alkyl and benzyl; W is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, *j*^-methoxybenzoyl, *p*-toluoyl, benzoyl, benzyl, /?-methoxybenzyl, 3,4-dimethoxybenzyl, silyl and tosyl groups; and $W^1$ is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, />-methoxybenzoyl, />-toluoyl, benzoyl, benzyl, carbamate, j^-methoxybenzyl, 3,4-dimethoxybenzyl, silyl and tosyl groups.

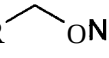
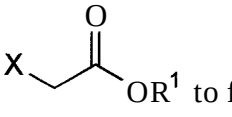
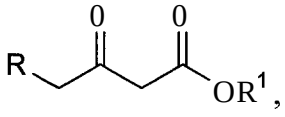
4. A process for preparing a compound of Formula I



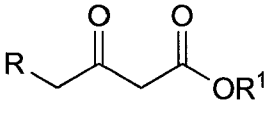
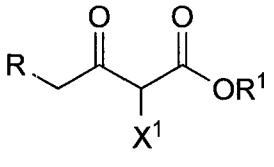
I

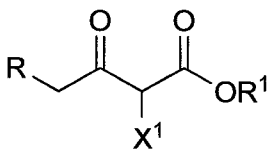
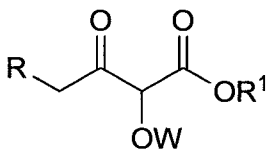
or salt thereof, wherein R is selected from the group consisting of $C_{3-8}$cycloalkyl and Ci.i$_0$alkyl, said process comprising:

(1) converting  to  ;

(2) coupling  with  to form  ,

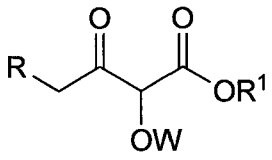
where $R^1$ is selected from the group consisting of Ci$_{-8}$alkyl and benzyl, and X is a halogen;

(3) halogenating  to form  , where $X^1$ is a halogen;

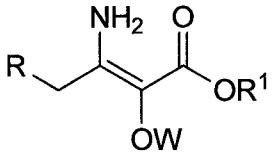
(4) reacting  with WOH to form  ,

where W is a protecting group;

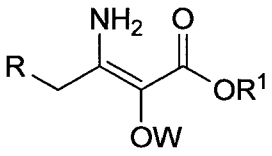
(5) conducting an enamine formation reaction to convert



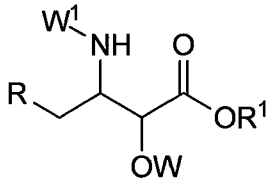
to



;

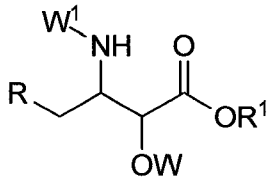


(6) reducing in the presence of $W^1$ to form

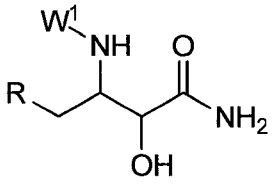


, where $W^1$ is a protecting group;

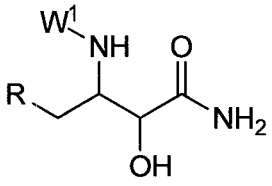
(7) performing aminolysis and deprotecting the protected hydroxyl



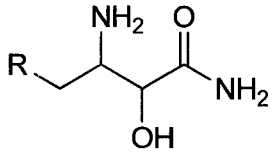
to form



; and



(8) deprotecting the protected amine of to form

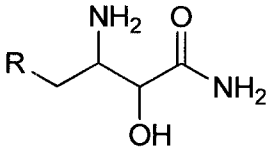


.

5. The process of claim 4, wherein R is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

6. The process of claim 5, wherein R is cyclobutyl.

7. The process of any one of claims 4-6, wherein step (8) further comprises



adding an acid to to form a salt.

8. The process of claim 7, wherein the acid is selected from the group consisting of ammonium sulfate, ammonium nitrate, ammonium chloride, trifluoroacetic acid, $H_2S0_4$, HCl, $H_3P0_4$, citric acid, methanesulfonyl chloride, methanesulfonyl acid, /,-toluenesulfonic acid, and p-toluenesulfonic acid pyridinium salt.

9. The process of claim 8, wherein the acid is selected from the group consisting of trifluoroacetic acid, $H_2S0_4$, HCl and $H_3P0_4$.

10. The process of claim 9, wherein the acid is selected from the group consisting of trifluoroacetic acid and HCl.

11. The process of any one of claims 4-10, further comprising:

(9) recrystallizing the product of step (8).

12. The process of claim 11, wherein step (9) comprises recrystallizing the product of step (8) from water and acetonitrile.

13. The process of any one of claims 4-12, wherein step (1) comprises:

(a) reacting  with a reagent selected from alkyl sulfonyl chlorides, aryl sulfonyl chlorides and halogenating agents to form  , wherein L is a leaving group selected from the group consisting of methanesulfonyloxy, ethanesulfonyloxy, chloromethanesulfonyloxy, p-toluenesulfonyloxy, benzensulfonyloxy, trifluoromethanesulfonyloxy and halogens, and

(b) further reacting  with at least one cyanating reagent to form R'^CN .

14. The process of claim 13, wherein L is selected from the group consisting of methanesulfonyloxy, ethanesulfonyloxy, chloromethanesulfonyloxy, />-toluenesulfonyloxy, benzensulfonyloxy, trifluoromethanesulfonyloxy, CI, Br and I.

15. The process of claim 13 or claim 14, wherein step (l)(a) comprises reacting R⌒OH with a sulfonyl chloride selected from the group consisting of methanesulfonyl chloride, ethanesulfonyl chloride, chloromethanesulfonyl chloride, />-toluenesulfonyl chloride, benzensulfonyl chloride and trifluoromethanesulfonyl chloride, to form R⌒L, where L is selected from the group consisting of methanesulfonyloxy, ethanesulfonyloxy, chloromethanesulfonyloxy, /?-toluenesulfonyloxy, benzensulfonyloxy and trifluoromethanesulfonyloxy.

16. The process of claim 13 or claim 14, wherein step (l)(a) comprises reacting R⌒OH with a halogenating agent selected from the group consisting of $Cl_2$, $Br_2$, $1_2$, $PC1_3$, $PBr_3$, $PI_3$, $PC1_5$, $PBr_5$, $PI_5$, $POCl_3$, $POBr_3$, $POI_3$, $SOCl_2$, $SOBr_2$, $SOI_2$, N-chlorosuccinimide, N-bromosuccinimide, N-iodosuccinimide, HC1, HBr, HI, $PPh_3$, $CC1_4$, $CBr_4$, $CI_4$, to form R⌒L.

17. The process of claim 16, wherein the halogenating agent is selected from the group consisting of POCI3 and $SOCI_2$.

18. The process of any one of claims 13-17, wherein said cyanating agent is selected from the group consisting of HCN, NaCN, KCN, $Cu(CN)_2$ and $Zn(CN)_2$.

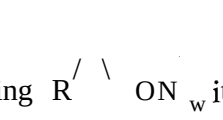
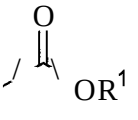
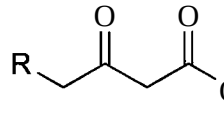
19. The process of claim 18, wherein said cyanating agent is selected from the group consisting of HCN, NaCN, KCN and $Zn(CN)_2$.

20. The process of claim 19, wherein the cyanating agent is NaCN or KCN.

21. The process of any one of claims 4-20, wherein, in step (2), $R^1$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert-butyl* and benzyl.

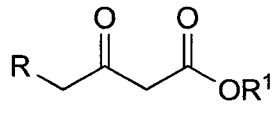
22. The process of claim 21, wherein $R^1$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, ter*t*-butyl and benzyl.

23. The process of claim 22, wherein $R^1$ is ethyl.

24. The process of any one of claims 4-23, wherein step (2) comprises reacting  with  in the presence of zinc dust and an activating agent to form  , wherein said activating agent is selected from the group consisting of, $(CH_3)_3SiCl$, $CH_3SO_3H$ and HCl.

25. The process of claim 24, wherein step (2) further comprises removing dimer impurities by use of an inorganic salt.

26. The process of claim 25, wherein the inorganic salt is $Na_2S_2O_5$.

27. The process of any one of claims 4-26, wherein step (3) comprises reacting  with a halogenating agent selected from the group consisting of $SO_2Cl_2$, N-chlorosuccinimide, 1,3-dichloro-5,5-dimethylhydantoin, trichloroisocyanuric acid, N-bromosuccinimide, bromine and 1,3-dibromo-5,5-dimethylhydantoin.

28. The process of claim 27, wherein the halogenating agent is selected from the group consisting of $SO_2Cl_2$, N-chlorosuccinimide, 1,3-dichloro-5,5-dimethylhydantoin, and N-bromosuccinimide.

29. The process of claim 28, wherein the halogenating agent is $SO_2Cl_2$.

30. The process of any one of claims 4-29, wherein X and $X^1$ are independently selected from the group consisting of F, CI, Br, and I.

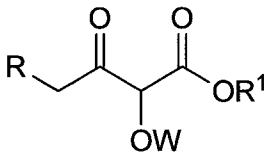
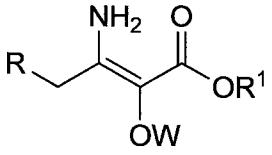
31. The process according to claim 30, wherein X and $X^1$ are independently selected from the group consisting of CI, Br, and I.

32. The process of claim 31, wherein X is Br and $X^1$ is CI.

33. The process of any one of claims 4-32, wherein, in step (4), W is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, *p*-methoxybenzoyl, *p*-toluoyl, benzoyl, benzyl, /?-methoxybenzoyl, 3,4-dimethoxybenzyl, silyl and tosyl groups.

34. The process of claim 33, wherein W is selected from the group consisting of benzyloxycarbonyl, *ter*/-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, /?-methoxybenzoyl, *p*-toluoyl and benzoyl.

35. The process of claim 34, wherein W is p-methoxybenzoyl.

36. The process of any one of claims 4-35, wherein the enamine formation reaction of step (5) comprises reacting  with an ammonia-containing compound selected from the group consisting of $NH_4OAc$, $NH_4C1$, $NH_3$, ammonium sulfate, ammonium formate and ammonium glycolate to form  .

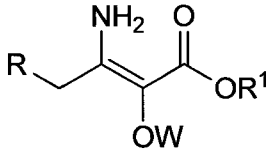
37. The process of claim 36, wherein the ammonia-containing compound is $NH_4OAc$.

38. The process of any one of claims 4-37, wherein, in step (6), $W^1$ is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, pivaloyl, acetyl, j>methoxybenzoyl,/?-toluoyl, benzoyl, benzyl, *p*-methoxybenzoyl, 3,4-dimethoxybenzyl, silyl and tosyl groups.

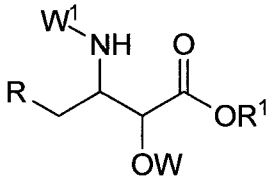
39. The process of claim 38, wherein $W^1$ is selected from the group consisting of benzyloxycarbonyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and *p*-methoxybenzyl.

40. The process of claim 39, wherein $W^1$ is *tert*-butyloxycarbonyl.

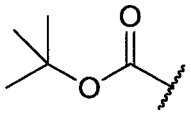
41. The process of any one of claims 4-40, wherein step (6) comprises

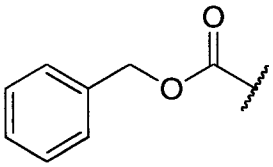


reacting with a reducing agent in the presence of a protecting reagent to

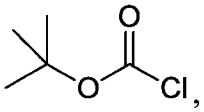


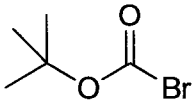
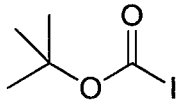
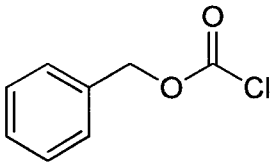
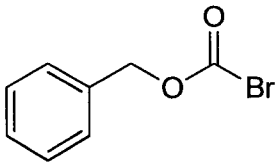
form , wherein:

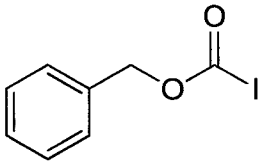
$W^1$ is a protecting group selected from the group consisting of  ,



and $(C_{1-6}alkyl)CO$-;

the protecting reagent is selected from the group consisting of  ,

 ,  ,  ,  ,



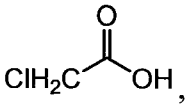
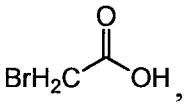
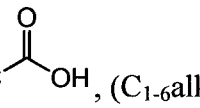
, $(C_{1-6}alkyl)COCl$, $(C_{1-6}alkyl)COBr$ and $(C_{1-6}alkyl)COI$; and

the reducing agent is selected from the group consisting of $NaBH_4$, $KBH_4$, $LiBH_4$, $Zn(BH_4)_2$, $KBH(OAc)_3$, $NaBH(OAc)_3$, $LiBH(OAc)_3$, $Zn(BH(OAc)_3)_2$, $KBH_3(CN)$, $NaBH_3(CN)$, $LiBH_3(CN)$, $Zn(BH_3(CN))_2$, $BH_3NH_3$, $BH_3C(CH_3)_3NH_2$, $BH_3N(CH_2CH_3)_2H$, $BH_3$-tetrahydrofuran, $BH_3S(CH_3)_2$ and $BH_3$-pyridine.

42. The process of claim 41, wherein step (6) further comprises treating the reaction mixture with an amine followed by treating with a base.

43. The process of claim 42, wherein the amine is selected from $NR^a_3$, where each $R^a$ is independently selected from the group consisting of H and $C_{1-6}$alkyl, where each $C_{1-6}$alkyl is substituted by 0, 1 or 2 independently selected substituents selected from the group consisting of OH and COOH.

44. The process of any one of claims 41-43, wherein the reducing agent is selected from the group consisting of $NaBH_4$ and $NaBH_3(CN)$.

45. The process of any one of claims 41-43, wherein step (6) is conducted in the presence of an acid selected from the group consisting of HC1, HBr, HI,  ,  , ,  ,  , $(C_{1-6}alkyl)SO_3H$, *p*-toluenesulfonic acid, $ArSO_3H$, $CF_3SO_3H$, glycolic acid, tartaric acid, citric acid, malonic acid, propionic acid, oxalic acid, trifluoroacetic acid, sulfamic acid, salicylic acid and succinic acid;

wherein Ar is one or more rings selected from the group consisting of:

a) 5- or 6-membered saturated or unsaturated monocyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S,

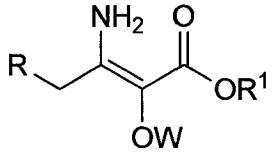
b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

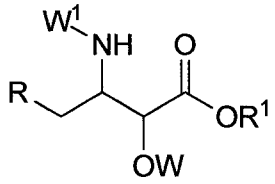
c) 11- to 15-membered saturated or unsaturated tricyclic rings with 0, 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein Ar is substituted with 0 to 4 independently selected substituents $R^{Ar}$ or oxo; wherein each $R^{Ar}$ is independently selected from the group consisting of H, halogen atoms, -OH, $C_{1-6}$alkoxy, $C_{1-6}$alkyl, -CN, $-CF_3$, $-OCF_3$, -C(0)OH, $-C(0)CH_3$, $C_{3-8}$cycloalkyl, $C_{3-8}$cycloalkoxy, $C_{1-6}$haloalkyl, $-NH_2$, $-NH(C_{1-6}alkyl)$ and $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$.

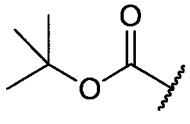
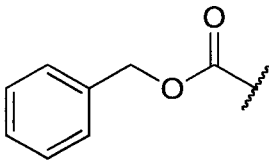
46. The process of claim 45, wherein the reducing agent is selected from the group consisting of $NaBH_4$ and $NaBH_3(CN)$, and the acid is selected from the group consisting of **$CH3SO_3H$** and glycolic acid.

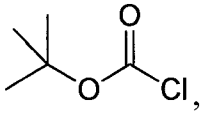
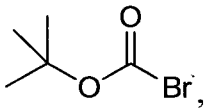
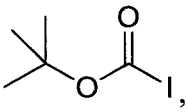
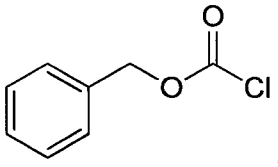
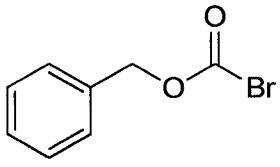
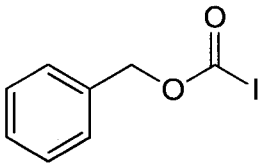
47. The process of any one of claims 4-40, wherein step (6) comprises

(a) reacting  with a reducing agent and an acid; and

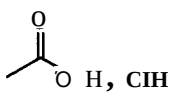
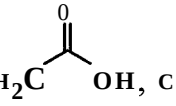
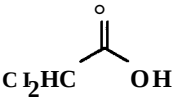
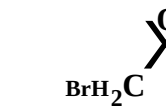
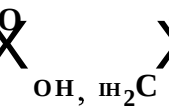
(b) further reacting the product of step (6)(a) with at least one protecting reagent in the presence of a base to form  ; wherein:

the reducing agent is selected from the group consisting of $NaBH_4$, $KBH_4$, $LiBH_4$, $Zn(BH_4)_2$, $KBH(OAc)_3$, $NaBH(OAc)_3$, $LiBH(OAc)_3$, $Zn(BH(OAc)_3)_2$, $KBH_3(CN)$, $NaBH_3(CN)$, $LiBH_3(CN)$, $Zn(BH_3(CN))_2$, **$BH_3NH_3$,** $BH_3C(CH_3)_3NH_2$, $BH_3N(CH_2CH_3)_2H$, $BH_3$-tetrahydrofuran, $BH_3S(CH_3)_2$ and $BH_3$-pyridine;

$W^1$ is a protecting group selected from the group consisting of  ,  and $(Ci_{-6}alkyl)CO$-; and

the protecting reagent is selected from the group consisting of  ,  ,  ,  ,  ,  , $(Ci_{-6}alkyl)COCl$, $(C_{1-6}alkyl)COBr$ and $(Ci_{-6}alkyl)COI$.

48. The process of claim 47, wherein the reducing agent is selected from the group consisting of $NaBH_4$ and $NaBH_3(CN)$.

49. The process of any one of claims 47 and 48, wherein the acid is selected from the group consisting of HCl, HBr, HI,  ,  ,  ,  ,  , $(C_{1-6}alkyl)SO_3H$, trifluoroacetic acid, *p*-toluenesulfonic acid, $ArSO_3H$, $CF_3SO_3H$, glycolic acid, tartaric acid, citric acid, malonic acid, propionic acid, oxalic acid, sulfamic acid, salicylic acid and succinic acid;

wherein Ar is one or more rings selected from the group consisting of:

a) 5- or 6-membered saturated or unsaturated monocyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S,

b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 0, 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

c) 11- to 15-membered saturated or unsaturated tricyclic rings with 0, 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein Ar is substituted with 0 to 4 independently selected substituents $R^{Ar}$ or oxo; wherein each $R^{Ar}$ is independently selected from the group consisting of H, halogen atoms, -OH, $C_{1-6}alkoxy$, $C_{1-6}alkyl$, -CN, $-CF_3$, $-OCF_3$, -C(0)OH, $-C(0)CH_3$, $C_{3-8}cycloalkyl$, $C_{3-8}cycloalkoxy$, $C_{1-6}$ haloalkyl, $-NH_2$, $-NH(C_{1-6}alkyl)$ and $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$.

50. The process of claim 49, wherein the reducing agent is selected from the group consisting of $NaBH_4$ and $NaBH_3(CN)$, and the acid is selected from the group consisting of $CH_3SO_3H$ and glycolic acid.

51. The process of any one of claims 47-50, wherein the base is selected from the group consisting of NaOH, $NaHCO_3$, $Na_2CO_3$, KOH, $K_2CO_3$, $K_3PO_4$ and $(C_{1-6}alkyl)_3N$.

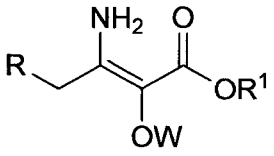
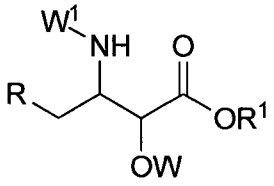
52. The process of claim 51, wherein the base is NaOH or $K_3PO_4$.

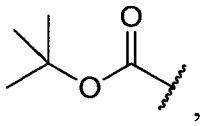
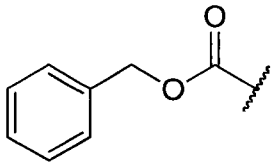
53. The process of any one of claims 47-52, wherein step (6)(b) further comprises treating the reaction mixture with an amine followed by treating with a base.

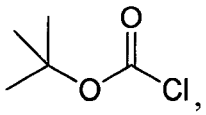
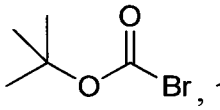
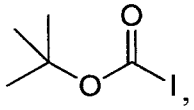
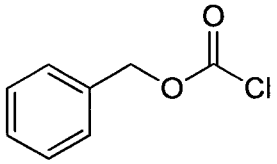
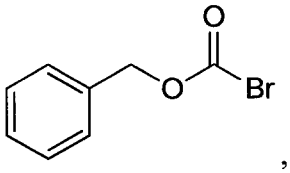
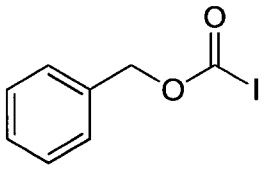
54. The process of claim 53, wherein the amine is selected from $NR^a_3$, where each $R^a$ is independently selected from the group consisting of H and $C_{1-6}$alkyl, where each $C_{1-6}$alkyl is substituted by 0, 1 or 2 independently selected substituents selected from the group consisting of OH and COOH.

55. The process of claim 54, wherein the amine is selected from the group consisting of diethanolamine and glycine.

56. The process of claim 55, wherein the amine is glycine.

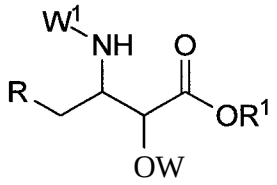
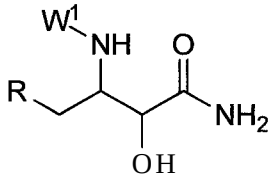
57. The process of any one of claims 4-40, wherein step (6) comprises reacting  with a reducing agent in the presence of $W^1$ to form  ; wherein:

$W^1$ is a protecting group selected from the group consisting of  ,  and $(C_{1-6}alkyl)CO$-;

the protecting reagent is selected from the group consisting of  ,  ,  ,  ,  ,  , $(C_{1-6}alkyl)COCl$, $(C_{1-6}alkyl)COBr$ and $(C_{1-6}alkyl)COI$; and

the reducing agent is a transition metal catalyst and hydrogen gas, where the transition metal catalyst is selected from the group consisting of Pd/C, Ru/C, $Ru0_2$, Rh/C, Pt/C, $Pt/Al_20_3$, $PtQ_2$, $Pd(OH)_2$, PdO, Ir/C, $Ir0_2$ and $Ir/CaC0_3$.

58. The process of claim 57, wherein the transition metal is $Ir/CaC0_3$.

59. The process of any one of claims 4-58, wherein step (7) comprises reacting  with ammonia to form  .

60. The process of claim 59, wherein the reacting is performed in the presence with of a catalyst.

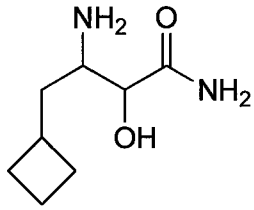
61. The process of claim 60, wherein the catalyst is selected from the group consisting of $CaCl_2$, $MgCl_2$, $ZnCl_2$ and $CeCl_2$.

62. The process of claim 61, wherein the catalyst is $CaCl_2$.

63. The process of claim 59, wherein the ammonia is provided as a gas at a pressure in a range of from 5 psi to 500 psi.

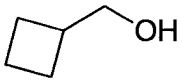
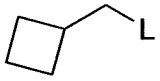
64. The process of claim 59, wherein the ammonia is provided as a solution at a concentration in a range of from 1M to 10M.

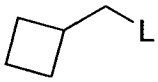
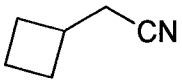
65. A process for preparing a compound of Formula la:

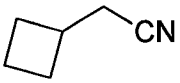
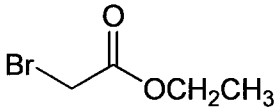
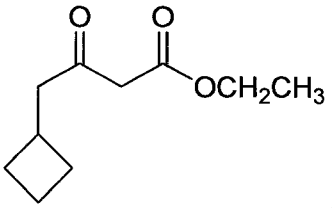


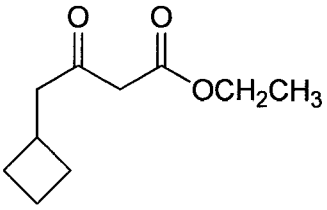
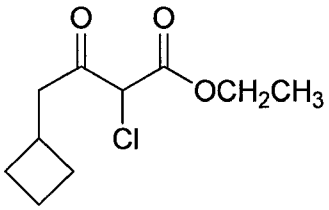
Ia

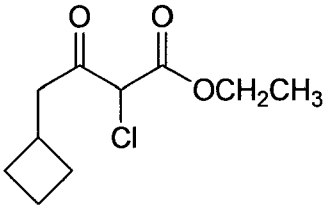
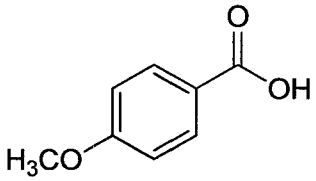
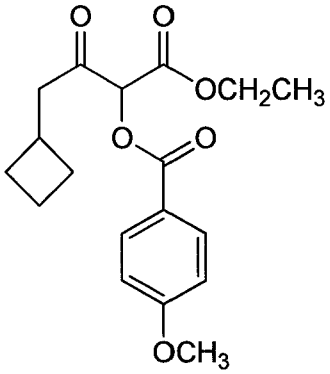
or a salt thereof, said process comprising:

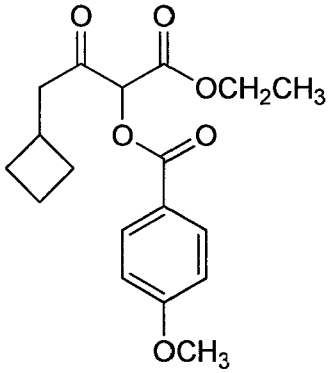
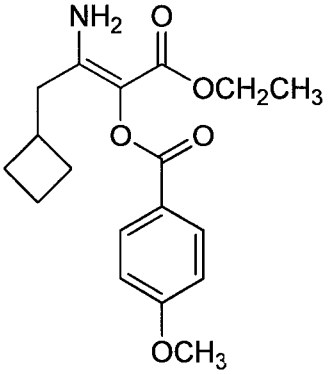
(l)(a) reacting  with methanesulfonyl chloride to form  , wherein L is methanesulfonyloxy, and

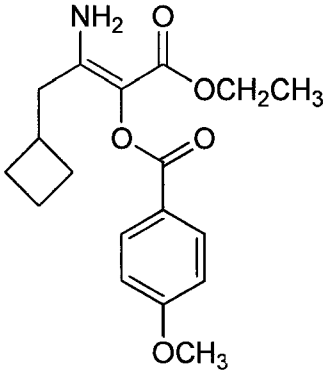
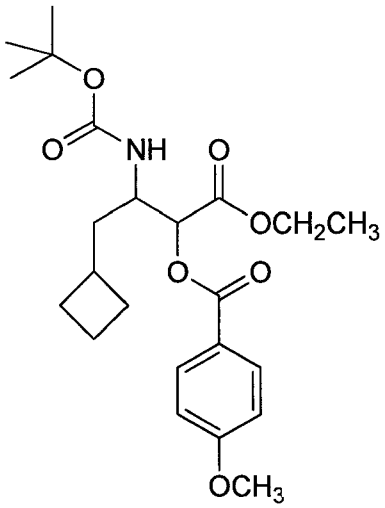
(1)(b) further reacting  with NaCN to form  ;

(2) coupling  with  to form  ;

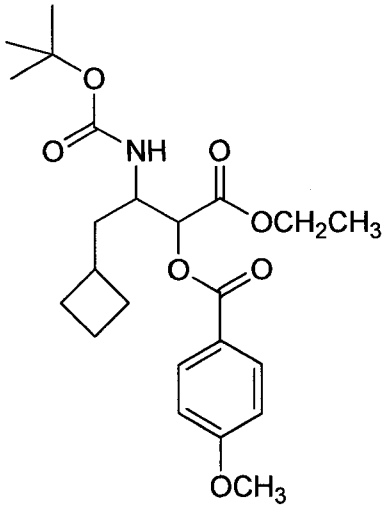
(3) halogenating  to form  ;

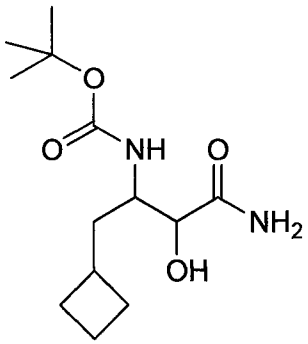
(4) reacting  with  to form  ;

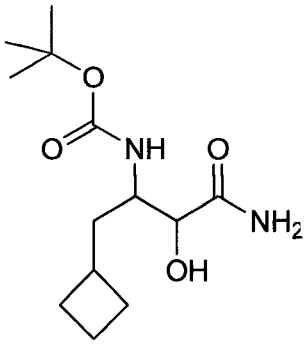
(5) conducting an enamine formation reaction by reacting  with $NH_4OAc$ to form  ;

(6) reducing  to form  ;

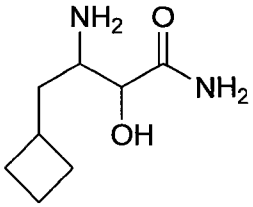
(7) performing aminolysis and deprotecting the protected hydroxyl



to form  ; and



(8) deprotecting the protected amine of to form



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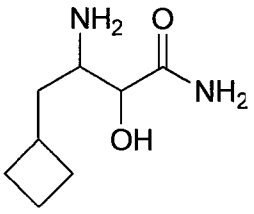
66. The process of claim 65, wherein step (8) further comprises adding an acid selected from the group consisting of ammonium, trifluoroacetic acid, $H_2S0_4$, HCl, $H_3P0_4$, citric acid, methanesulfonyl acid, p-toluenesulfonic acid, and

*p*-toluenesulfonic acid pyridinium salt to form an acid salt of  .

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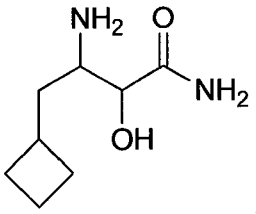
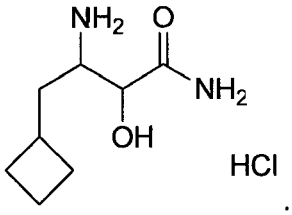
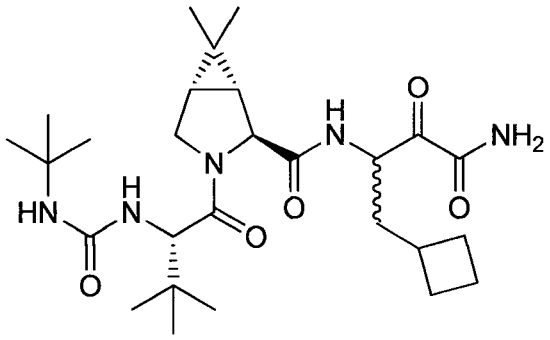
67. The process of claim 66, wherein step (8) comprises adding HC1 to form an HC1 salt of  .

68. The process of any one of claims 65-67, further comprising recrystallizing the product of step (8) from water and acetonitrile.

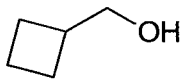
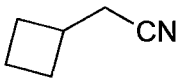
69. The process of any one of claims 4-68, wherein the compound of Formula I or Formula 1a is  .

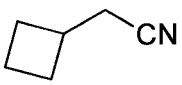
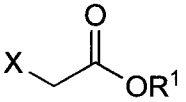
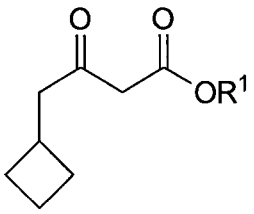
70. A process for preparing a compound of Formula II,



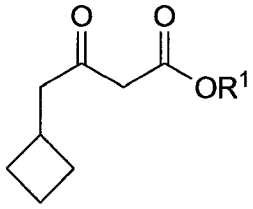
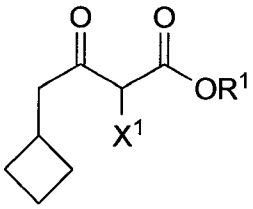
II

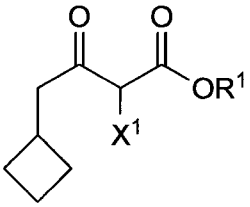
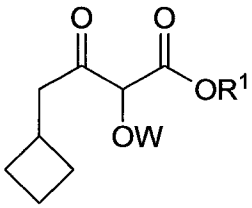
or a pharmaceutically acceptable salt or hydrate thereof, said process comprising:

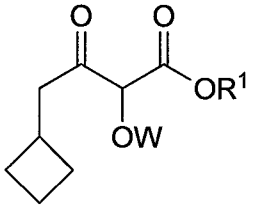
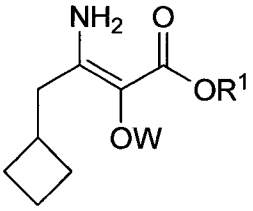
(1) converting  to  ;

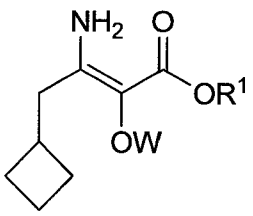
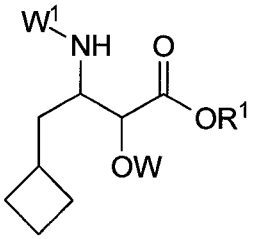
(2) coupling  with  to form  ,

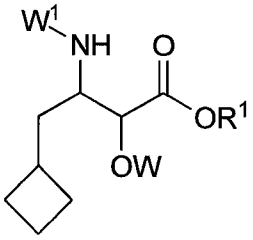
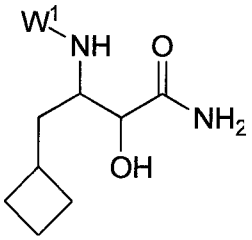
where $R^1$ is selected from the group consisting of Ci-salkyl and benzyl, and X is a halogen;

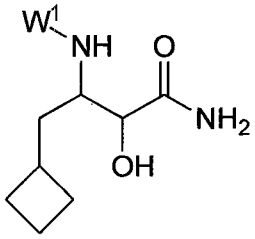
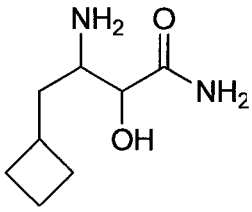
(3) halogenating  to form  , where $X^1$ is a halogen;

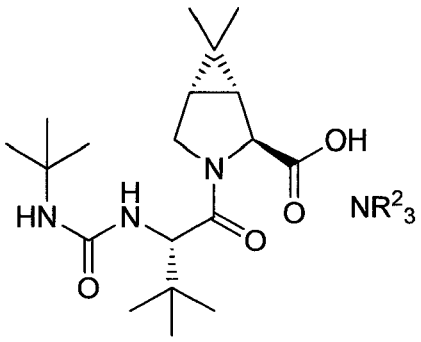
(4) reacting  with WOH to form  , where W is a protecting group;

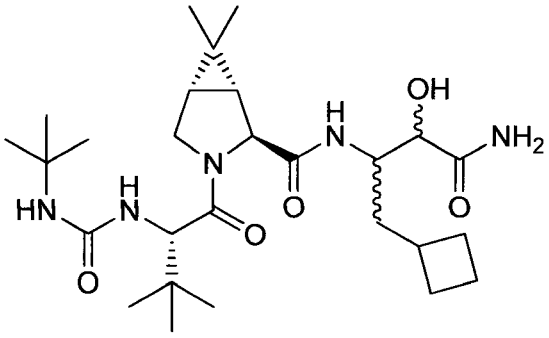
(5) conducting an enamine formation reaction to convert  to  ;

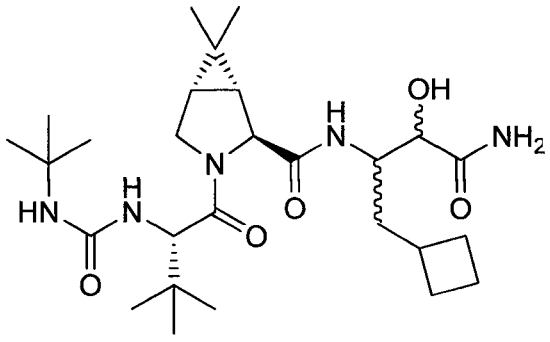
(6) reducing  to form  , where $W^1$ is a protecting group;

(7) performing aminolysis and deprotecting the protected hydroxyl  to form  ;

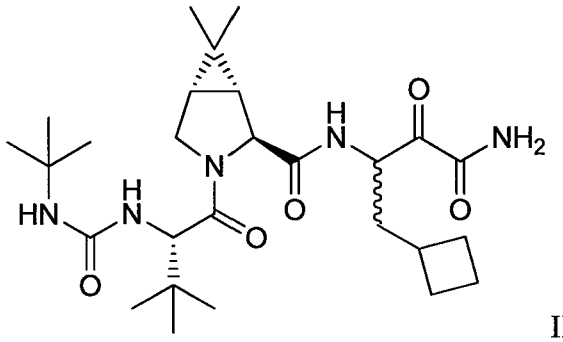
(8) deprotecting the protected amine of  to form  , adding an acid to form an acid salt and optionally recrystallizing the acid salt;

(9) coupling the acid salt of step (8) with  ,

wherein $R^2$ is selected from the group consisting of $C_{1-6}$alkyl, $C_{1-6}$cycloalkyl and $C_{1-6}$alkyl$C_{1-6}$cycloalkyl, in the presence of a peptide coupling agent to form  ; and

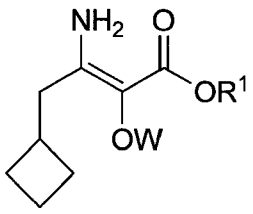
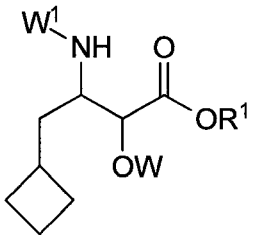
(10) oxidizing  to form the compound of Formula II.

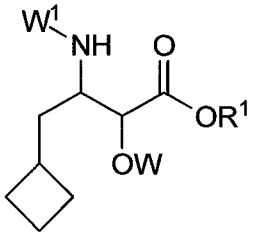
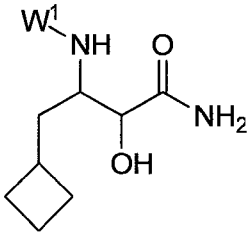
71. A process for preparing a compound of Formula II,

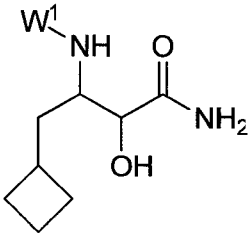
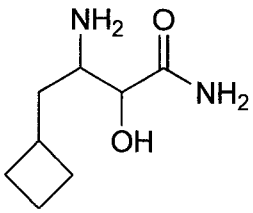


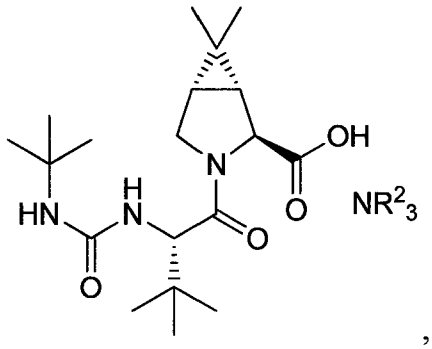
II

or a pharmaceutically acceptable salt or hydrate thereof, said process comprising:

(1) reducing  to form  , where $W^1$ is a protecting group;

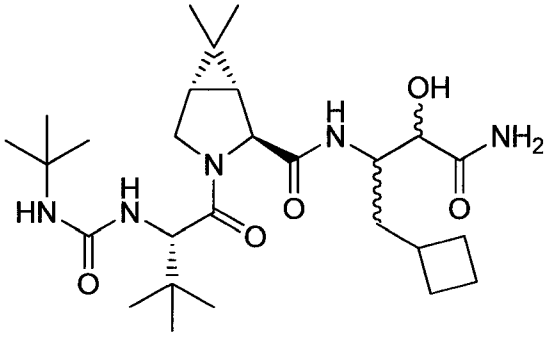
(2) performing aminolysis and deprotecting the protected hydroxyl  to form  ;

(3) deprotecting the protected amine of  to form  , adding an acid to form an acid salt and optionally recrystallizing the acid salt:

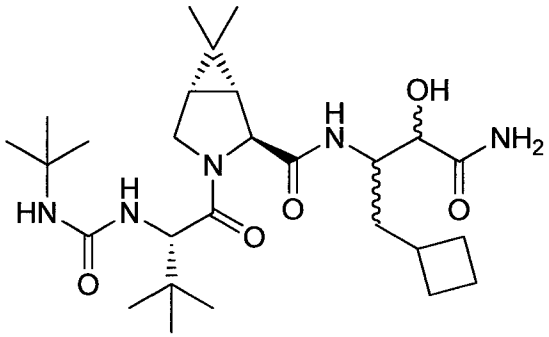


(4) coupling the acid salt of step (8) with ,

wherein $R^2$ is selected from the group consisting of $C_{1-6}$alkyl, $C_{1-6}$cycloalkyl and Ci-**6alkylCi**$_{-6}$cycloalkyl, in the presence of a peptide coupling agent to form



; and



(5) oxidizing to form the compound of Formula II.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/62025

**A. CLASSIFICATION OF SUBJECT MATTER**
**IPC(8) - C07C 69/74 (2013.01)**
**USPC - 560/123**
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) -C07C 69/74 (2013.01)
USPC -560/123

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 560/123;562/505;564/191;518/704

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase Google Patents, Google Scholar, WIPO, Surechem (hepatitis, hepatitis c, butanamide, p-methoxybenzoyl, 3-AMINO-4-CYCLOBUTYL-2-HYDROXYBUTANAMIDE, alpha-carboxylic-beta-ketoesters, cyclobutyl, HCV, NS3, protease, inhibitors, intermediates, methoxybenzoate, enamine, reducing, 4-Cyclobutyl-1-ethoxy-1,3-dioxobutan-2-yl 4-methoxybenzoate)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2011/125006 A2 (BRODNEY, et al.) 13 October 2011 (13.10.2011) entire document, especially pg 11, ln 5 | 1 |
| A | US 2011/0034705 A1 (DONG, et al.) 10 February 2011 (10.02.2011) entire document, especially para [0003], [0023] | 2-3 |
| A | WO 2010/138889 A1 (MASSE) 02 December 2010 (02.12.2010) entire document, especially para [170] | 2-3 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 February 2013 (11.02.2013) | 06 MAR 2013 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Hetpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/62025

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 11-64, 69
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. Ill Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

**Please See Continuation Sheet**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US 12762025

Continuted from Box III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1 . In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-3 directed to a compound selected from the group listed in instant claim 1

Group II: claims 4-10 and 65-68 directed to a process for preparing a compound of Formula I and Ia

Group III: claims 70-71 directed to a process for preparing a compound of Formula II

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The compounds of Groups I-III represent distinct chemical entities, which would be expected to possess distinct chemical or pharmacological properties. US 7,012,066 B2 to Saksena et al. (hereafter 'Saksena') discloses the compound of formula II of group III (col 113, second compound form the top). Saksena further teaches the preparation of similar compounds (col 455-463, synthetic process as shown). Therefore, based on this disclosure, it would have been obvious to one of skill in the art to identify the synthesis process of group III by choosing appropriate starting material.

Thus, the inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

Note: claims 11-64 and 69 are determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).