MACROCYCLIC INHIBITORS OF *FLAVIVIRIDAE* VIRUSES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial Number 61/657,562, filed on June 8, 2012, the entirety of which is incorporated herein by reference.

FIELD

The present application provides novel compounds inhibiting viruses, compositions containing such compounds, and therapeutic methods comprising the administration of such compounds.

BACKGROUND

RNA viruses comprising the *Flaviviridae* family include at least three distinguishable genera including *pestiviruses*, *flaviviruses*, and *hepaciviruses* (Calisher, *et al.*, J. Gen. Virol., 1993, 70, 37-43). While *pestiviruses* cause many economically important animal diseases such as bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, hog cholera) and border disease of sheep (BDV), their importance in human disease is less well characterized (Moennig, V., *et al.*, Adv. Vir. Res. 1992, 48, 53-98). *Flaviviruses* are responsible for important human diseases such as dengue fever and yellow fever while *hepaciviruses* cause hepatitis C virus infections in humans. Other important viral infections caused by the *Flaviviridae* family include West Nile virus (WNV) Japanese encephalitis virus (JEV), tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis, St Louis enchaplitis, Omsk hemorrhagic fever virus and Zika virus.

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide (Boyer, N. et al. J Hepatol. 32:98-112, 2000) so a significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A.M. and Bacon, B. R., Scientific American, Oct.: 80-85, (1999); Gordon, C. P., et al., *J. Med. Chem.* 2005, *48*, 1-20; Maradpour, D., et al., *Nat. Rev. Micro.* 2007, 5(6), 453-463). A number of HCV treatments are reviewed by Dymock et al. in Antiviral Chemistry & Chemotherapy, 11:2; 79-95 (2000). Virologic cures of patients with chronic HCV

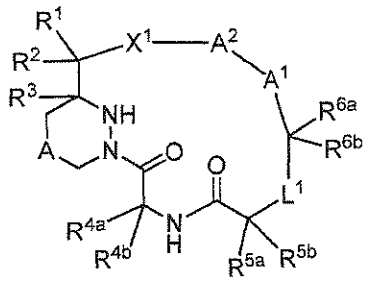
infection are difficult to achieve because of the prodigious amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV virus (Neumann, et al., *Science* 1998, *282*, 103-7; Fukimoto, et al., *Hepatology*, 1996, *24*, 1351-4; Domingo, et al., *Gene* 1985, *40*, 1-8; Martell, et al., *J. Virol.* 1992, *66*, 3225-9.

Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), that are used for the treatment of chronic HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. *Drugs* 2002, *62*, 507-556) but less than half the patients given this treatment show a persistent benefit. Therefore, there is a need to develop more effective anti-HCV therapies.

The macrocycle sanglifehrin and derivatives are immunomodulatory and bind peptidyl-prolyl cis/trans isomerase (PPIase) cyclophilins in a unique manner (WO 97/02285; WO 98/07743; *J. Am. Chem. Soc* 2003, 125, 3849-3859; *J. Org. Chem.* 2000, 65, 9255-9260; *Angew. Chem. Int. Ed.* 1999, 38, 2443-2446). The cyclophilins are peptidyl-prolyl cis/trans isomerases (PPIase) that regulate protein folding *in vivo* and inhibit hepatitis C virus (Lin et al., WO2006/138507). However, none of the sanglifehrins or their derivatives has become available for human anti-viral therapy. Therefore, there is a continuing need to develop macrocyclic sanglifehrins with anti-*Flaviviridae* virus activity and particularly anti-HCV activity.

SUMMARY

In one embodiment, there is provided a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

A is a bond, -O-, -S(O)$_n$-, -NH-, -N((C$_1$-C$_4$)alkyl)- or (C$_1$-C$_2$)alkylene;

A^1 is (C$_1$-C$_5$)alkylene, (C$_2$-C$_5$)alkenylene, (C$_2$-C$_5$)alkynylene, arylene, heteroarylene, cycloalkylene, heterocycloalkylene, aryl(C$_1$-C$_2$)alkylene, heteroaryl(C$_1$-C$_2$)alkylene, cycloalkyl(C$_1$-C$_2$)alkylene or heterocycloalkyl(C$_1$-C$_2$)alkylene, wherein a sp^3 carbon atom of A^1 is optionally replaced by -O-, -S(O)$_n$-, -NH- or -N((C$_1$-C$_4$)alkyl)-, and wherein a sp^3 or sp^2 carbon atom of A^1 is optionally substituted with one or more substituents selected from the group consisting of halo, (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl, aryl, heterocycloalkyl, cycloalkyl, aryl(C$_1$-C$_4$)alkyl, cycloalkyl(C$_1$-C$_4$)alkyl, heterocycloalkyl(C$_1$-C$_4$)alkyl, arylheterocycloalkyl(C$_1$-C$_4$)alkyl, -OR^9, -SR^9, -S(O)R^9, -S(O)$_2$R^9 and -N(R^9)$_2$ where such an optional substitution is chemically feasible;

A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene, arylene, cycloalkylene, (C$_1$-C$_3$)alkylene, (C$_2$-C$_3$)alkenylene or (C$_2$-C$_3$)alkynylene, wherein the arylene, heteroarylene, heterocycloalkylene or cycloalkylene moiety of A^2 is optionally substituted with one or more substituents selected from the group consisting of -OR^9, -SR^9, -S(O)R^9, -S(O)$_2$R^9, -N(R^9)$_2$, halo, halo(C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkoxy cyano and (C$_1$-C$_8$)alkyl where such an optional substitution is chemically feasible;

L^1 is -O-C(O)-, -O-CH$_2$-, -NR^{11}-C(O)-, -NR^{10}-CH$_2$-, -NH-C(R^{10})$_2$- or -NH-S(O)$_2$-, wherein each R^{10} is independently H, (C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkenyl or cycloalkyl; and R^{11} is (C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkenyl or cycloalkyl;

X^1 is a bond, -O-, -NH-, -N((C$_1$-C$_4$)alkyl)- or heterocycloalkylene;

R^1 and R^2 are independently H, (C$_1$-C$_4$)alkyl, (C$_2$-C$_4$)alkenyl, (C$_2$-C$_4$)alkynyl, halo, cyano or -C(O)-(C$_1$-C$_4$)alkyl; or

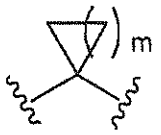
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-, -C(=S)- or –C(=N(C$_1$-C$_4$)alkyl)-;

R^3 is H or (C$_1$-C$_4$)alkyl which is optionally substituted with halo, cyano, hydroxyl or (C$_1$-C$_4$)alkoxy;

R^{4a} and R^{4b} are independently H, (C$_1$-C$_8$)alkyl, aryl, aryl(C$_1$-C$_4$)alkyl, heterocycloalkyl, heterocycloalkyl(C$_1$-C$_4$)alkyl, cycloalkyl or cycloalkyl(C$_1$-C$_4$)alkyl, wherein each R^{4a} and R^{4b} is optionally substituted with one or more substituents selected from the group consisting of cyano, -COOH, halo, hydroxyl, (C$_1$-C$_8$)alkoxy, amino, mono(C$_1$-C$_8$)alkylamino, di(C$_1$-C$_8$)alkylamino, aryl and heteroaryl where such an optional substitution is chemically feasible;

R^{5a} and R^{5b} are independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, aryl, heterocycloalkyl, cycloalkyl, aryl$(C_1\text{-}C_4)$alkyl, cycloalkyl$(C_1\text{-}C_4)$alkyl or heterocycloalkyl$(C_1\text{-}C_4)$alkyl, wherein each R^{5a} and R^{5b} is optionally substituted with one or more substituents selected from the group consisting of $-N_3$, cyano, -COOH, halo, hydroxyl, amino, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, $(C_1\text{-}C_8)$alkoxy, aryl and heteroaryl, or

R^{5a} and R^{5b} together form a spirocycle having Formula (a):



(a),

wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, =N$(C_1\text{-}C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$;

R^{6a} and R^{6b} are independently H, hydroxyl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $-CH_2CH_2CR^9$(=N$(C_1\text{-}C_4)$alkoxy), aryl, heterocycloalkyl, cycloalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ and $-N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, cyano, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$ and $(C_1\text{-}C_8)$alkanoyl where such an optional substitution is chemically feasible; or R^{6a} and R^{6b} together form a spirocycle having Formula (a);

each R^8 is independently H, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl, wherein R^8 is optionally substituted with -OR, $-N(R^9)_2$, $-CON(R^9)_2$ or cyano;

each R^9 is independently H, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl;

each n is independently 0, 1 or 2; and

m is 1, 2, 3, 4 or 5.

In another embodiment, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof and one or more pharmaceutically acceptable

carriers or excipients. In one aspect of the embodiment, the pharmaceutical composition further comprises one or more additional therapeutic agents.

In yet another embodiment, a method for treating *Flaviviridae* viral infection is provided comprising administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof to a mammal in need thereof. In one aspect of the embodiment, the treatment results in the reduction of the in viral load or clearance of viral RNA in a patient.

In yet another embodiment, a method for treating *Coronaviridae* viral infection is provided comprising administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereofto a mammal in need thereof. In one aspect of the embodiment, the treatment results in the reduction of the in viral load or clearance of viral RNA in a patient.

DETAILED DESCRIPTION

Definitions

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

"Alkanoyl" is RC(O)-; "alkanoyloxy" is RC(O)O-; and "alkanoylamino" is RC(O)NR'-; where R is an alkyl group as defined herein, and R' is hydrogen or alkyl.

"Alkenyl" refers to a straight or branched hydrocarbyl group with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond. In some embodiments, alkenyl is a C_2-C_{20} alkenyl group, a C_2-C_{10} alkenyl group or a C_2-C_6 alkenyl group. Examples of alkenyl group include, but are not limited to, vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), cyclopentenyl (-C_5H_7), and 5-hexenyl (-$CH_2CH_2CH_2CH_2$CH=CH_2).

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, and alkenylene group can have 2 to 20 carbon atoms, 2 to 10 carbon atoms, or 2 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethenylene (-CH=CH-).

"Alkoxy" is RO- where R is alkyl, as defined herein. Non-limiting examples of alkoxy groups include methoxy, ethoxy and propoxy.

"Alkyl" refers to a straight or branched chain hydrocarbyl group. In an embodiment, alkyl has from 1 to 20 carbon atoms (i.e., C_1-C_{20} alkyl). In some embodiments, alkyl is a C_1-C_{10} alkyl group or a C_1-C_6 alkyl group. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl.

"Alkylene" refers to a saturated, branched or straight chain radical or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Examples of alkylene radicals include, but are not limited to, methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-) and butylene (-$CH_2CH_2CH_2CH_2$-).

"Alkynyl" refers to a hydrocarbon containing normal, secondary or tertiary carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (i.e., C_2-C_{20} alkynyl), 2 to 12 carbon atoms (i.e., C_2-C_{12} alkyne,) or 2 to 6 carbon atoms (i.e., C_2-C_6 alkynyl). Examples of alkynyl groups include, but are not limited to, acetylenic (-C≡CH) and propargyl (-CH_2C≡CH).

"Amino" refers to $-NH_2$.

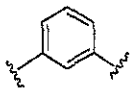
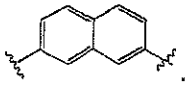
"Alkylamino" refers to an amino group substituted with one or more alkyl groups. "Mono(alkyl)amino" or "(alkyl)amino" is RNH-, and "di(alkyl)amino" or "$(alkyl)_2$amino" is R_2N-, where each of the R groups is alkyl as defined herein and are the same or different. Examples of alkylamino groups include, but are not limited to, methylamino, ethylamino, propylamino, butylamino, dimethylamino, diethylamino and methylethylamno.

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 2 to 20 carbon atoms, 2 to 10 carbon atoms, or 2 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargylene (-CH_2C≡C-), and 4-pentynylene (-$CH_2CH_2CH_2$C≡C-).

"Aryl" refers to any monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic, or an aromatic ring system of 5 to 14 carbons atoms which includes a carbocyclic aromatic group fused with a 5-or 6-membered cycloalkyl group.

Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl and indanyl.

"Arylalkyl" refers to an alkyl as defined herein substituted with an aryl radical.

"Arylene" refers to an aryl as defined above having two monovalent radical centers derived by the removal of two hydrogen atoms from two different carbon atoms of a parent aryl. Typical arylene radicals include, but are not limited to, phenylene, e.g.,  , and naphthylene, e.g.,  .

"Arylalkylene" refers to an arylalkyl as defined above having two monovalent radical centers derived by the removal of one hydrogen atom from the aryl radical and the other hydrogen removed from the alkyl radical of the group.

"Cycloalkyl" refers to a hydrocarbyl group containing at least one saturated or partially unsaturated ring structure, and attached via a ring carbon. Cycloalkyl groups include hydrocarbon mono-, bi-, and poly-cyclic rings, whether fused, bridged, or spiro. In various embodiments, it refers to a saturated or a partially unsaturated C_3-C_{12} cyclic moiety, examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl and cyclooctyl.

"Cycloalkylalkyl" refers to an alkyl moiety substituted with a cycloalkyl group. Examples of cycloalkylalkyl groups include cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl and cyclohexylmethyl.

"Cycloalkylalkylene" refers to an alkylene moiety substituted with a cycloalkyl group. Examples of cycloalkylalkylene groups include cyclopropylmethylene, cyclobutylmethylene, cyclopentylethylene and cyclohexylmethylene.

"Cycloalkylene" refers to a cycloalkyl, as defined herein, having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent cycloalkyl. Examples of cycloalkylene include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene and cyclohexylene.

"Dialkylaminoalkyl" refers to an alkyl moiety substituted with a dialkylamino group, wherein dialkylamino is as defined herein.

"Ester" means any ester of a compound in which any of the -COOH functions of the molecule is replaced by a –C(O)OR function, or in which any of the –OH functions of the molecule are replaced with a –OC(O)R function, in which the R moiety of the ester is any carbon-containing group which forms a stable ester moiety, including but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl and substituted derivatives thereof.

"Halo" refers to chloro (-Cl), bromo (-Br), fluoro (-F) or iodo (-I).

"Haloalkoxy" refers to alkoxy, as defined herein, substituted with one or more halo radicals.

"Haloalkoxyalkyl" refers to an alkyl moiety substituted with a haloalkoxy group, as defined herein.

"Haloalkyl" refers to an alkyl group, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. Examples of haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CFH_2$ and $-CH_2CF_3$.

"Heterocycloalkyl" refers to a saturated or partially unsaturated monocyclic, bicyclic or tricyclic group of 2 to 14 ring-carbon atoms and, in addition to ring-carbon atoms, 1 to 4 heteroatoms selected from the group consisting of P, N, O and S. The heterocyclic group can be attached through a carbon atom or through a heteroatom, and when substituted, the substituent can be bonded to a carbon atom or a heteroatom. Examples of heterocyclyl include azetidinyl, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl,

dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl and N-oxides thereof.

"Arylheterocycloalkyl" refers to a heterocycloalkyl group, as defined herein, in which a hydrogen atom has been replaced with an aryl group.

"Arylheterocycloalkylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heterocycloalkyl group, and a hydrogen atom of the heterocycloalkyl group has been replaced with an aryl group.

"Heterocycloalkylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heterocycloalkyl group.

"Heterocycloalkylalkylene" refers to an alkylene group, as defined herein, in which a hydrogen atom has been replaced with a heterocycloalkyl group.

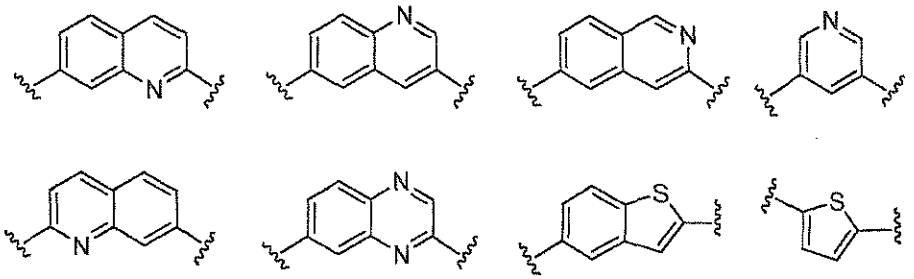
"Heterocycloalkylene" refers to a heterocycloalkyl, as defined above, having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent heterocycloalkyl group.

"Heteroaryl" refers to a monocyclic, bicyclic or tricyclic ring having up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms in the ring selected from the group consisting of N, O and S. Non-limiting examples of heteroaryl include pyridyl, thienyl, furanyl, pyrimidyl, imidazolyl, pyranyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, oxazolyl, isoxazoyl, pyrrolyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, benzothienyl, indolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoindolyl, benzotriazolyl, purinyl, thianaphthenyl and pyrazinyl. Attachment of heteroaryl can occur via an aromatic ring, or, if heteroaryl is bicyclic or tricyclic and one of the rings is not aromatic or contains no heteroatoms, through a non-aromatic ring or a ring containing no heteroatoms. "Heteroaryl" is also understood to include the N-oxide derivative of any nitrogen containing heteroaryl.

"Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group.

"Heteroarylalkylene" refers to an alkylene group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group.

"Heteroarylene" refers to a heteroaryl, as defined above, having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent heteroaryl group. Non-limiting examples of heteroarylene groups are:



"Hydroxyalkoxy" refers to an alkoxy, as defined herein, substituted with a hydroxyl group (-OH). An example of hydroxyalkoxy is hydroxyethoxy.

"Hydroxyalkyl" refers to an alkyl group substituted with at least one hydroxyl group. Examples of hydroxyalkyl groups include, but are not limited to, hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

"Prodrug" refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound. Non-limiting examples of prodrugs include ester moieties, quaternary ammonium moieties, glycol moieties, and the like.

The term "optionally substituted" refers to a moiety wherein all substituents are hydrogen or wherein one or more of the hydrogens of the moiety are replaced by non-hydrogen substituents. Multiple substitutions on the same atom are also permitted where chemically feasible (e.g., a dioxo substitution to provide $-S(O)_2-$, geminal substituents, spiro cycloalkyl or heterocycloalkyl rings, etc.). In some embodiments, "one or more" substituents is from one to three substituents.

Embraced herein, where applicable, are permissible isomers such as tautomers, racemates, enantiomers, diastereomers, atropisomers, configurational isomers of double bonds (E- and/or Z-), cis- and trans- configurations in ring substitution patterns, and isotopic variants.

"Pharmaceutically acceptable" means suitable for use in pharmaceutical preparations, generally considered as safe for such use, officially approved by a regulatory agency of a

national or state government for such use, or being listed in the U. S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

"Pharmaceutically acceptable carrier" refers to a diluent, adjuvant, excipient, or carrier, or other ingredient which is pharmaceutically acceptable and with which a compound of the invention is administered.

"Pharmaceutically acceptable salt" refers to a salt which may enhance desired pharmacological activity. Examples of pharmaceutically acceptable salts include acid addition salts formed with inorganic or organic acids, metal salts and amine salts. Examples of acid addition salts formed with inorganic acids include salts with hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Examples of acid addition salts formed with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxy-benzoyl)-benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethane-sulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methyl-bicyclo[2.2.2]oct-2-ene1-carboxylic acid, gluco-heptonic acid, 4,4'-methylenebis(3-hydroxy-2-naphthoic) acid, 3-phenylpropionic acid, trimethyl-acetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxy-naphthoic acids, salicylic acid, stearic acid and muconic acid. Examples of metal salts include salts with sodium, potassium, calcium, magnesium, aluminum, iron, and zinc ions. Examples of amine salts include salts with ammonia and organic nitrogenous bases strong enough to form salts with carboxylic acids.

A compound of a given formula (e.g. the compound of Formula I, which also includes Formula I, II, II-a, II-b, II-c and/or III) is intended to encompass the compounds of the disclosure, and the pharmaceutically acceptable salts, stereoisomers, mixture of stereoisomers or tautomers of such compounds. Additionally, the compounds of the disclosure may possess one or more asymmetric centers, and can be produced as a racemic mixture or as individual enantiomers or diastereoisomers. The number of stereoisomers present in any given compound of a given formula depends upon the number of asymmetric centers present (there are 2^n stereoisomers possible where n is the number of asymmetric centers). The individual stereoisomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis or by resolution of the compound by

conventional means. The individual stereoisomers (including individual enantiomers and diastereoisomers) as well as racemic and non-racemic mixtures of stereoisomers are encompassed within the scope of the present disclosure, all of which are intended to be depicted by the structures of this specification unless otherwise specifically indicated.

"Isomers" are different compounds that have the same molecular formula. Isomers include stereoisomers, enantiomers and diastereomers.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. Stereoisomers include enantiomers and diastereomers.

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate.

"Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

The absolute stereochemistry is specified according to the Cahn Ingold Prelog R S system. When the compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown are designated (+) or (-) depending on the direction (dextro- or laevorotary) that they rotate the plane of polarized light at the wavelength of the sodium D line.

Some of the compounds exist as tautomeric isomers or "tautomers". Tautomeric isomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown, and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

"Therapeutically-effective amount" refers to an amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect treatment for the disease. "Therapeutically effective amount" can vary depending on the compound, the disease and its severity, the age, the weight, etc. of the subject to be treated.

The term "treating", and grammatical equivalents thereof, when used in the context of treating a disease, means slowing or stopping the progression of a disease, or ameliorating at

least one symptom of a disease, more preferably ameliorating more than one symptom of a disease. For example, treatment of a hepatitis C virus infection can include reducing the HCV viral load in an HCV infected human being, and/or reducing the severity of jaundice present in an HCV infected human being.

Any formula or structure given herein, including Formula I, II, II-a, II-b, II-c or III, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. An "isotope" may have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl and ^{125}I. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated. Such isotopically labeled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

The disclosure also included compounds of Formula I, II, II-a, II-b, II-c or III in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half life of any compound of Formula I, II, II-a, II-b, II-c or III when administered to a mammal. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

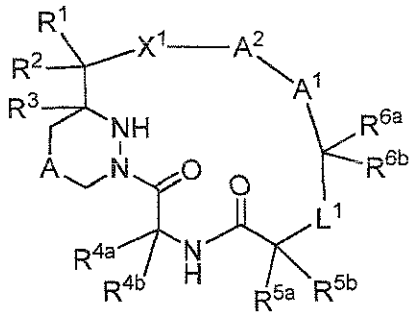
Deuterium labeled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below

by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compound of Formula I, II, II-a, II-b, II-c or III.

The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

Compounds

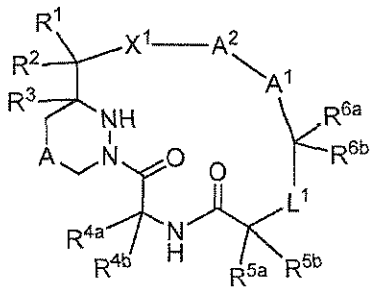
The present application provides a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein L^1, A^1, A^2, X^1, R^1, R^2, R^3, R^{4a}, R^{4b}, R^5 and R^{6a}, R^{6b} are as defined above.

In one embodiment, provided is a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

A is a bond, -O-, -S(O)$_n$-, -NH-, -N((C$_1$-C$_4$)alkyl)- or (C$_1$-C$_2$)alkylene;

A^1 is (C$_1$-C$_5$)alkylene, (C$_2$-C$_5$)alkenylene, (C$_2$-C$_5$)alkynylene, arylene, heteroarylene, cycloalkylene, heterocycloalkylene, aryl(C$_1$-C$_2$)alkylene, heteroaryl(C$_1$-C$_2$)alkylene, cycloalkyl(C$_1$-C$_2$)alkylene or heterocycloalkyl(C$_1$-C$_2$)alkylene, wherein a sp^3 carbon atom of A^1 is optionally replaced by -O-, -S(O)$_n$-, -NH- or -N((C$_1$-C$_4$)alkyl)-, and wherein a sp^3 or sp^2 carbon atom of A^1 is optionally substituted with one or more groups selected from halo, (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl, aryl, heterocycloalkyl, cycloalkyl, aryl(C$_1$-C$_4$)alkyl, cycloalkyl(C$_1$-C$_4$)alkyl, heterocycloalkyl(C$_1$-C$_4$)alkyl, arylheterocycloalkyl(C$_1$-C$_4$)alkyl, -OR^9, -SR^9, -S(O)R^9, -S(O)$_2$R^9 and -N(R^9)$_2$;

A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene, arylene, cycloalkylene, (C$_1$-C$_3$)alkylene, (C$_2$-C$_3$)alkenylene or (C$_2$-C$_3$)alkynylene, wherein A^2 is optionally substituted with one or more substituents selected from OR^9, -SR^9, -S(O)R^9, -S(O)$_2$R^9, -N(R^9)$_2$, halo, halo(C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkoxy, cyano and (C$_1$-C$_8$)alkyl;

L^1 is -O-C(O)-, -O-CH$_2$-, -NR^{10}-C(O)-, -NR^{10}-CH$_2$-, -NH-C(R^{10})$_2$- or -NH-S(O)$_2$-, wherein each R^{10} is independently H, (C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkenyl or cycloalkyl;

X^1 is bond, -O-, -NH-, -N((C$_1$-C$_4$)alkyl)- or heterocycloalkylene;

R^1 and R^2 are independently H, (C$_1$-C$_4$)alkyl, (C$_2$-C$_4$)alkenyl, (C$_2$-C$_4$)alkynyl, halo, cyano or -C(O)-(C$_1$-C$_4$)alkyl; or

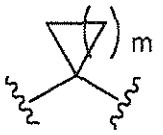
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-, -C(=S)- or –C(=N(C$_1$-C$_4$)alkyl)-;

R^3 is H or (C$_1$-C$_4$)alkyl which is optionally substituted with halo, cyano, hydroxyl or (C$_1$-C$_4$)alkoxy;

R^{4a} and R^{4b} are independently H, $(C_1\text{-}C_8)$alkyl, aryl, aryl$(C_1\text{-}C_4)$alkyl, heterocycloalkyl, heterocycloalkyl$(C_1\text{-}C_4)$alkyl, cycloalkyl or cycloalkyl$(C_1\text{-}C_4)$alkyl, wherein each of R^{4a} and R^{4b} is optionally substituted with one or more substituent selected from cyano, -COOH, halo, hydroxyl, amino, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, aryl and heteroaryl;

R^{5a} and R^{5b} are independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, aryl, heterocycloalkyl, cycloalkyl, aryl$(C_1\text{-}C_4)$alkyl, cycloalkyl$(C_1\text{-}C_4)$alkyl or heterocycloalkyl$(C_1\text{-}C_4)$alkyl, wherein R^5 is optionally substituted with one or more substituent selected from $-N_3$, cyano, -COOH, halo, hydroxyl, amino, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, aryl and heteroaryl, or

R^{5a} and R^{5b} together form a spirocycle having Formula (a):



(a),

wherein a carbon ring atom of Formula (a) is optionally substituted with one or more heteroatom selected from SO, SO_2, O and N, and wherein a carbon ring atom of Formula (a) optionally has one or more substituents selected from halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$alkoxy;

R^{6a} and R^{6b} are independently H, hydroxyl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $-CH_2CH_2CR^9(=N(C_1\text{-}C_4)\text{alkoxy})$, aryl, heterocycloalkyl, cycloalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ and $-N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from halo, hydroxyl, cyano, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$ and $(C_1\text{-}C_8)$alkanoyl; or R^{6a} and R^{6b} together form a spirocycle having Formula (a);

each R^8 is independently H, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl, wherein R^8 is optionally substituted with -OR, $-N(R^9)_2$, $-CON(R^9)_2$, or cyano;

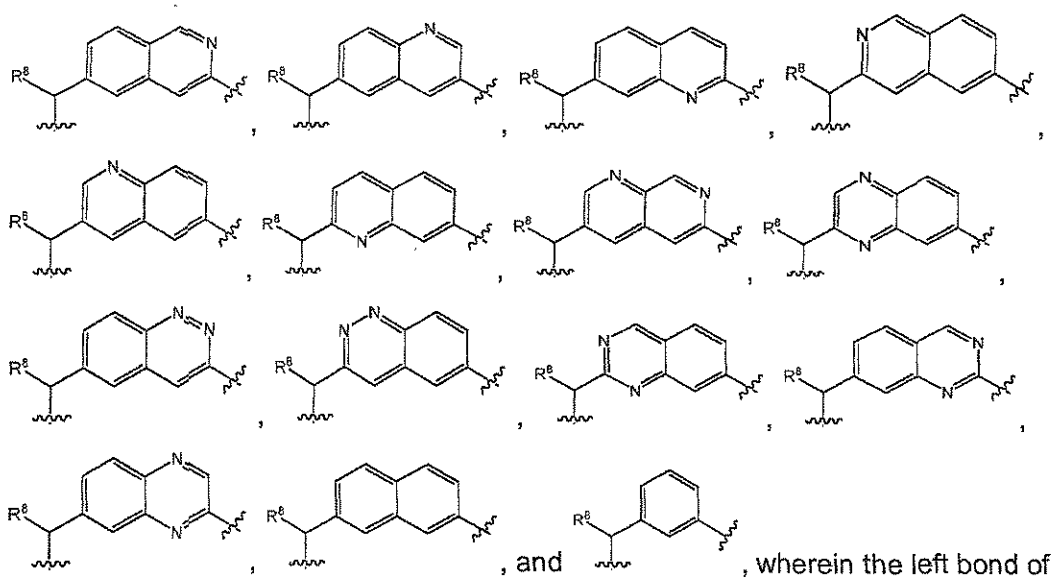
each R^9 is independently H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl;

each n is independently 0, 1 or 2; and

m is 1, 2, 3, 4 or 5.

In one aspect of the embodiment, A^1 is ethenylene, propenylene, butenylene, ethylene, propylene, butylene, oxypropylene, oxypropenylene, pyrazolylene, phenylene or pyrimidinylene.

In another aspect of the embodiment, A^2 is -CH(R^8)-quinolinylene, -CH(R^8)-isoquinolinylene, -CH(R^8)-naphthyridinylene, -CH(R^8)-cinnolinylene, -CH(R^8)-quinoxalinylene, -CH(R^8)-phenylene, -CH(R^8)-naphthylene or -CH(R^6)-halophenylene. In various aspects of the embodiment, A^2 is selected from the group consisting of



, wherein the left bond of A^5 linker is attached to X^1. In certain embodiments, R^8 is methyl.

In some embodiments, X^1 is -O-, -NH- or –N(CH_3)-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; and R^3 is H. In another embodiments, X^1 is -O-, -NH- or –N(CH_3)-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; R^3 is H; one of R^{4a} and R^{4b} is H and the other is methyl; and one of R^{5a} and R^{5b} is H and the other is iso-propyl.

In one embodiment, X^1 is -O-, -NH- or –N(CH_3)-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; R^3 is H; one of R^{4a} and R^{4b} is H and the other is methyl; one of R^{5a} and R^{5b} is H and the other is iso-propyl ; A^2 is -CH(R^8)-heteroarylene, and R^8 is methyl.

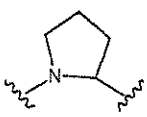
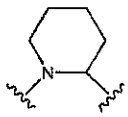
In another embodiment, X^1 is -O- or -NH-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; R^3 is H; R^{4a} is H; R^{4b} is methyl; R^5 is isopropyl; and R^8 is methyl.

In one embodiment, one of R^{6a} and R^{6b} is H; and the other H, hydroxyl, -$CH_2CH_2CR^9$(=N(C_1-C_4)alkoxy), (C_1-C_8)alkyl or (C_1-C_8)alkoxy, wherein R^{6a} or R^{6b} is optionally substituted with one or more substituents selected from the group consisiting of halo, hydroxyl,

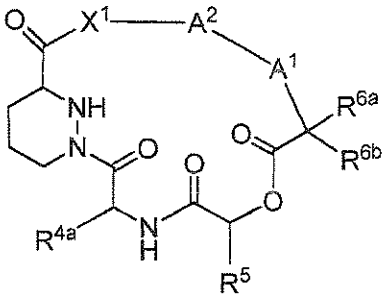
$(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, heterocycloalkyl, $(C_1\text{-}C_4)$alkanoyl or di$(C_1\text{-}C_4)$alkylamino. In another embodiment, R^{6a} is H; and R^{6b} is H, $(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$alkyl substituted with heterocycloalkyl, $(C_1\text{-}C_4)$alkanoyl or di$(C_1\text{-}C_4)$alkylamino.

In one embodiment, L^1 is -O-C(O)-. In another embodiment, L^1 is $-O-CH_2-$. In yet another embodiment, L^1 is $-N(CH_3)-C(O)-$. In still another embodiment, L^1 is $-NH-CH_2-$. In certain embodiments, L^1 is $-NH-S(O)_2-$.

In another aspect of the embodiment, X^1 is 4- to 7-membered heterocycloalkylene. In a particular embodiment, the heterocycloalkylene has a N ring atom which is bonded to $-C(R^1)(R^2)-$, and non-limiting examples include:

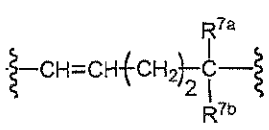
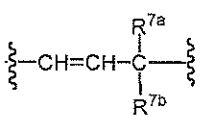
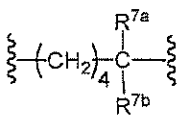
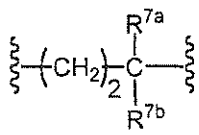
 and  .

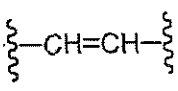
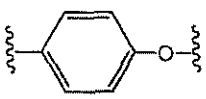
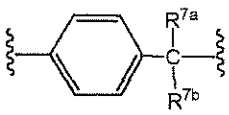
In another embodiment, there is provided a compound of Formula II:



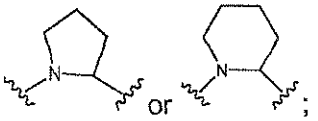
Formula II

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

A^1 is  ,  ,  ,  ,

 ,  or  ;

A^2 is $-CH(R^8)$-arylene, $-CH(R^8)$-heteroarylene, $-CH(R^8)$-heterocycloalkylene, $-CH(R^8)$-cycloalkylene, arylene or cycloalkylene;

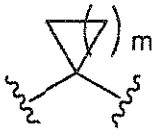
X^1 is a bond, $-CH_2-$, -O-, -NH-, $-N(CH_3)-$,  or ;

R^{4a} is H, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, hydroxyl(C_1-C_8)alkyl, (C_1-C_4)alkoxy(C_1-C_8)alkyl or (C_1-C_8)alkyl;

R^5 is H, (C_1-C_4)alkyl, halo(C_1-C_8)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_8)alkyl, cycloalkyl or heterocycloalkyl;

R^{6a} and R^{6b} are independently H, hydroxyl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, $-CH_2CH_2CR^9(=N(C_1-C_4)$alkoxy), aryl, heterocycloalkyl, cycloalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ and $-N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$ and (C_1-C_8)alkanoyl where such an optional substitution is chemically feasible; or R^{6a} and R^{6b} together form a spirocycle having Formula (a); or

R^{6a} and R^{6b} together form a spirocycle having Formula (a):



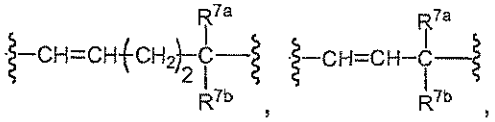
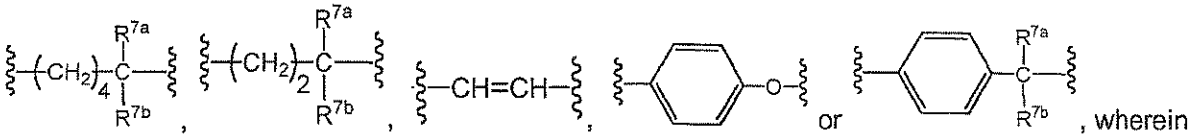
(a),

wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1-C_4)$alkoxy, halo, hydroxyl, $-NH_2$, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$;

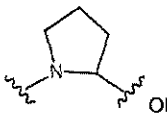
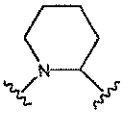
R^{7a} and R^{7b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl;

R^8 is H or (C_1-C_4)alky; and

each R^9 is independently H, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl.

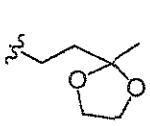
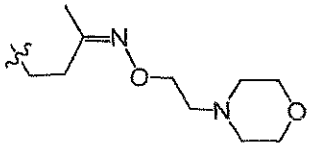
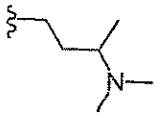
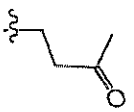
In certain embodiments of Formula II, A^1 is   wherein the left bond of A^1 linker is attached to A^2;

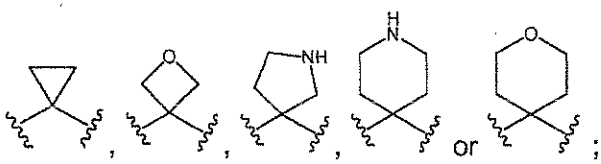
A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene, arylene or cycloalkylene, wherein the left bond of A^2 linker is attached to X^1;

X^1 is bond, -CH_2-, -O-, -NH-, -N(CH_3)-,  or  ;

R^{4a} is H, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl;

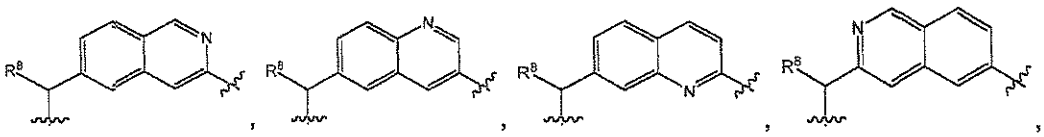
R^5 is H or (C_1-C_4)alkyl;

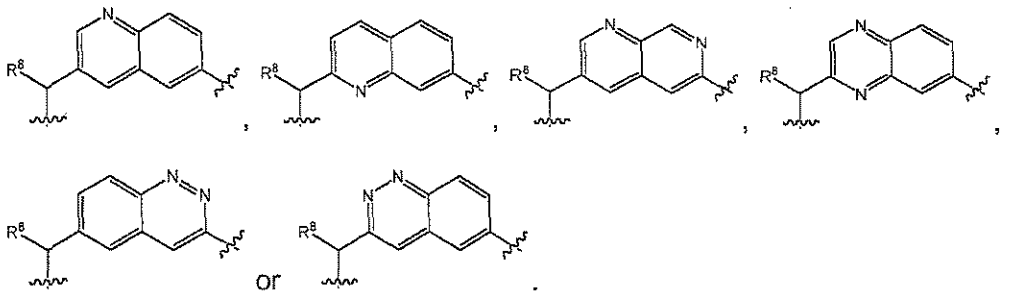
R^{6a} and R^{6b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl,    or  ; or

R^{6a} and R^{6b} together form  ;

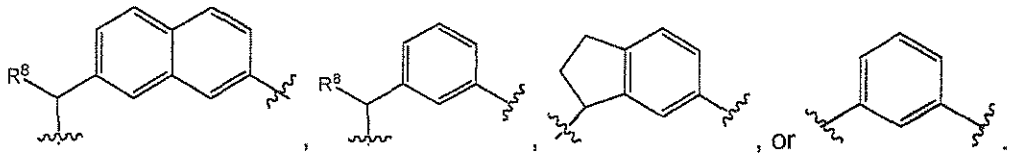
R^{7a} and R^{7b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl; and

R^8 is H or (C_1-C_4)alkyl.

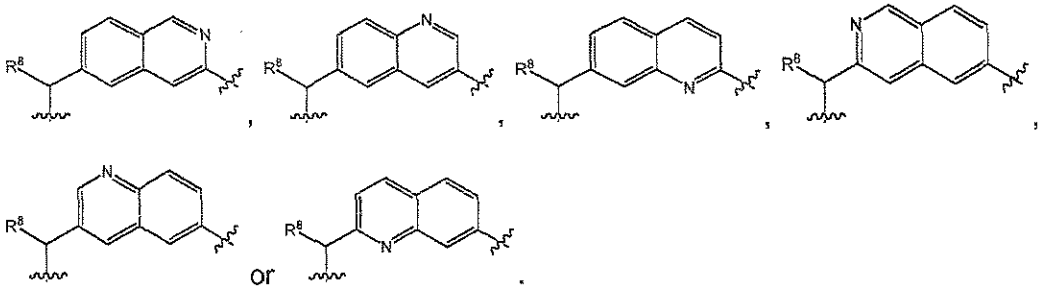
In certain embodiments of Formula II, R^{4a} is methyl; R^5 is iso-propyl; R^8 is methyl; and A^2 is 



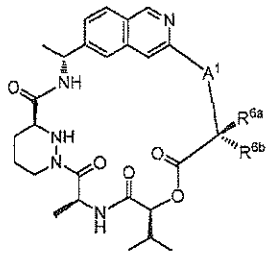
In certain embodiments of Formula II, R^{4a} is methyl; R^5 is iso-propyl; R^8 is methyl; and A^2 is



In one embodiment, R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is

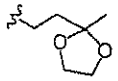
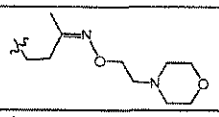
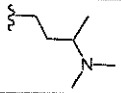
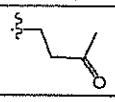
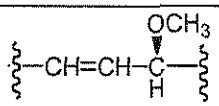


Non-limiting examples of such compounds include the following compounds and pharmaceutically acceptable salts thereof:



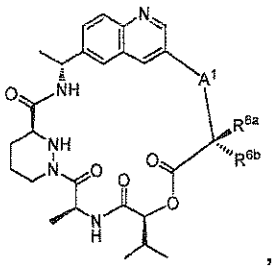
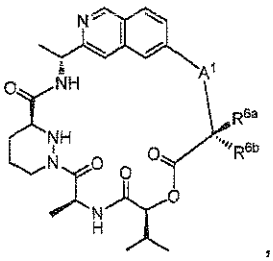
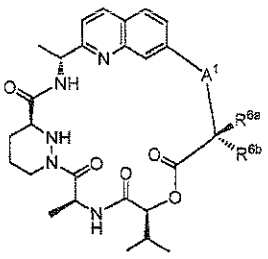
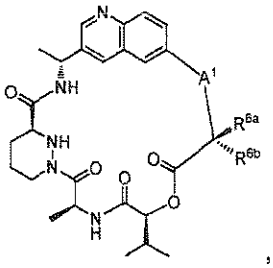
Formula (II-a)

Compound No.	A^1	R^{6a}	R^{6b}
a-1 (Example 3)	-CH=CH-	H	H
a-2 (Example 5)	-CH=CH-	Methyl	H
a-3 (Example 5)	-CH=CH-	H	Methyl
a-4	-CH=CH-	Methyl	Methyl
a-5 (Example 4)	-CH=CHCH$_2$-	Propyl	H

Compound No.	A^1	R^{6a}	R^{6b}
a-6 (Example 12)	-CH=CHCH$_2$-	Methyl	Methyl
a-7 (Example 13)	-CH=CHCH$_2$-		H
a-8 (Example 15)	-CH=CHCH$_2$-		H
a-9 (Example 16)	-CH=CHCH$_2$-		H
a-10 (Example 14)	-CH=CHCH$_2$-		H
a-11		Methyl	H
a-12 (Example 11)	-CH=CHCH(CH$_3$)-	-CH$_3$	H
a-13 (Example 11)	-CH=CHCH(CH$_3$)-	H	-CH$_3$
a-14 (Example 9)	-CH$_2$CH$_2$CH$_2$-	Propyl	H

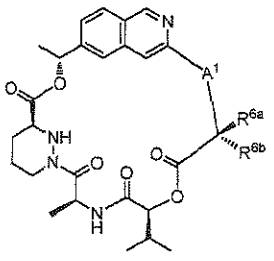
wherein the left bond of A^1 linker is attached to A^2.

A^2 linker of the compounds above can be replaced by various position isomers. Non-limiting examples thereof include compounds having the following formulae:

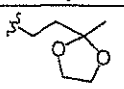
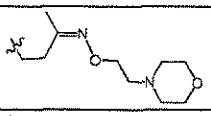
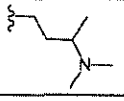
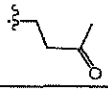
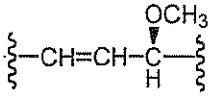
 ,  ,  and  ,

wherein the compounds of the formulae above have the same combination or pattern of substituents given in the table for Compounds a-1 to a-14.

Also included are compounds having the following formulae:

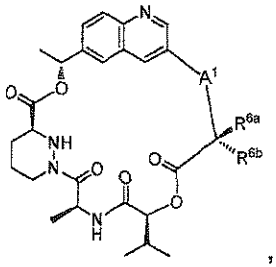
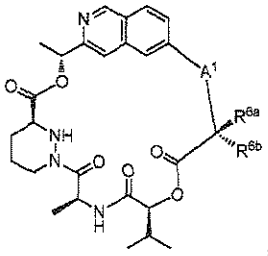
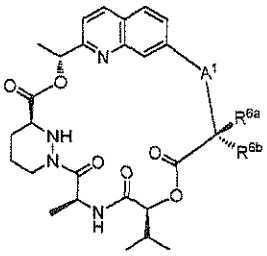
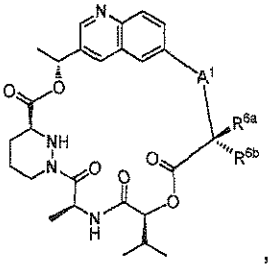


Formula (II-a2)

Compound No.	A^1	R^{6a}	R^{6b}
a2-1	-CH=CH-	H	H
a2-2	-CH=CH-	Methyl	H
a2-3	-CH=CH-	H	Methyl
a2-4	-CH=CH-	Methyl	Methyl
a2-5	$-CH=CHCH_2-$	Propyl	H
a2-6	$-CH=CHCH_2-$	Methyl	Methyl
a2-7	$-CH=CHCH_2-$		H
a2-8	$-CH=CHCH_2-$		H
a2-9	$-CH=CHCH_2-$		H
a2-10	$-CH=CHCH_2-$		H
a2-11 (Example 2)		Methyl	H
a2-12	$-CH=CHCH(CH_3)-$	$-CH_3$	H
a2-13	$-CH=CHCH(CH_3)-$	H	$-CH_3$
a2-14	$-CH_2CH_2CH_2-$	Propyl	H

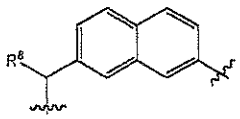
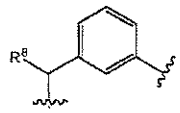
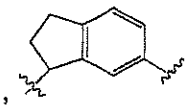
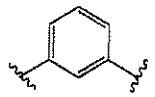
wherein the left bond of A^1 linker is attached to A^2.

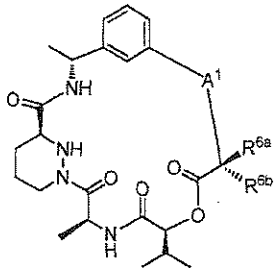
A^2 linker of the compounds above can be replaced by various position isomers. Non-limiting examples thereof include compounds having the following formulae:

 ,  ,  and  ,

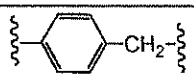
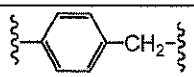
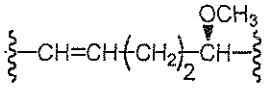
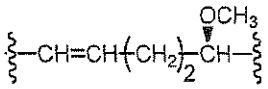
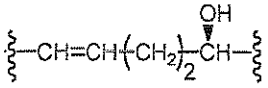
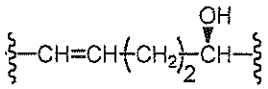
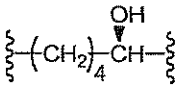
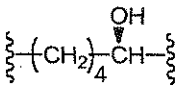
wherein the compounds of the formulae above have the same combination or pattern of substituents given in the table for Compounds a2-1 to a2-14.

In another aspect of the embodiment, R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is

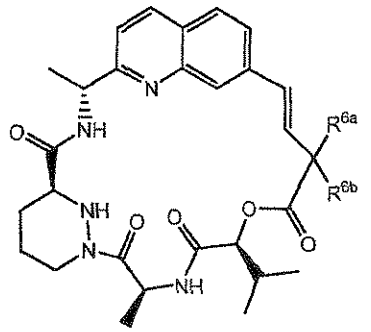



, or  . Non-limiting examples of such compounds include the following compounds and pharmaceutically acceptable salts thereof:



Formula (II-b)

Compound No.	A^1	R^{6a}	R^{6b}
b-1 (Example 6)		H	H
b-2		Methyl	H
b-3		H	H
b-4 (Example 1)		Methyl	H
b-5 (Example 8)	-CH=CH-$(CH_3)_3$-	H	H
b-6	-CH=CH-$(CH_3)_3$-	Methyl	H
b-7		H	H
b-8 (Example 7)		Methyl	H
b-9		H	H
b-10 (Example 10)		Methyl	H

In another embodiment, is provided a compound of Formula II-c:

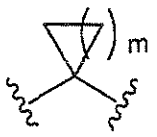


Formula II-c

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

R^{6a} and R^{6b} are independently H, hydroxyl, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $-CH_2CH_2CR^9(=N(C_1$-$C_4)$alkoxy), aryl, heterocycloalkyl, cycloalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ and $-N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, cyano, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono$(C_1$-$C_8)$alkylamino, di$(C_1$-$C_8)$alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$ and $(C_1$-$C_8)$alkanoyl where such an optional substitution is chemically feasible; or R^{6a} and R^{6b} together form a spirocycle having Formula (a); or

R^{6a} and R^{6b} together form a spirocycle having Formula (a):

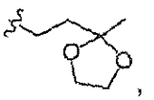


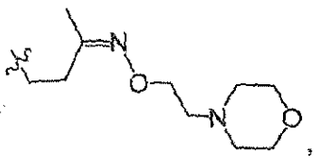
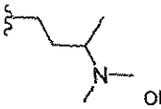
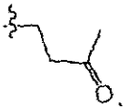
(a),

wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1$-$C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$;

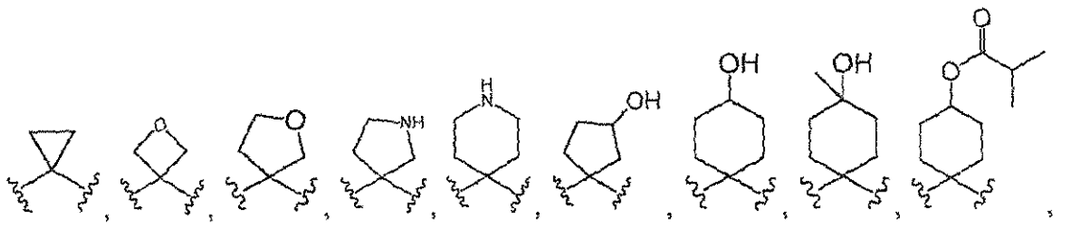
each R^9 is independently H, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl or $(C_2$-$C_4)$alkynyl.

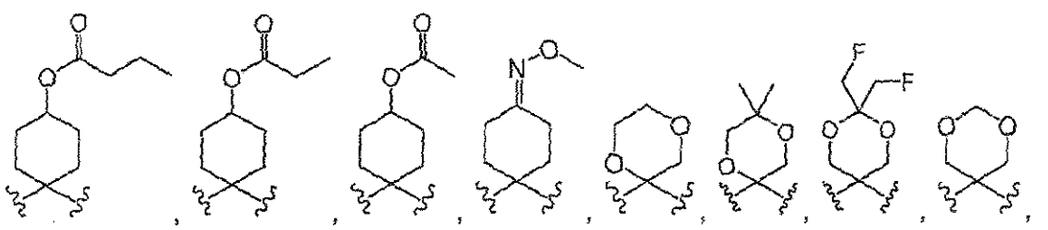
In one embodiment of the compounds described herein, R^{6a} and R^{6b} are independently H, -OH, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_8)$alkyl, hydroxy$(C_1$-$C_8)$alkyl,

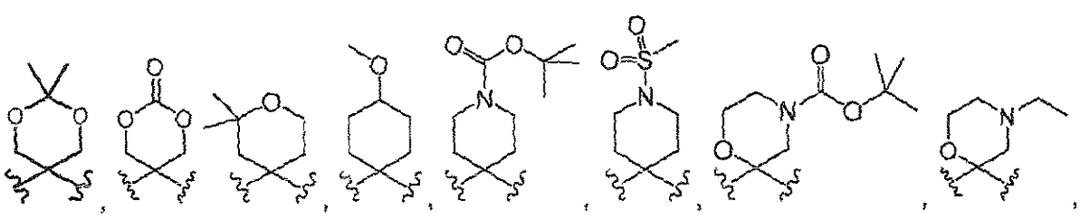
(C_1-C_4)alkoxy(C_1-C_8)alkyl, halo(C_1-C_4)alkoxy(C_1-C_8)alkyl,  ,

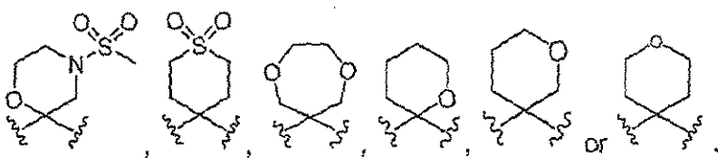
 ,  or  .

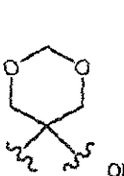
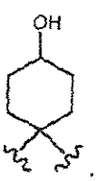
In one embodiment of the compounds described herein, R^{6a} and R^{6b} together form

 ,

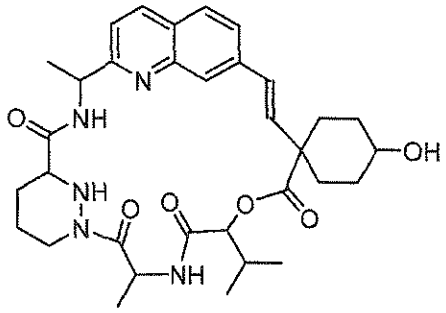
 ,

 ,

 or .

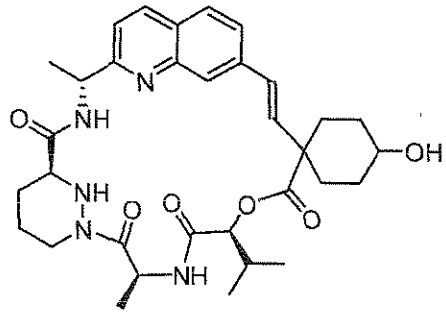
In some embodiments, R^{6a} and R^{6b} together form  or  .

In one embodiment, the compound is



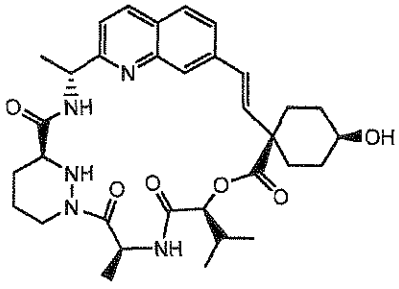
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

In another embodiment, the compound is



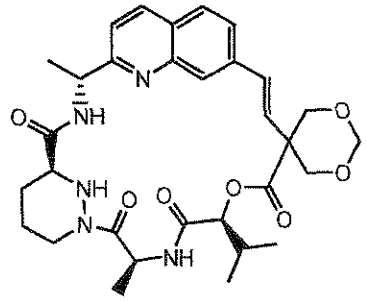
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

In yet another embodiment, the compound is



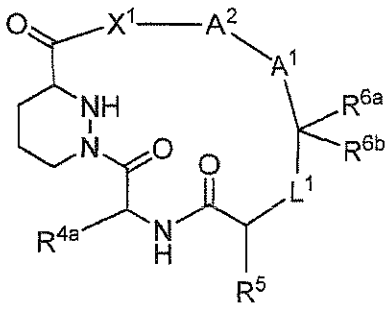
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

In one embodiment, the compound is



or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

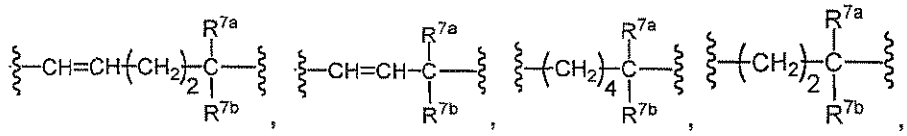
In certain embodiments, there is provided a compound of Formula III:

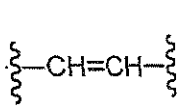
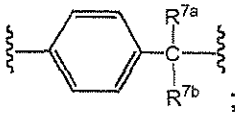


Formula III

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein

L^1 is -O-CH_2-, -N(CH_3)-C(O)-, -NH-CH_2-, -N(CH_3)-CH_2-, -NH-CH(CF_3)- or -NH-$S(O)_2$-;

A^1 is  ,

 or  ;

A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene, arylene or cycloalkylene;

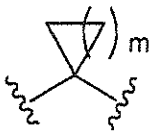
X^1 is -O-, -N(CH_3)- or -NH-;

R^{4a} is H, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl;

R^5 is H or $(C_1\text{-}C_4)$alkyl;

R^{6a} and R^{6b} are independently H, hydroxyl, $-CH_2CH_2CR^9(=N(C_1\text{-}C_4)\text{alkoxy})$, $(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$alkoxy, optionally substituted with one or more substituents selected from the group consisiting of halo, hydroxyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, heterocycloalkyl, $(C_1\text{-}C_4)$alkanoyl or di$(C_1\text{-}C_4)$alkylamino; or

R^{6a} and R^{6b} together form a spirocycle having Formula (a):



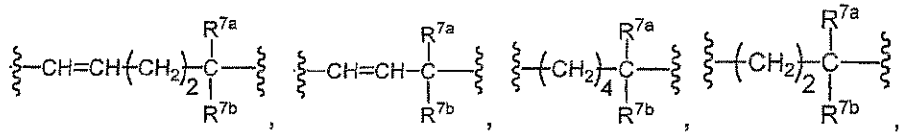
(a),

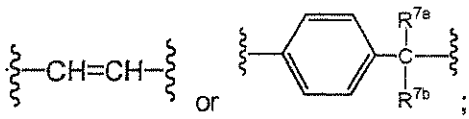
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$;

R^{7a} and R^{7b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl; and

R^8 is H or $(C_1\text{-}C_4)$alkyl.

In some embodiments of Formula IIi, L^1 is $-O\text{-}CH_2\text{-}$, $-N(CH_3)\text{-}C(O)\text{-}$, $-NH\text{-}CH_2\text{-}$ or $-NH\text{-}S(O)_2\text{-}$;

A^1 is 



;

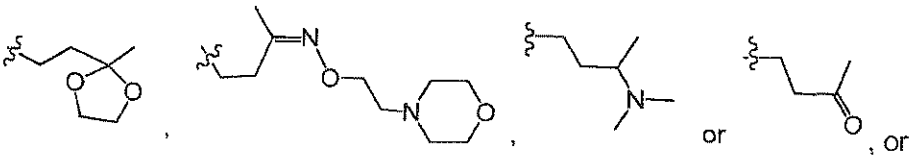
A^2 is $-CH(R^8)$-arylene, $-CH(R^8)$-heteroarylene, $-CH(R^8)$-heterocycloalkylene, $-CH(R^8)$-cycloalkylene, arylene or cycloalkylene;

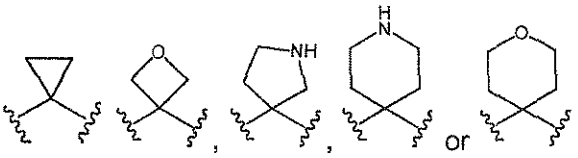
X^1 is -O-, $-N(CH_3)$- or -NH-;

R^{4a} is H, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl;

R^5 is H or $(C_1\text{-}C_4)$alkyl;

R^{6a} and R^{6b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl,

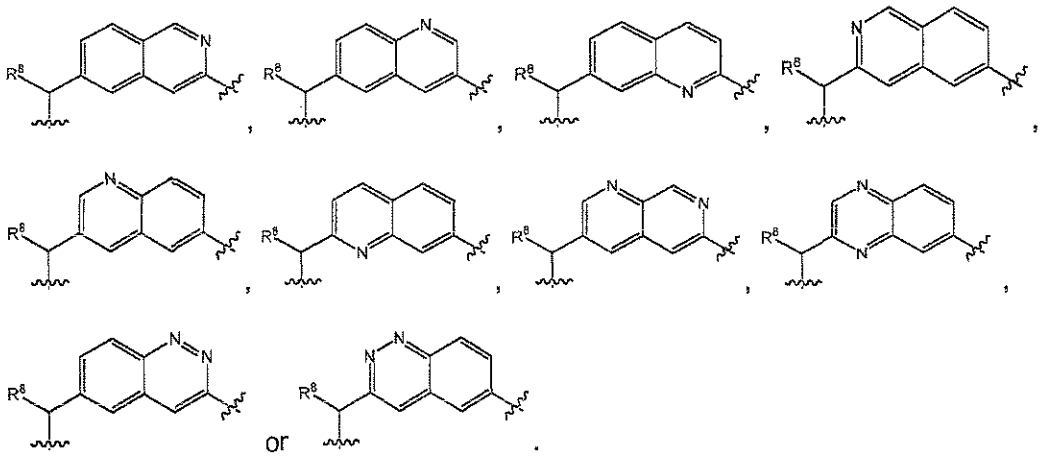


R^{6a} and R^{6b} together form  ;

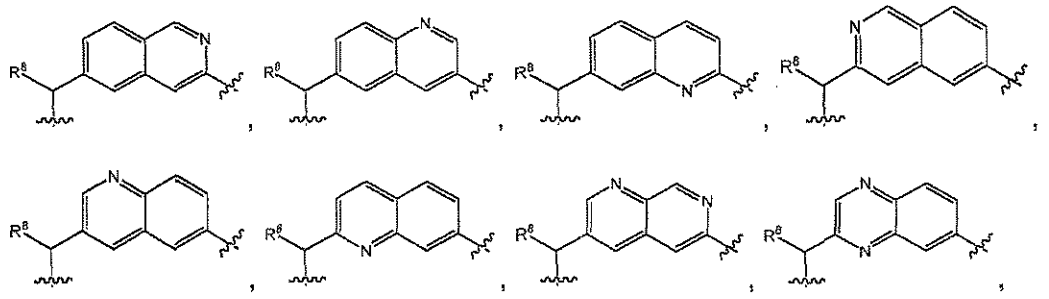
R^{7a} and R^{7b} are independently H, -OH, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy or $(C_1$-$C_8)$alkyl; and

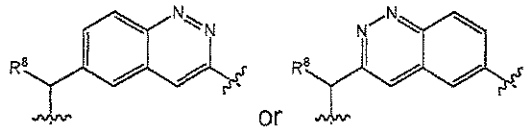
R^8 is H or $(C_1$-$C_4)$alkyl.

In one embodiment, L^1 is -NH-CH_2-; R^{4a} is methyl; R^5 is iso-propyl; R^8 is methyl; and A^2 is

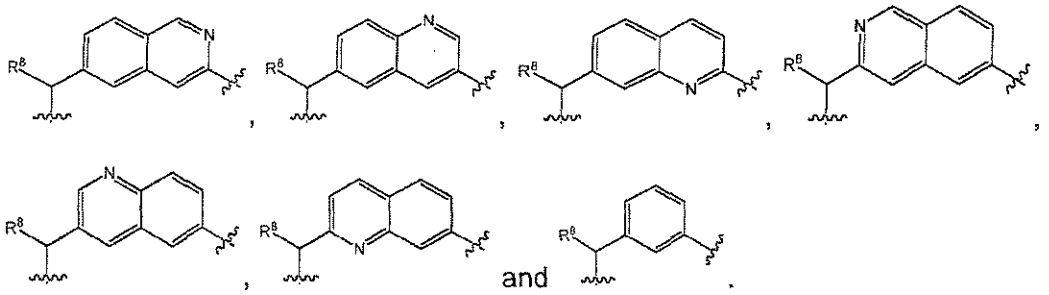


In one embodiment, L^1 is -NH-$S(O)_2$-; R^{4a} is methyl; R^5 is iso-propyl; R^8 is methyl; and A^2 is

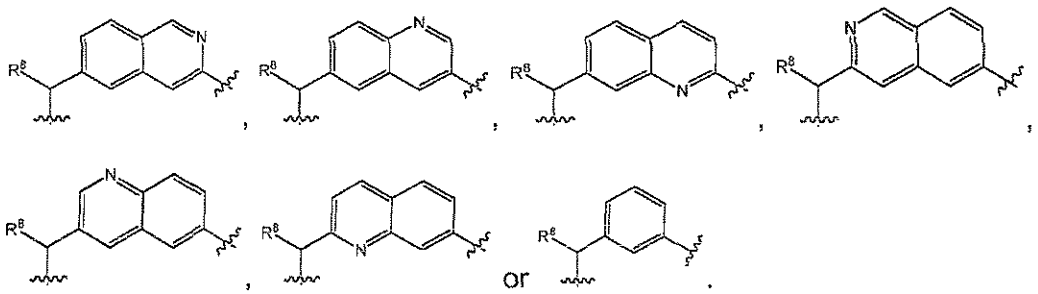




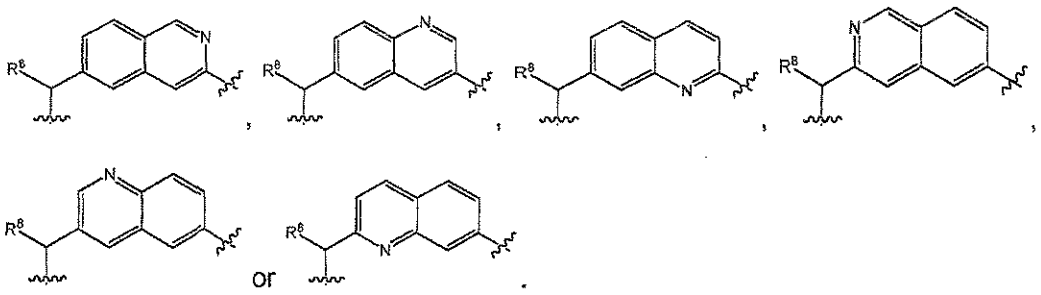
In various aspects of this embodiment, A^2 is selected from



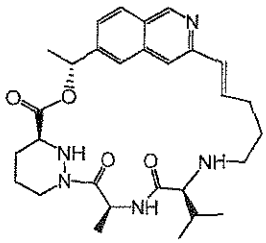
In one embodiment, L^1 is $-N(CH_3)-C(O)-$; R^{4a} is methyl; R^5 is iso-propyl; R^6 is methyl; and A^2 is



In one embodiment, L^1 is $-O-CH_2-$; R^{4a} is methyl; R^5 is iso-propyl; R^8 is methyl; and A^2 is



In one aspect of the embodiment, L^1 is $-NH-CH_2-$; R^{4a} is methyl; R^5 is isopropyl; and R^8 is methyl. Non-limiting examples of such compounds include the following compounds and pharmaceutically acceptable salts thereof: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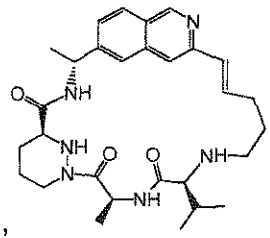
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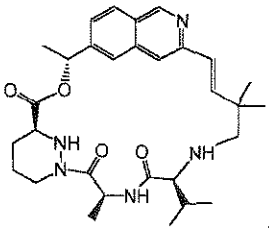
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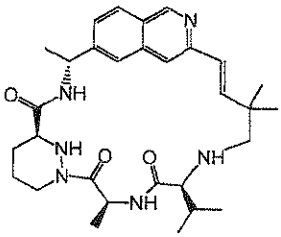
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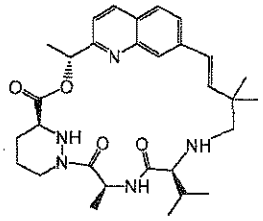
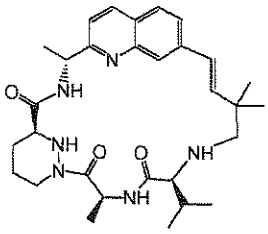
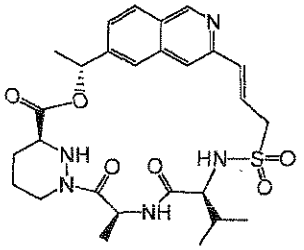
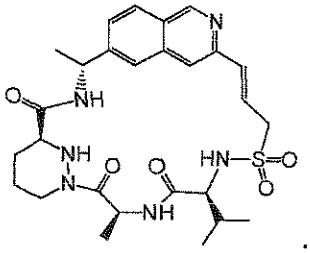

and

.

In one aspect of the embodiment, L^1 is -NH-$S(O)_2$-; R^{4a} is methyl; R^5 is isopropyl; and R^8 is methyl. Non-limiting examples of such compounds include the following compounds and pharmaceutically acceptable salts thereof:


and

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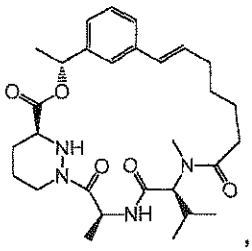
In one aspect of the embodiment, L^1 is -$N(CH_3)$-C(O)-; R^{4a} is methyl; R^5 is isopropyl; and R^8 is methyl. Non-limiting examples of such compounds include the following compounds and pharmaceutically acceptable salts thereof: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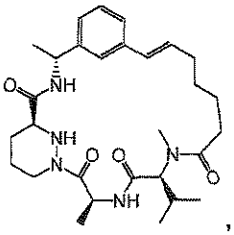
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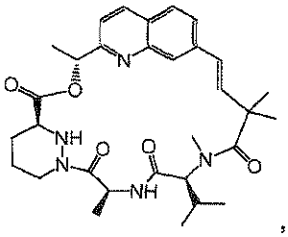
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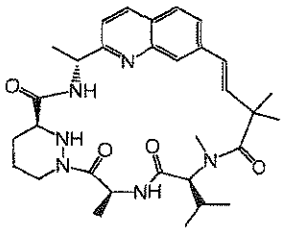
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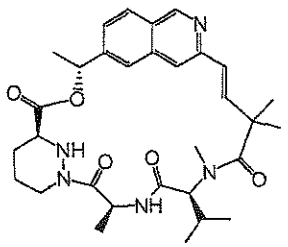
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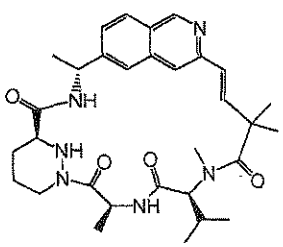
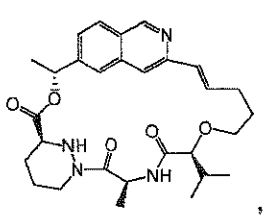

.

In one aspect of the embodiment, L^1 is -O-CH_2-; R^{4a} is methyl; R^5 is isopropyl; and R^8 is methyl. Non-limiting examples of such compounds include the following compounds and pharmaceutically acceptable salts thereof: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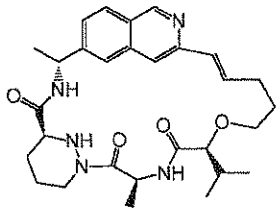
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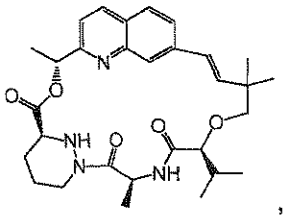
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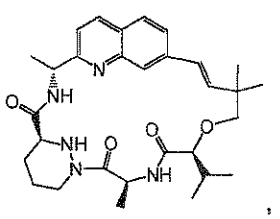
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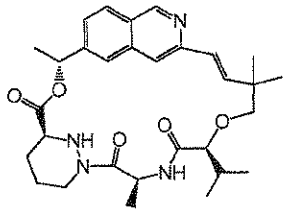
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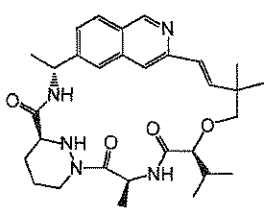
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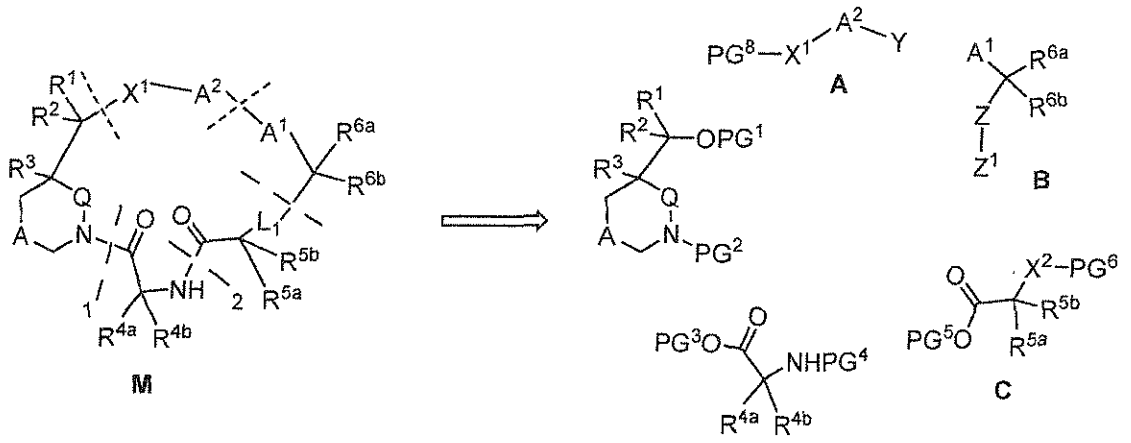
One skilled in the art will recognize that substituents and other moieties of the compounds of the generic formulae herein should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds which have such stability are contemplated as falling within the scope of the present invention. It should be understood by one skilled in the art that any combination of the definitions and substituents described above should not result in an inoperable species or compound.

Preparation of Macrocyclic Compounds

A compound of the present invention such as those of Formula I, II, II-a, II-b, II-c or III can be prepared according to the schemes described below, but it shall be appreciated that modifications of the illustrated process or other process can also be used. As illustrated in Scheme 1, the macrocyclic compounds M are synthesized from the five key components A-E by combining them together in sequence with the appropriate use of protecting groups (PG_1-PG_8) by one skilled in the art. The hashed lines numbered 1-5, hereby referred to as Connection 1, Connection 2, etc, respectively, are the 5 connections for combining Components A-E. The order in which the specific connections occur, can vary, and are dependent on the choice of protecting groups and chemistry required. Typically Connections 3, 4 or 5 are used as the final macrocylization step.

Scheme 1



PG^X = *protecting group as needed*
X^1 and X^2 are O, NH, or N-alkyl, etc.
Z and Z^1 taken together = CO_2H, COCl, SO_3H, SO_2Cl, CH_2-OH, CH_2-halo, C(O)-alkyl, or C(O)-H, etc.
Y = alkene, halide, O-alkenyl, or OTf.
Q = NH or N-PG^X as needed.

Illustratively, Connections 1 through 5 can be performed as described below:

Connections 1 and 2 are amide bonds. The connections are made between the respective acid and amine using standard peptide coupling agents (EDC/HOBT, DCC, PyBOP, PyBROP, HATU, HBTU, COMU, etc) known to one skilled in the art. The acid and amine coupling partners are combined with the coupling agent in an organic solvent, e.g., DMF, dichloromethane, acetonitrile, etc, in the presence of a base, e.g., DIPEA, triethylamine, etc, at room temperature or slightly elevated temperature. When either of these steps is chosen as the final macrocyclization step, then macrolactamization conditions are preferred. Suitable macrolactamization procedures include, but are not limited to, those found in the following reference: Davies, J. S. J. Peptide Sci. 2003, *9*, 471-501.

Connection 4 is typically a carbon-carbon bond or a heteroatom-carbon bond where the heteroatom is O, S or N. When Connection 4 is a carbon-carbon bond, then standard carbon-carbon bond forming procedures typically involving metal mediated cross coupling reactions are preferred. Preferably the carbon–carbon bond is formed using a Heck type coupling between an *sp2* halide group and an terminal alkene, a Suzuki coupling between an *sp2* halide group and a vinyl or aryl boronate, or a ring closing metathesis (RCM) between two alkenes. Stille reactions can also be performed between a vinyl stannane and an aryl or vinyl halide as

described in *Journal of American Chemical Society* 2000, 122, 3830 Nicolaou et al. In each of the examples above the aryl or vinyl halide group can also be an aryl or vinyl triflate.

For example, when Y in A is an alkene, preferably -CH=CH_2, and A_1 in B contains a terminal alkene or Me-CH=CH-, then a cross metathesis reaction is performed. The two components are mixed in solvent, e.g., acetonitrile, toluene and a metathesis catalyst, e.g., Grubbs I, Grubbs II or Hoyveda-Grubbs I, Hoyveda-Grubbs II is added followed by heating. If this connection is the final procedure to close the macrocyclic ring, RCM conditions are preferred (e.g., more dilute conditions to avoid dimerization). For relevant RCM conditions and examples see *Journal of American Chemical Society* 2003, 125, 3849 Sedrani et al and *Journal of American Chemical Society* 2000, 122, 3830 Nicolaou et al. A typical RCM procedure includes heating (either conventionally or by microwave) of the acyclic precursor in a solvent such as toluene, or 1,2-dichloroethane, in the presence of a RCM catalyst, e.g., Grubbs I, Grubbs II or Hoyveda-Grubbs I, Hoyveda-Grubbs II.

Alternatively, when connection 4 is made via a Heck coupling reaction, the vinyl or aryl halide, or the triflate A and the alkene component B are mixed in a polar solvent, e.g., acetonitrile or toluene, in the presence of a Palladium(II) catalyst, e.g., Palladium$(OAc)_2$, a phosphine ligand, e.g., P(o-toluene)$_3$, P(t-butyl)$_3$, etc, and a base, e.g., triethylamine. The reaction mixture is heated either conventionally or in a microwave reactor.

Alternatively, when Connection 4 is made via a Suzuki coupling reaction, the vinyl or aryl halide, or the triflate A and the vinyl or aryl boronate B are mixed in a suitable solvent, e.g., cyclopentyl methyl ether, toluene, DMF, DME, etc., in the presence of a Palladium catalyst (e.g., Palladium(II)Cl_2(p-NMe_2Ph)$_2$ and K_3PO_4 or tetrakis(triphenylphosphine)palladium(0) and a base, such as potassium carbonate). The reaction mixture is heated either conventionally or in a microwave reactor. It is also possible in in such a coupling reaction to reverse the reactive functionalities on the two starting materials, such that A is an aryl or vinyl boronate and B contains a vinyl or aryl halide or triflate.

Alternatively, Connection 4 can be a carbon-oxygen bond and in this case, typical alkylation or nucleophilic aromatic substitution conditions can be used between a hydroxyl group and an alkyl halide, or aryl (or heteroaryl) halide. The hydroxyl reagent is mixed with the alkyl or heteroaryl halide (preferably an iodide or bromide), in an inert solvent, e.g., CPME, DMF, THF, etc, in the presence base, e.g., cesium carbonate, cesium hydroxide, sodium hydride, NaHMDS, etc, and heated.

Alternatively, Connection 4 can be a carbon-nitrogen bond and in this case, typical alkylation, nucleophilic aromatic substitution or Buchwald conditions can be used between an amine group and an alkyl halide or heteroaryl halide. For example, the amine and the alkyl or heteroaryl halide are mixed and heated in an inert solvent, e.g., CPME, in the presence base, e.g., cesium carbonate, sodium hydride etc. An alternative procedure for the carbon-nitrogen connection is to perform a reductive amination between an amine and a carbonyl compound. Typically the amine and aldehyde or ketone are mixed in an inert solvent, e.g., THF, dioxane and treated after a period of time with sodium acetoxy borohydride or alternative reducing agent.

Connection 5 is typically an amide (X_1 is NH or substituted N), or ester (X_1 is O) bond. When forming the amide bond, standard coupling procedures described for Connection 1-3 can be used. Often, this is the final step in closing the macrocycle. As such, macrolactamization types of coupling procedures are more effective. Suitable macrolactamization procedures include, but are not limited to, those found in the following reference: Davies, J. S. J. Peptide Sci. 2003, 9, 471-501.

When forming the ester bond coupling reagents (e.g., EDC, DCC, PyBOP, HATU, COMU) can be used, or when this is the final step in formation of the macrocycle, macrolactonization procedures are preferred (e.g., Shiina, Yamaguchi). An example method for the macrolactonization step can be found in *Journal of American Chemical Society* 2002, 124, 4257 Paquette et al or *Chemical Reviews* 2006, 106(3), 911-939. Typically, the acid and alcohol are mixed in a polar solvent, e.g., DMF, acetonitrile, etc. in the presence of the coupling agent and a base, e.g., DIPEA, DMAP.

Connection 5 can also be an ether bond where R^1 and R^2 are both hydrogen or alkyl groups. In this example, the carbon-oxygen bond forming procedures described above for Connection 4 are used to connect the 2 components. Connection 5 can also be an amine bond where R^1 and R^2 are both hydrogen or alkyl groups and the procedures for connecting the amine and carbonyl components are also described above with respect to Connection 4.

Connection 3 is a C-N, C-O, or $S(O)_2$-N. Suitable bond forming reactions for Component C and Component B include the following methods.

When the bond formed in Connection 3 is L^1 is -OC(O)- (i.e., X^1 is O in C and Z/Z^1 is $-CO_2H$ or -CO-halogen in B), this is performed using standard ester formation procedures

utilizing coupling reagents described above. When this is the final step in formation of the macrocycle, macrolactonization procedures are preferred, as described above.

Alternatively, when Connection 3 is L^1 is -N(alkyl)C(O)- (i.e., X^1 is N(alkyl) in C and Z/Z^1 is CO_2H or CO-halogen in B) this step is performed using standard ester formation procedures utilizing coupling reagents described above. When this is the final step in formation of the macrocycle, macrolactamization procedures are preferred as described above.

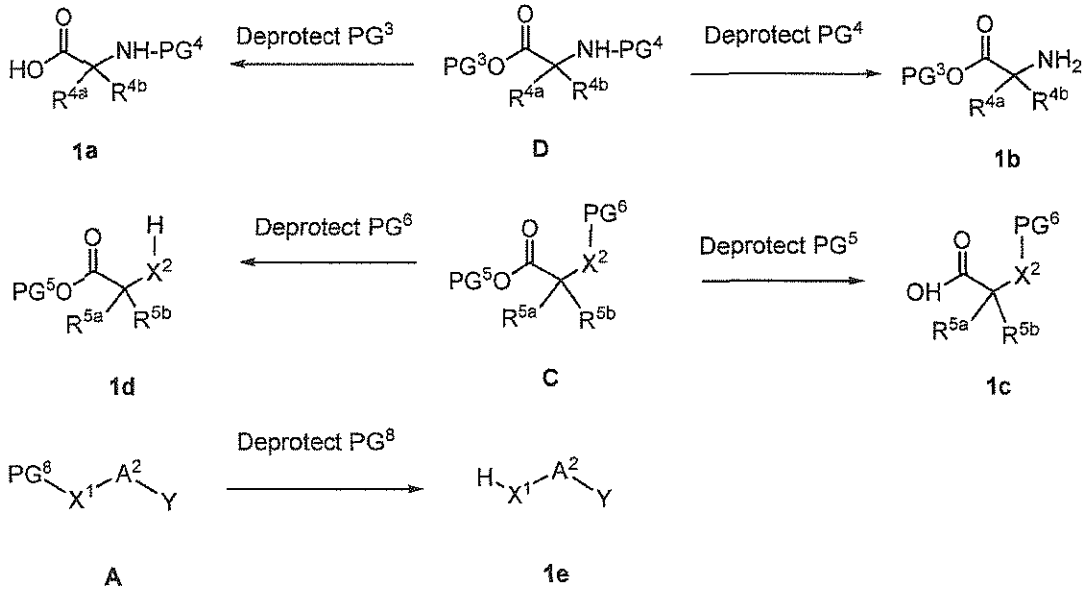
Alternatively, when connection 3 is L^1 is $-NHS(O)_2-$ (i.e., X^1 is -NH- in C and Z/Z^1 is $-S(O)_2OH$ or $-S(O)_2$-halogen in B), this is performed using standard amide formation procedures utilizing coupling reagents described above, or when this is the final step in formation of the macrocycle, macrolactamization procedures are preferred as described above.

Alternatively, when Connection 3 is L^1 is $-NH-CH_2-$ (i.e., X^1 is -NH- in C and Z/Z^1 is ketone or aldehyde in B), this is performed using standard reductive amination procedures as described above.

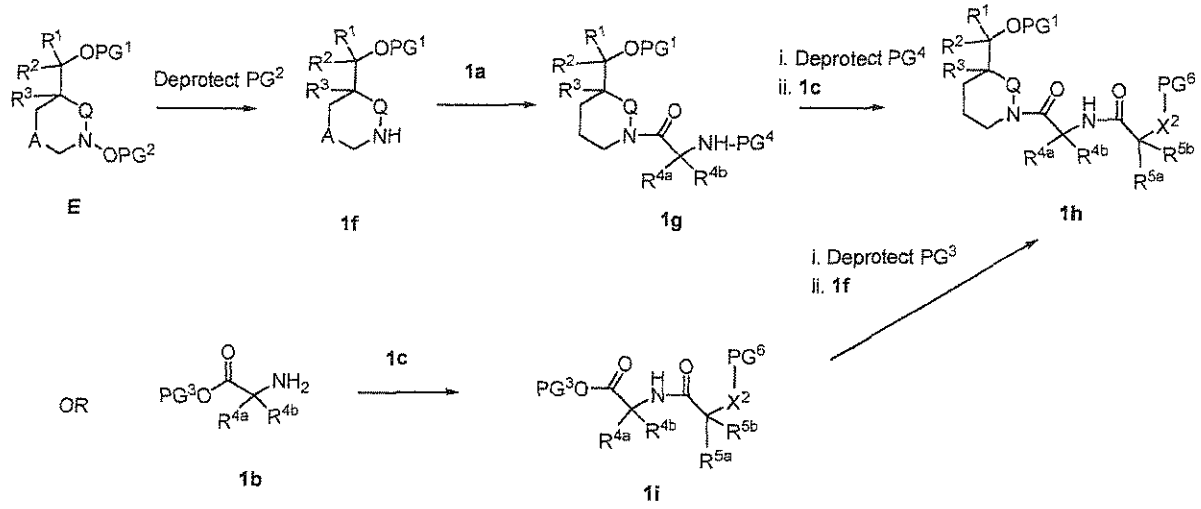
Alternatively, when Connection 3 is L^1 is $-O-CH_2-$ (i.e., X^1 is O in C and Z/Z^1 contains a leaving group such as a halide or triflate in B), this is performed using standard nucleophilic alkylation procedures described above.

The following general schemes provide general examples and sequences for constructing the macrocyclic compounds M from the common precursors A-E.

Scheme 2: RCM method



Scheme 2 (cont.): RCM method



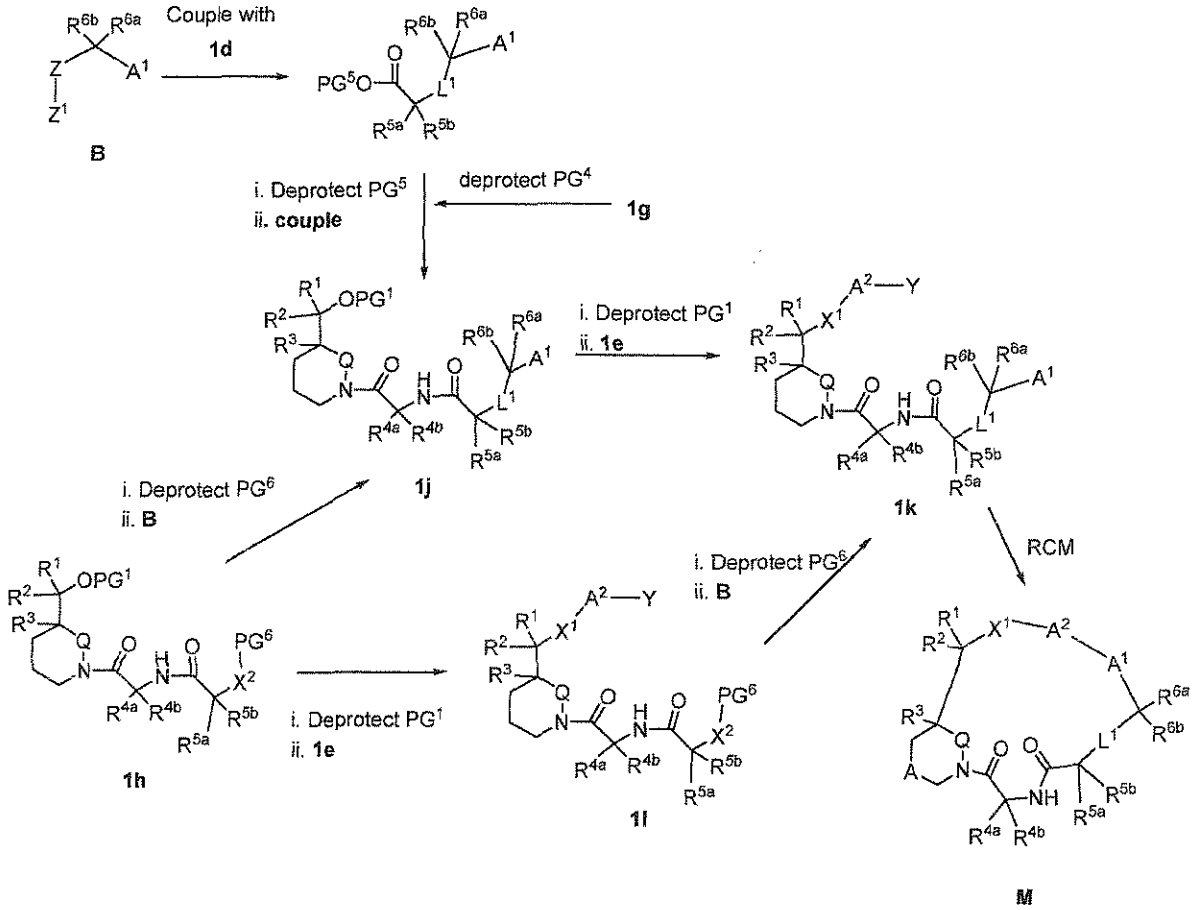
Compounds A-E are first deprotected (PG^2-PG^8) using conditions described in Greene and Wuts, Protective Groups in Organic Synthesis, John Wiley and Sons, Inc. to provide Compounds 1a-1f.

In many cases the optimal protecting groups and their deprotection methods are as follows. For Compound E the typical protecting group PG^1 for the acid (when R^1 and R^2 are C=O) is a methyl or trichloroethyl ester. The methyl and trichloroethyl esters can be removed by base, e.g., LiOH in a polar solvent, e.g., aqueous THF, etc. The trichloroethyl ester can also be removed by treatment with zinc and ammonium acetate in a polar solvent, e.g., THF. Typically, PG^2 and PG^4 are acid labile groups, e.g., BOC and are deprotected using HCl in dioxane or TMSOTf in dioxane, dichloromethane. Typically, PG^3 and PG^5 are ester groups, removed by treatment with alkali metal hydroxide in aqueous THF or dioxane. Typically PG^6 is an acid labile group, e.g., BOC for amine and removed as described for PG^2; or silyl ether for a hydroxyl group and removed by treatment with HF.pyridine or TBAF in an organic solvent, e.g., dichloromethane. Typically PG^8 is an amine protecting group, e.g., BOC and removed as described for PG^2 or a silyl ether of a hydroxyl group removed as described for PG^6, or an acetate protecting group removed by treatment with alkali metal hydroxide in aqueous THF or dioxane.

Compound 1f is coupled to acid 1a using the conditions described above for connection 1 to produce Compound 1g. Compound 1g is then PG^4 deprotected using conditions described in Greene and Wuts and coupled to acid 1c to provide 1h using the conditions described above for Connection 2. An alternative sequence for generating 1h, is first coupling amine 1b to acid

1c using conditions as described for connection 2 above, to form 1i; deprotection of the protecting group PG^3 in 1i using conditions described in Greene and Wuts, and finally coupling with amine 1f using conditions described for Connection 1 above to form 1h.

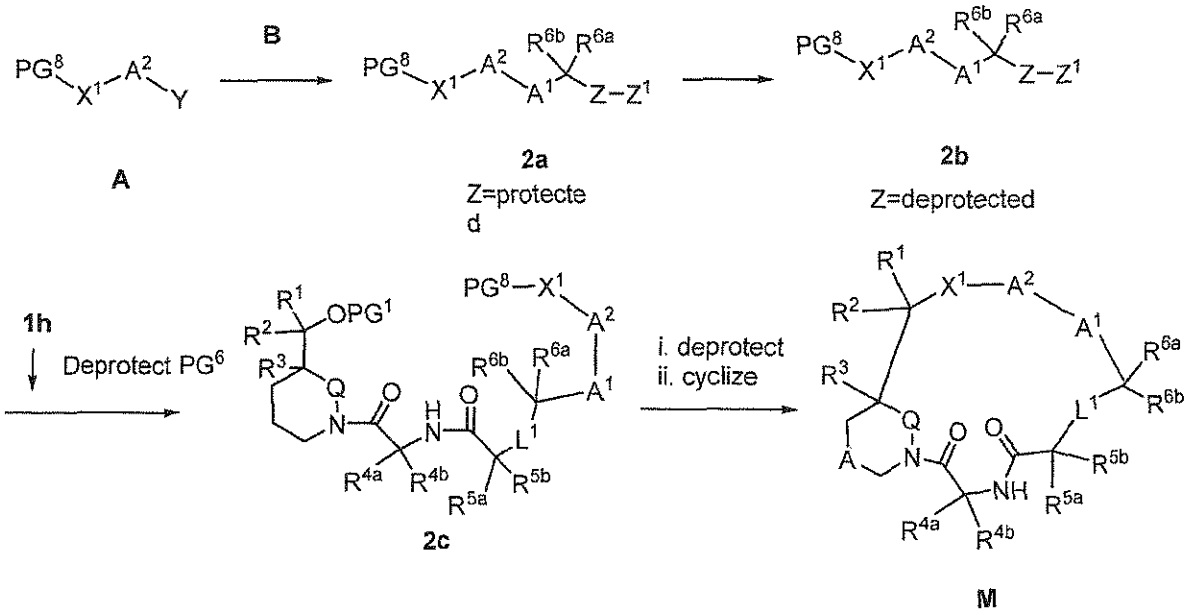
Scheme 3: RCM method



Compound 1h is deprotected at PG^6 using conditions described in Greene and Wuts and is then coupled to B using the conditions described above for connection 3 to form 1j. An alternative route to 1j is also illustrated. Component B is coupled to 1d using the methods described above for Connection 3. The protecting group PG^5 is then removed using conditions described in Greene and Wuts and the product coupled with the dipeptide produced from PG^4 deprotected 1g, to provide 1j. Protecting group PG^1 in Compound 1j is then removed using conditions described in Greene and Wuts, and the acid is then coupled to 1e using conditions described for Connection 5 to form the intermediate 1k. An alternative sequence to 1k from the intermediate 1h is first, deprotection of PG^1 and then coupling to 1e as described for Connection 5; and then deprotection of PG^6 as described in Greene and Wuts, followed by coupling to B

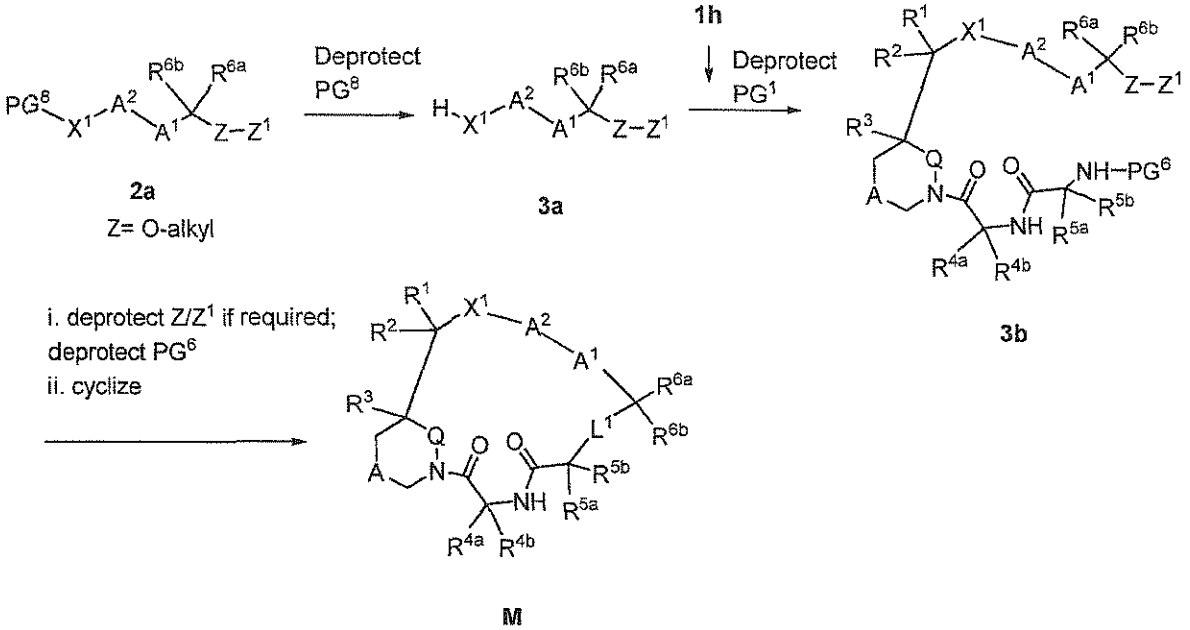
using the conditions described for Connection 3 to form 1k. Product 1k is then subjected to the RCM as described above for Connection 4 to form Compound M.

Scheme 4: Macrolactamization/Macrolactonization Connection 5



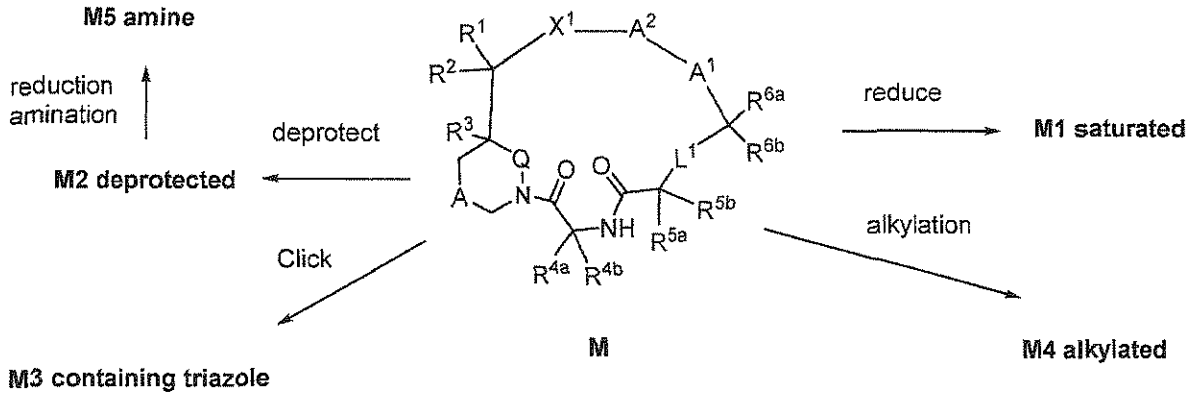
Compound A is coupled to Compound B using the conditions described above for Connection 4 to generate 2a. Typically in this sequence Compound B would be protected, e.g., an acid would be an ester, a sulfonic acid, a sulfonate ester, a ketone or aldehyde an acetal for example. Compound 2a is then deprotected as described in Greene and Wuts to generate acid 2b. Acid 2b is then coupled to the deprotected product of 1h (prepared from 1h by deprotection of PG^6 described in Greene and Wuts) to generate the precursor 2c. Deprotection of 2c at both PG^8 and PG^1 is carried out using conditions described in Greene and Wuts, and then the product is cyclized using the conditions described above for macrolactamization or macrolactonization in Connection 5, to provide Compound M.

Scheme 5: Macrolactamization/Macrolactonization Connection 5



Compound 2a is deprotected at PG_8 as described in Greene and Wuts to generate 3a which is then coupled, using conditions described above for connection 5, to the PG^1 deprotected product of 1h, (prepared from 1h by deprotection of PG^1 described in Greene and Wuts), to generate the precursor 3b. Deprotection of 3b at both PG^6 and Z/Z^1 if required is carried out using conditions described in Greene and Wuts, and then the product is cyclized using the conditions described above for macrolactamization or macrolactonization in Connection 3, to provide Compound M.

Scheme 6: Further transformation of macrocyclic compounds M to M1-M5

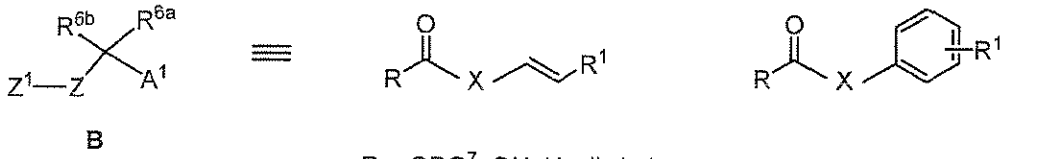


The final macrocycle M from Schemes 4-6 often contains functionalities of protecting groups on sidechains that require further removal to generate the final compound M. For

example, when M contains a C=C as a result of RCM Compound M is mixed in a solvent such as ethanol, methanol, etc, in the presence of palladium on carbon catalyst under an atmosphere of hydrogen gas to provide reduced Compound M1. Protecting groups on the R^{4a}, R^{4b}, R^5, A^1, A^2 and/or X^1 are removed using conditions described in Greene and Wuts to generate Compound M2. Another transformation is click chemistry, to produce triazole M3. This transformation is performed by treating the alkyne or azide in M, in solvent (e.g., DMF) with an alkyne or azide as appropriate in the presence of CuI to form M3.

Deprotected compound M2 can be further transformed after deprotection to additional macrocycle M, for example: Treatment of M2 containing OH with an alkyl halide in the presence of base, e.g., cesium carbonate, in solvent, e.g., DMF, acetonitrile forms alkylated product M4. M2 containing a ketone group is treated in solvent (e.g., DMF, methanol, etc) with an amine followed by the addition of sodium acetoxyborohydride to form amine product M5.

Scheme 7: Preparation of acids, esters, ketones and aldehydes B



B

Z^1 = OH, OPG^7, H, alkyl etc
Z = CO

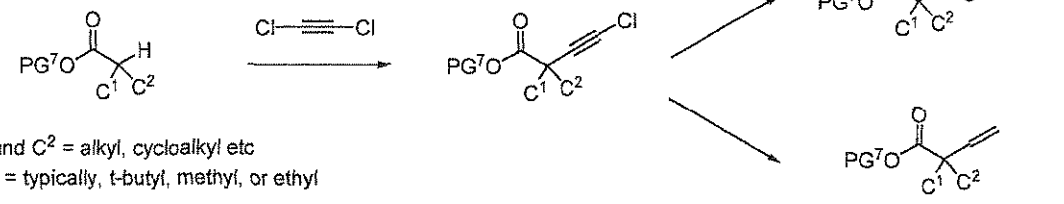
R = OPG^7, OH, H, alkyl etc
X = varied
R^1 = H or Me, $B(pinn)_2$

R = OPG_7, OH, H, alkyl, etc
X = varied
R^1 = halide, (pinn)

Many acids, esters, ketones, aldehyde, sulfonic acid or halide component B with a terminal alkene, Me-CH=C-, or vinyl/aryl boronate, or halide in A1 are commercially available or described in the literature and these can be used in the above schemes directly. In addition, the following schemes below are examples of methods that can be used by one skilled in the art to generate additional B.

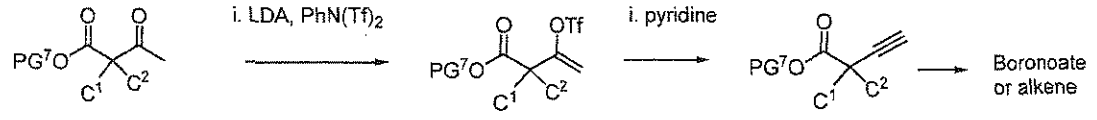
Scheme 8: Preparation of acids, esters, ketones and aldehydes B

1.



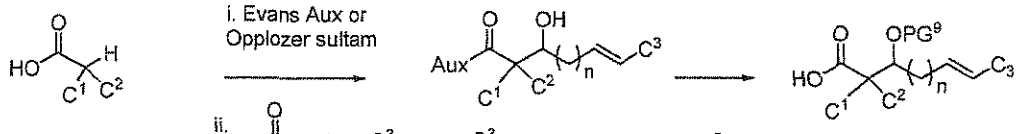
C^1 and C^2 = alkyl, cycloalkyl etc
PG^7 = typically, t-butyl, methyl, or ethyl

2.



C^1 and C^2 = alkyl, or cycloalkyl, etc.
PG^7 = typically, t-butyl, methyl, or ethyl

3.

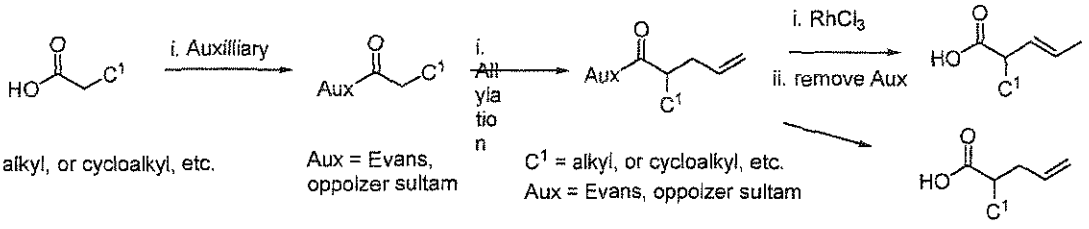


C^1 and C^2 = H, alkyl, or cycloalkyl, etc.

C^3 = methyl or H

PG^9 = protecting group, or alkylated product e.g. haloalkyl

4.

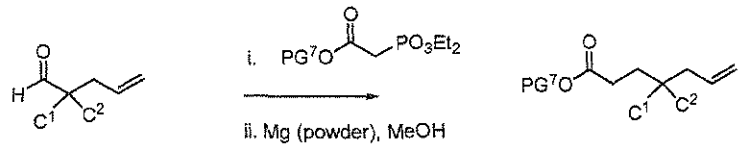


C^1 = alkyl, or cycloalkyl, etc.

Aux = Evans, oppolzer sultam

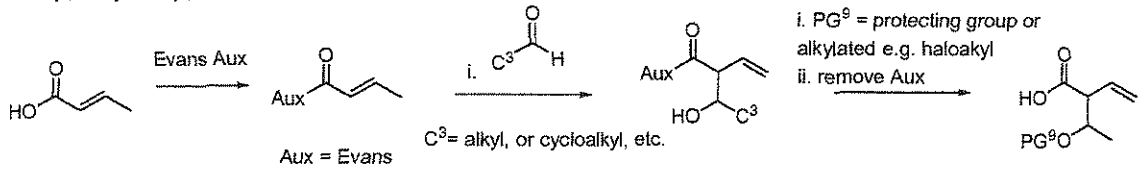
C^1 = alkyl, or cycloalkyl, etc.
Aux = Evans, oppolzer sultam

5.



C^1 = alkyl, or cycloalkyl, etc.
C^2 = alkyl, or cycloalkyl, etc.

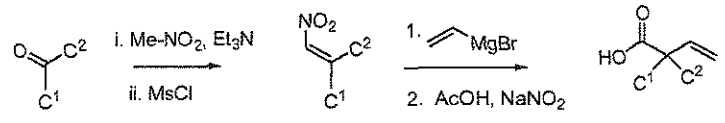
6.



Aux = Evans

C^3= alkyl, or cycloalkyl, etc.

7.



5

In Scheme 8, part 1, a protected acid is treated with a strong deprotonating base, e.g., LDA in an inert solvent, e.g., THF at -78°C and HMPA. A pre-cooled solution of dichloroacteylene (prepared by treatment of trichlorethene with potassium hydride and MeOH (catalytic) in THF) is then added to generate the chloro acetylene product. This product is then reduced, for example, by treatment with Cu in acetic acid and THF to generate the alkyne which is then further reduced to the alkene, for example, by treatment of an alcoholic solution of the alkyne with a poisoned palladium reducing agent (e.g. Lindlar) in the presence of hydrogen gas. Alternatively the alkyne is treated with Cp_2ZrHCl in dichloromethane, in the presence of pinnacolborane to form the vinyl boronate.

In Scheme 8, part 2 a *beta*-keto ester with *alpha* substitution is converted to the vinyl triflate, for example by treating a THF solution of the *beta*-keto ester with a base, e.g., LDA in THF at -78°C, followed by addition of $PhN(Tf)_2$. The triflate product is then treated with pyridine at elevated temperature to form the alkyne. The alkyne is then treated as described above in Example 1 to generate the alkene or vinyl boronate products.

In Scheme 8, part 3, a chiral aldol reaction is used. An acyl group is first attached to a chiral auxiliary, e.g., Evans, Oppolzer sultam (see *JACS* 1990, 112, p2767) using standard amide bond formation conditions described for connection 1-3. The Oppolzer auxiliary product is treated with the aldehyde of choice, TBDMSOTf and base, e.g., triethylamine in anhydrous solvent, e.g., dichloromethane. The Evans auxiliary is treated with base, e.g., LDA, KHMDS, DIPEA in organic solvent, e.g., THF at -78°C and the aldehyde of choice in the presence of a Lewis acid, e.g., $TiCl_4$, $SnCl_4$ or BF_3OEt_2. Protection of the resulting alcohol from the aldol reaction is performed as described in Greene and Wuts, or alternatively alkylation with an alkyl halide or Meerwein's reagent, i.e. treatment with trimethyloxonium tetrafluoroborate in an inert solvent, e.g., dichloromethane is performed. The auxiliary is then removed using standard alkali metal hydroxide removal conditions, e.g., LiOH in THF, or LiOH and hydrogen peroxide in THF to provide the free acids product.

In Scheme 8, part 4, an Evans auxiliary is allylated with an allyl halide as described in *Synlett* 2002, 12, 2039-2040. The product is then isomerized by treatment with $RhCl_3$ in ethanol and then the auxiliary removed by base and peroxide, e.g., LiOH and H_2O_2 in THF/Water. Alternatively the auxiliary is directly removed by LiOH and H_2O_2 in THF/Water to provide the terminal alkene.

In Scheme 8, part 5, a Horner Wadsworth Emmons reaction is used on an aldehyde (containing a terminal alkene) to generate the alpha-beta unsaturated ester which is then

selectively reduced to the ester. For example the phosphonate is treated with base, e.g., sodium hydride in THF at low temperature, followed by addition of the aldehyde and warming to generate the unsaturated ester. The product is reduced by treatment with magnesium powder in methanol.

In Scheme 8, part 6, an *alpha-beta* unsaturated acid or is converted to the unsaturated Evans auxiliary (see *Organic Letters* 2007, 9, p1635) and is treated with an aldehyde to generate the corresponding alkene product. The hydroxyl group is then protected using methods described in Greene and Wuts and then the auxiliary is removed by treatment with base and peroxide, e.g., LiOH and H_2O_2 in THF/Water. The hydroxyl can also be alkylated by as described above for aldol Scheme 8, part 3.

In Scheme 8, part 7 a ketone is transformed via the nitro olefin as described in *Angew. Chem. Int. Ed.* 2006, 45 (46), 7736. The nitro olefin is then treated with vinyl magnesium bromide in an inert solvent, e.g., THF, in the presence of a copper(I)salt, e.g., CuI and trimethylsilyl chloride. The nitro alkyl product after addition of the vinyl group is then converted to the acid by treating with sodium nitrite and acetic acid in an inert polar solvent, e.g., DMSO.

To generate the ketones, aldehydes, hydroxy, or halide compounds the acid/ester products described in Scheme 8 can be transformed using standard methods known to one skilled in the art. For example, conversion of the acid to the Weinreb amide with a coupling agent in a solvent, e.g., THF, dichloromethane, followed by treatment with a nucleophile, e.g., MeMgBr, CF_3SiMe and the like, generates ketones; hydroxyl groups are produced by treatment of the esters with lithium aluminum hydride in a solvent, e.g., THF, dichloromethane etc. Hydroxyls are activated to triflates with treatment with triflic anhydride, and a base, e.g., diisopropylethylamine in solvent, e.g., THF. Conversion of the hydroxyl to a halide, e.g., bromide is performed by treatment with PPh_3 and carbon tetrabromide.

Several types of A (or A1 as shown) are available commercially or described in the literature where X^1 is O or NH and Y is a halide or alkene. The schemes below describe additional general methods for generating A1.

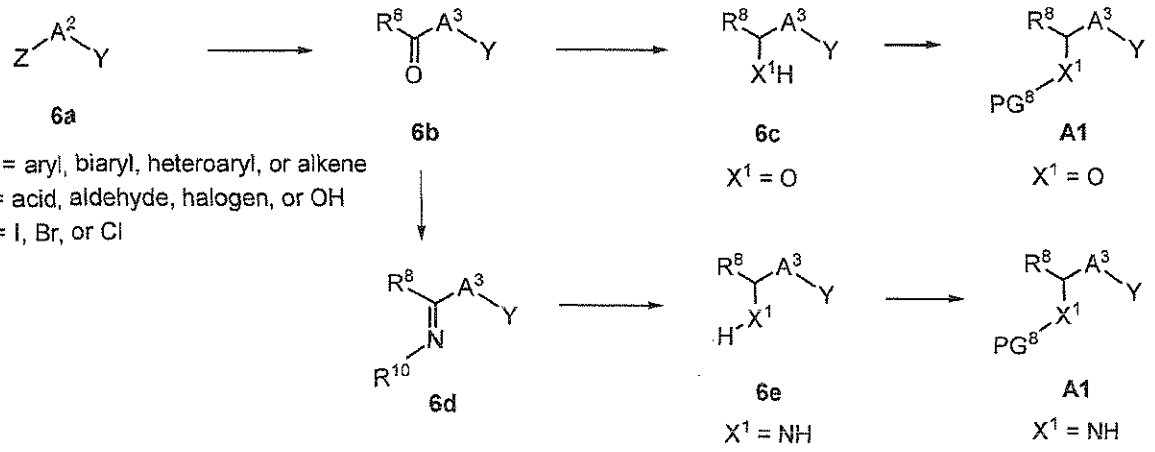
Scheme 9: Preparation of A



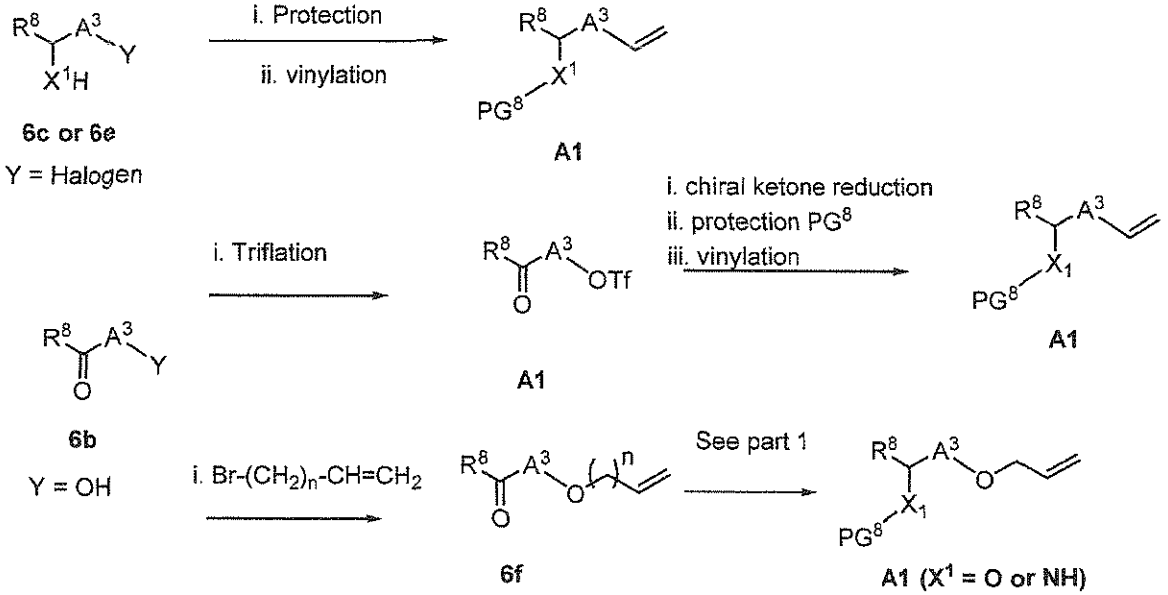
X^1 = O, NH, N(alkyl), or substituted N, etc.
Y = halogen, alkene, or O-alkylene

A^3 = aryl, heteroayl, or biaryl, etc.
X^1 = O, NH, or NR
Y = halogen, alkene, or O-alkylene
R^8 = H, lower alkyl, or haloalkyl

*1. When Y = Halogen in **A1***



*2. When Y =alkene in **A1***



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In Scheme 9, part 1 (Y is a halogen in A1); the starting compound 6a is typically a commercially available aromatic compound, that contains halogen Y and a group Z that can be transformed to the ketone 6b. Typical Z groups are halide, acid, aldehyde, for example.

When Z is an acid, 6a is treated with a coupling agent, e.g., HATU, EDC in the presence of a base, e.g., DIPEA and the Weinreb amine (Me-NH-OMe) to form the Weinreb amide. The amide is then treated with a nucleophile, e.g., TMS-CF_3 to form the CF_3 substituted ketone 6b or with a Grignard agent, e.g., MeMgBr in a solvent, e.g., THF at -78°C to form the methyl ketone 6b.

When Z is halogen, then the initial conversion, if required, to a more reactive halogen is performed by treatment with NaI and acetyl chloride in an inert solvent, e.g., acetonitrile. The halogen is then transformed to the ketone by a Stille reaction with an ethoxyvinyl stannane. The halide is treated in an inert solvent, e.g., toluene, with the stannane and a palladium (II) catalyst, e.g., $PdCl_2(PPh_3)_2$, followed by treatment of the product with 2M HCl to afford ketone 6b. In some cases, the formation of an alkyl lithium reagent from the halide group can be performed by treatment with nBuLi at -78°C in THF and then addition of a N-methoxy-N-methyl amide to afford the ketone 6b (e.g., N-methoxy-N-methylacetamide affords the R^8=methyl ketone 6b). A final method to generate the ketone 6b is through a vinyl group. 6a is treated with a vinyltrifluoroborate in the presence of a palladium catalyst, e.g., $PdCl_2$(dppf) and then the vinyl product is subsequently ozonolysed in a polar solvent, e.g., methanol at low temperature to give an aldehyde. The aldehyde is then reacted with a nucleophile, e.g., TSM-CF_3 or a Grignard reagent, e.g., MeMgBr to afford a secondary alcohol product. The secondary alcohol is then oxidized with Dess Martin Periodinane to give the desired ketone 6b or can be used as A1 itself.

Chiral alcohol (X^1 is O) and amine (X^1 is NH) A1 are generated using Chiral reduction methods on the ketone 6b. Chiral alcohol 6c is formed from 6b using one of the numerous chiral reduction methods available in the literature. Typically, dichloro(p-cumene)ruthenium(II) dimer and (1R,2R)-(-)-*N*-p-tosyl-1,2-diphenylethylenediamine are combined in water, and sodium formate and 6b is added in a water miscible solvent such as tetrahydrofuran. The reaction is then stirred at a temperature between ambient and reflux to produce 6c where X^1 is O. Alternatively, a chiral CBS reduction can be performed in an inert solvent, e.g., THF at low temperature to also afford the chiral alcohol 6c. Protection of the OH in 6c is performed using methods described in Greene and Wuts, typically a TBS ether or acetyl group are used to provide A1 (X^1 is O).

Alternatively to make chiral A1 (X^1 is NH), ketone 6b is first converted to a chiral imine (R^{10} is chiral group) and then reduced using a variety of methods described in the literature. For example, a chiral sulfinamide is reacted with the ketone 6b to afford a chiral sulfinimine 6d, which is then reduced with a suitable reducing agent, typically $NaBH_4$, or selectride, or a Noyori type reduction as described for the chiral alcohol above, with dichloro(p-cumene)ruthenium(II) dimer and (1R,2R)-(-)-*N*-p-tosyl-1,2-diphenylethylenediamine. The sulfinamide auxiliary is then removed by treatment with mineral acid, preferably HCl in a suitable organic solvent such as methanol, to afford 6e where X_1=NH. Protection of the NH group can then be performed as described in Greene and Wuts to generate A1 (X^1 is NH).

In part 2 of Scheme 9, the synthesis of compound A1 where Y is -CH=CH_2, a precursor for metathesis and cross coupling reactions is illustrated. Examplary methods are as follows.

Compound 6c or 6e generated in Scheme 9, part 1 is first optionally protected on X^1 using a suitable protecting group as described in Greene and Wuts, and then a vinyl group is introduced by a suitable cross coupling method onto the aryl or sp2 halide. For example, a transition metal mediated coupling with an vinyl stannane or vinyl tetrafluoroborate using a suitable palladium catalyst, e.g., $PdCl_2(dppf)_2$ or Pd $Cl_2(PPh_3)_2$ in a suitable organic solvent, e.g., acetontrile, dichloromethane, etc., with either thermal or microwave heating affords alkene A1.

Another typical method that can be used to introduce a vinyl group is starting from the ketone 6b where Y is OH. Initially, triflation of the alcohol is performed by treatment with Tf_2O in the presence of a base, e.g., pyridine. The ketone group is then reduced with a Noyori reduction, or as described above through the sulfonamide, to provide the chiral alcohol or amine. The chiral alcohol or amine is then protected as described in Greene and Wuts, and then the triflate is reacted with a vinyl cross coupling reagent, e.g., vinyl stannane in a Stille coupling, or a vinyltrifluoroborate as described above to introduce the alkene. A further example of alkene generation using 6b ketone is via introduction of an allyl group. Thus, 6b where Y is OH is treated in an inert solvent in the presence of a suitable base, e.g., alkali metal carbonate, preferably potassium carbonate with allyl bromide to form 6f. Compound 6f is then similar to ketone 6b and is therefore able to be transformed as described above in part 1 to compound A1 where X^1 is O or NH with protecting group PG^8.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations of the invention, both for veterinary and for human use, comprise at least one active ingredient, together with one or more acceptable carriers and optionally other therapeutic ingredients.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

The effective dose of an active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. The effective dose can be expected to be from about 0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01 to about 10 mg/kg body weight per day; more typically, from about .01 to about 5 mg/kg body weight per day; most typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Combination Therapy

The compounds of the present invention may be combined with one or more active agents. Non-limiting examples of suitable active agents to be combined include one or more interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, mevalonate decarboxylase antagonists, antagonists of the renin-angiotensin system, other anti-fibrotic agents, endothelin antagonists, nucleoside or

nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers and other drugs for treating HCV; or mixtures thereof.

More specifically, one or more compounds to be combined are selected from the group consisting of:

1) interferons, *e.g.*, pegylated rIFN-alpha 2b (PEG-Intron), pegylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon), interferon-beta (Avonex, DL-8234), interferon-omega (omega DUROS, Biomed 510), albinterferon alpha-2b (Albuferon), IFN alpha XL, BLX-883 (Locteron), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-Infergen, PEGylated interferon lambda (PEGylated IL-29), and belerofon;

2) ribavirin and its analogs, *e.g.*, ribavirin (Rebetol, Copegus), and taribavirin (Viramidine);

3) HCV NS3 protease inhibitors, *e.g.*, boceprevir (SCH-503034 , SCH-7), telaprevir (VX-950), VX-813, TMC-435 (TMC435350), ABT-450, BI-201335, BI-1230, MK-7009, SCH-900518, VBY-376, VX-500, GS-9256, GS-9451, BMS-790052, BMS-605339, PHX-1766, AS-101, YH-5258, YH5530, YH5531, and ITMN-191 (R-7227);

4) alpha-glucosidase 1 inhibitors, *e.g.*, celgosivir (MX-3253), Miglitol, and UT-231B;

5) hepatoprotectants, e.g., emericasan (IDN-6556), ME-3738, GS-9450 (LB-84451), silibilin, and MitoQ;

6) nucleoside or nucleotide inhibitors of HCV NS5B polymerase, *e.g.*, R1626, R7128 (R4048), IDX184, IDX-102, PSI-7851, BCX-4678, valopicitabine (NM-283), GS-6620 and MK-0608;

7) non-nucleoside inhibitors of HCV NS5B polymerase, e.g., filibuvir (PF-868554), ABT-333, ABT-072, BI-207127, VCH-759, VCH-916, JTK-652, MK-3281, VBY-708, VCH-222, A848837, ANA-598, GL60667, GL59728, A-63890, A-48773, A-48547, BC-2329, VCH-796 (nesbuvir), GSK625433, BILN-1941, XTL-2125, and GS-9190;

8) HCV NS5A inhibitors, *e.g.*, AZD-2836 (A-831), AZD-7295 (A-689), and BMS-790052;

9) TLR-7 agonists, *e.g.*, imiquimod, 852A, GS-9524, ANA-773, ANA-975, AZD-8848 (DSP-3025), PF-04878691, and SM-360320;

10) cyclophillin inhibitors, *e.g.*, DEBIO-025, SCY-635, and NIM811;

11) HCV IRES inhibitors, *e.g.*, MCI-067;

12) pharmacokinetic enhancers, *e.g.*, BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350, GS-9585, and roxythromycin;,

13) other drugs for treating HCV, *e.g.*, thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), GS-9525, KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOc-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, BMS-791325, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, FK-788, and VX-497 (merimepodib);

14) mevalonate decarboxylase antagonists, e.g., statins, HMGCoA synthase inhibitors (e.g., hymeglusin), squalene synthesis inhibitors (e.g., zaragozic acid);

15) angiotensin II receptor antagonists, e.g., losartan, irbesartan, olmesartan, candesartan, valsartan, telmisartan, eprosartan;

16) angiotensin-converting enzyme inhibitors, e.g., captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril;

17) other anti-fibrotic agents, e.g., amiloride; and

18) endothelin antagonists, e.g. bosentan and ambrisentan.

In yet another embodiment, the present application provides a combination therapy comprising a composition of the present invention and a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, *e.g.*, amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir + ritonavir,

nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.*, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, Mb-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.*, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, Mb-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosalvudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.*, tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir, 5) a HIV integrase inhibitor, e.g., curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, *e.g.*, AMD-070, 8) an entry inhibitor, *e.g.*, SP01A, TNX-355, 9) a gp120 inhibitor, *e.g.*, BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin, 10) a CCR5 inhibitor, *e.g.*, aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, e.g., A-831, A-689 and BMS-790052, 14) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), IDX184, PSI-7851, HCc-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and

phenylalanine derivatives, 19) other drugs for treating HCV, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOc-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, *e.g.*, BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350, GS-9585, and roxythromycin, 20)RNAse H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGc-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

In a specific aspect of this embodiment, the additional therapeutic agent is selected from ribavirin, telaprevir, boceprevir and sofosbuvir (GS-7977 (formerly PSI-7977)).

A combination therapy described herein may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active agents, such that therapeutically effective amounts of the compound of the invention and one or more other active agents are both present in the body of the patient.

One or more compounds of the disclosure are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this disclosure is that they are orally bioavailable and can be dosed orally.

Method for treating viral infection

The present application provides a method for treating a *Flaviviridae* viral infection comprising administering a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, to a human subject in need thereof.

Also provided is a method for treating a *Coronaviridae* viral infection comprising administering a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, to a human subject in need thereof.

In one embodiment, the method of inhibiting or treating a disease comprises administering to an animal a composition comprising an effective amount of one or more compounds of the invention and a pharmaceutically acceptable carrier. The composition to be administered may further contain a secondary therapeutic agent as described above.

A method of the present application is particularly suitable for use with humans, but may be used with other animals, particularly mammals, such as, for example, non-human primates, companion animals, farm animals, laboratory animals, and wild and zoo animals.

A method of the present application is particularly useful to treat diseases caused directly or indirectly by *Flaviviridae* virus since the compounds of the present invention have inhibitory activity against those viruses. In some embodiments, therefore, a method of the present invention is used in inhibiting or treating diseases caused by a Hepatitis C virus. In some embodiments, therefore, a method of the present invention is used in inhibiting or treating diseases caused by a Hepatitis B virus. In an aspect, such a method is applied to a patient with a disease caused by the viral infection such as dengue fever, yellow fever, hepatitis C, Japanese encephalitis, Kyasanur forest disease, Murray valley encephalitis, St. Louis encephalitis, tick-borne encephalitis or West Nile encephalitis.

In some embodiments, a sustained virologic response is achieved at about 12 weeks, at about 10 weeks, at about 8 weeks, at about 6 weekes, or at about 4 weeks, or at about 4 months, or at about 5 months, or at about 6 months, or at about 1 year, or at about 2 years.

A method of the present application is also particularly useful to treat diseases caused directly or indirectly by *Coronaviridae* virus since the compounds of the present invention have inhibitory activity against those viruses. In some embodiments, therefore, a method of the present invention is used in inhibiting or treating diseases caused by a SARS coronarirus. In an aspect, such a method is applied to a patient with a disease caused by the viral infection such as severe acute respiratory syndrome (SARS), cancer, inflammation, obesity, acquired immune deficiency syndrome (AIDS), or cirrhosis.

In another aspect, the compounds disclosed herein can be used for treating cancer. In yet another aspect, the compounds disclosed herein can be used for immunomodulation. In

some embodiments, therefore, a method of the present invention comprises adjusting an immune response to a desired level, as in immunopotentiation, immunosuppression, or induction of immunologic tolerance.

In some embodiments, the compound is administered for about 12 weeks. In further embodiments, the compound is administered for about 12 weeks or less, for about 10 weeks or less, for about 8 weeks or less, for about 6 weeks or less, or for about 4 weeks or less. The compound may be administered once daily, twice daily, once every other day, two times a week, three times a week, four times a week, or five times a week.

EXAMPLES

The following examples are merely illustrative, and do not limit this disclosure in any way.

List of Abbreviations and Acronyms

Abbreviation	**Meaning**
°C	Degree Celsius
di-tBuXPhos	2-Di-tert-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl
2,6-lut.	2,6-lutidine
MNBA	2-Methyl-6-nitrobenzoic Anhydride
4AMS	4 Angstrom molecular sieves
Ac	Acetyl
app	Apparent
aq	Aqueous
atm	atmosphere
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Bn	Benzyl
Boc	tert-Butoxycarbonyl
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
br	Broad
Bu	Butyl
cat	Catalytic
cm	Centimeter
cod	cyclooctadiene
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
CP/Cp	Cyclopentyl
CPME	Cyclopentyl methyl ether
CSA	Camphorsulfonic acid
Cy/cHex	Cyclohexyl
d	Doublet

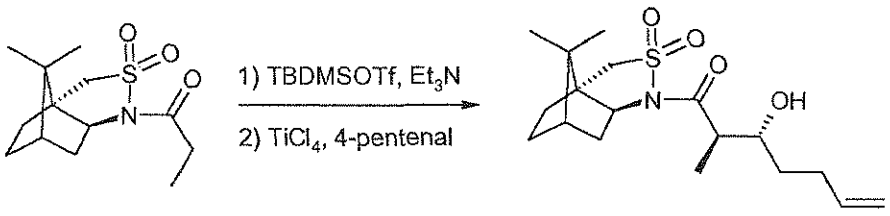
DAST	Diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dq	Double quartet
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv	Equivalents
ESI	Electron Spray Ionization
Et	Ethyl
g	Grams
HATU	(Dimethylamino)-N,N-dimethyl(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methaniminium hexafluorophosphate
HDMS	Hexamethyldisilazane
HOBT	Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
hrs/h	Hours
Hz	Hertz
IC_{50}	The half maximal inhibitory concentration
i-Pr/iPr	Isopropyl
J	Coupling constant
Kg	Kilogram
LCMS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide
M	Molar
m	Multiplet
m/z	mass-to-charge ratio
M+	Mass peak
m-CPBA	meta-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mM	Millimolar
mm	Millimeter
mmol	Millimole
mol	Mole
Ms	Methanesulfonyl
MW	Microwave
nM	Nanomolar
NMR	Nuclear magnetic resonance
o-Tol	o-Tolyl
Ph	Phenyl
Pin	Pinacolato

Piv	Pivaloyl
ppm	parts per million
pTSA	p-Toluenesulfonic acid
py	Pyridine
q	Quartet
quant	Quantitative
rac	Racemic
Rf	Retention factor
RT/rt/r.t.	Room temperature
s	Singlet or seconds
sat.	Saturated
SEMCl	2-Trimethylsilylethyoxymethyl chloride
t	Triplet
TBAF	Tetra-n-butylammonium fluoride
TBDMS/TBS	tert-Butyldimethylsilyl
td	Triplet of doublets
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tr/tr	Retention time
Ts	Tosyl
UV	Ultraviolet
δ	Chemical shift
µL	Microliter
µM	Micromolar
µmol	Micromole

For Examples 1 to 58, and Examples 93 to 107, unless otherwise stated, preparative HPLC was performed on a Gilson HPLC system, using an Agilent Eclipse XDB/C18 7 micron, 250 x 21.2 mm semi-preparative column and an acetonitrile/water mobile phase at a flow rate of 20mL/min.

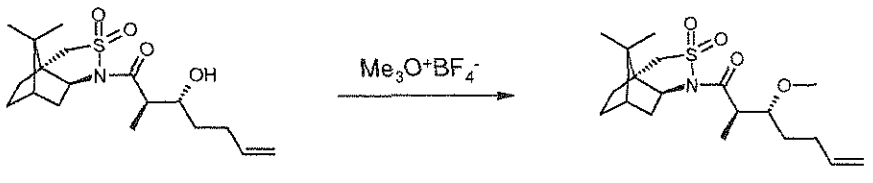
For Examples 59 to 92, and Examples 108 to 112, unless otherwise stated, preparative HPLC was performed on a Shimadzu HPLC system, using a 21.2 x 250mm 10 micron C18 Phenomenex Gemini semi-preparative column and acetonitrile/water mobile phase at a flow rate of 20mL/min.

EXAMPLE 1: (E)-(2R,3R)-7-(3-{(R)-1-[(S)-Hexahydro-pyridazine-3-carbonyl)-amino]-ethyl}-phenyl)-3-methoxy-2-methyl-hept-6-enoic acid (S)-2-methyl-1-((S)-1-methyl-2-oxo-ethylcarbamoyl)-propyl ester - Compound 1



Compound 1a

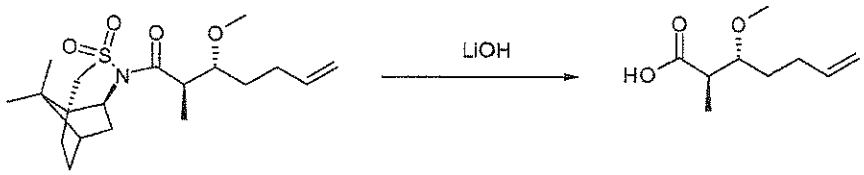
Synthesis of Compound 1a: A solution of 1-((1R,5S)-10,10-dimethyl-3,3-dioxo-3lambda*6*-thia-4-aza-tricyclo[5.2.1.0*1,5*]dec-4-yl)-propan-1-one (3.95 g, 14.55 mmol) in toluene (50 mL) was prepared, then evaporated to dryness. This process was repeated and the resulting white solid was dissolved in anhydrous dichloromethane (16 mL). A small quantity of calcium hydride was added before adding *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.83 mL, 14.5 mmol) and anhydrous triethylamine (2.33 mL, 16.7 mmol). The reaction mixture was stirred at room temperature (RT) under a nitrogen atmosphere for 15 hours ("h"). The resulting solution was evaporated to yield a thick paste, which was re-dissolved in anhydrous dichloromethane (15 mL) and added drop-wise to a stirred solution of 4-pentenal (2.69 g, 32.0 mmol) and titanium tetrachloride (1 M in dichloromethane, 32 mL, 32 mmol) in anhydrous dichloromethane (20 mL) at –78 °C, under a nitrogen atmosphere. The reaction was stirred at -78 °C for 30 min before diluting with saturated aqueous ammonium chloride solution (100 mL). The layers were separated and the aqueous layer was extracted with further dichloromethane (2 x 50 mL). The combined extract was dried over sodium sulfate, filtered and evaporated to give a brown gum. This was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 4:1 to yield the title compound (3.09 g, 60%) as a colorless gum.



Compound 1b

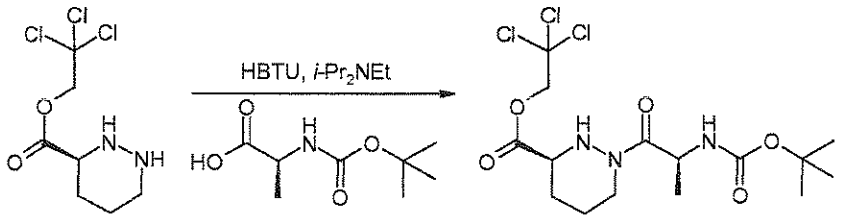
Synthesis of Compound 1b: A solution of 1a (250 mg, 0.703 mmol) in anhydrous dichloromethane (7 mL) was prepared and trimethyloxonium tetrafluoroborate (208 mg, 1.406 mmol) was added. The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was treated with methanol (1 mL), then 2 M hydrochloric acid (20 mL) and saturated brine (20 mL). The mixture was extracted with ethyl acetate (3 x 15 mL) and the extract was dried over sodium sulfate, filtered and evaporated to give a yellow gum. The gum was purified

by silica gel chromatography using *iso*-hexane/ethyl acetate 4:1 to give the title compound (223 mg, 86%) as a colorless gum.



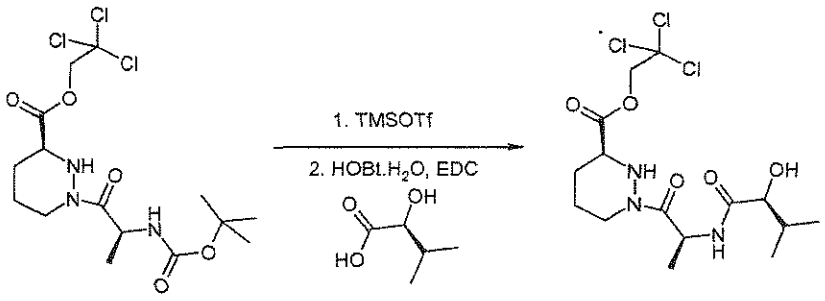
Compound 1c

Synthesis of Compound 1c: A solution of 2 M lithium hydroxide in water (5 mL) was added to a stirred solution of 1b (223 mg, 0.60 mmol) in tetrahydrofuran (15 mL). The stirred mixture was heated to 60°C for 15 h. The reaction mixture was partially evaporated before adding 2 M hydrochloric acid (20 mL). The solution was extracted with ethyl acetate (3 x 15 mL). The extract was dried over sodium sulfate, filtered and evaporated to give a yellow gum (209 mg). The gum was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 3:1 to yield the title compound (68 mg, 66%) as a yellow gum.



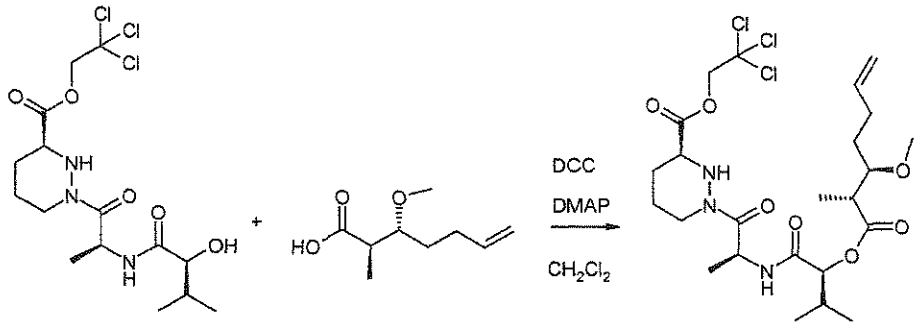
Compound 1d

Synthesis of Compound 1d: A solution of (S)-2-*tert*-butoxycarbonylamino-propionic acid (3.28 g, 17.32 mmol) in acetonitrile (160 mL) was cooled to 0 °C before addition of *N,N*-diisopropylethylamine (12 mL, 69.3 mmol) then 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (6.57 g, 17.32 mmol). The reaction mixture was stirred at 0°C for 20 min and a solution of (S)-hexahydropyridazine-3-carboxylic acid 2,2,2-trichloroethyl ester trifluoroacetic acid salt (preparation described in *Angew. Chem. Int. Ed. Engl.* 1999, *38*, 2443, 6.49 g, 17.3 mmol) in acetonitrile (80 mL) was added. The reaction was allowed to warm to room temperature and was stirred for 15 h. The reaction mixture was evaporated then re-dissolved in ethyl acetate (150 mL). The solution was washed with brine (150 mL). The brine was back extracted with ethyl acetate (50 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated to give a dark oil. The oil was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1:1 to yield the title compound (6.88 g, 92%) as a colorless gum.



Compound 1e

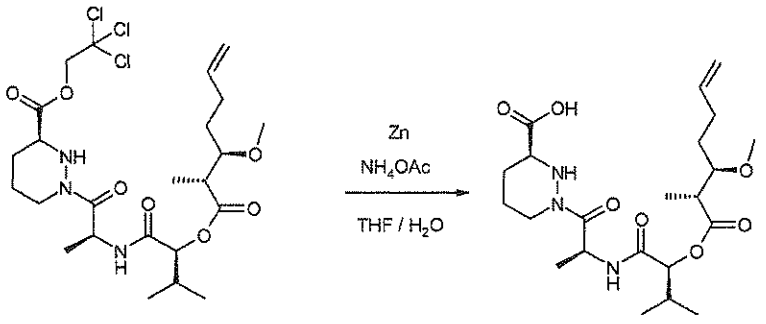
Synthesis of Compound 1e: To 1d (1.5 g, 3.5 mmol) in anhydrous dichloromethane (30 mL) at 0°C and under an atmosphere of nitrogen was added trimethylsilyl trifluoromethanesulfonate (941 µL, 5.2 mmol). The reaction mixture was stirred at 0°C for 1 h before adding *N,N*-diisopropylethylamine (2.2 mL, 13.9 mmol) and then concentrated *in vacuo* to afford (S)-1-[(S)-2-((S)-2-amino-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloroethyl ester. The resulting residue was dissolved in anhydrous acetonitrile (20 mL) and cooled to 0°C before adding (S)-2-hydroxy-3-methyl-butyric acid (413 mg, 3.5 mmol), hydroxybenzotriazole monohydrate (796 mg, 5.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.02 g, 5.2 mmol) and *N,N*-diisopropylethylamine (1.7 mL, 10.4 mmol). The reaction mixture was stirred at 0°C for 90 min, warmed to room temperature and stirred for 72 h and concentrated *in vacuo*. Ethyl acetate was added to the residue, which was then washed with saturated ammonium chloride and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexane/acetone 2:1 to give the title compound (1.1 g, 73% over 2 steps) as a white solid.



Compound 1f

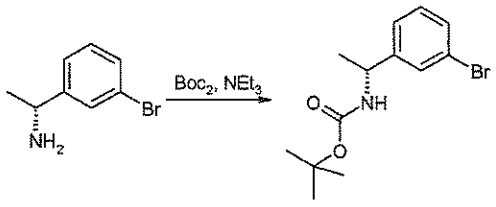
Synthesis of Compound 1f: A stirred solution of 1e (830 mg, 1.92 mmol) in dichloromethane (20 mL) was prepared and 1c (34 mg, 2.00 mmol), *N,N'*-dicyclohexylcarbodiimide (594 mg, 2.88 mmol) and *N,N*-dimethylaminopyridine (23 mg, 0.192

mmol) were added. The reaction was stirred at room temperature for 18 h. A further quantity of 1c (34 mg, 2.00 mmol), *N,N'*-dicyclohexylcarbodiimide (594 mg, 2.88 mmol) and *N,N*-dimethylaminopyridine (23 mg, 0.192 mmol) were added and the reaction was stirred at room temperature for a further 22 h. The reaction mixture was washed with water and the aqueous layer was back extracted with dichloromethane (2 x 15 mL) and ethyl acetate (2 x 15 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated to give a brown gum. The gum was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1:1 then ethyl acetate to give the title compound (656 mg, 58%) as a white solid.



Compound 1g

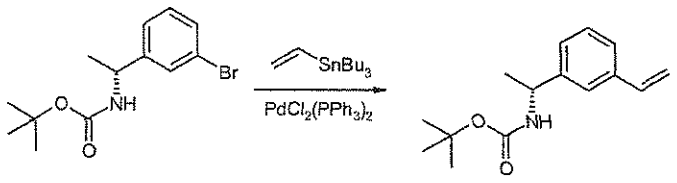
Synthesis of Compound 1g: A solution of 1f (656 mg, 1.12 mmol) in tetrahydrofuran (30 mL) was prepared and zinc powder (732 mg, 11.2 mmol) and aqueous ammonium acetate solution (1 M, 8 mL, 8 mmol) were added. The reaction was stirred at room temperature for 18 h. The mixture was filtered through hyflo-supercel then acidified with ammonium chloride then further with 2 M hydrochloric acid to pH 1. The mixture was extracted withy ethyl acetate (3 x 25 mL). The extract was dried over sodium sulfate, filtered and evaporated to give a solid which was azeotroped with toluene (40 mL) to give the title product (343 mg, 67%) as a colorless solid.



Compound 1h

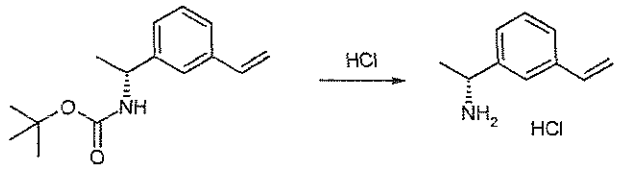
Synthesis of Compound 1h: A solution of (R)-bromo-α-methylbenzylamine (1.023 g, 5.112 mmol) in dichloromethane (20 mL) was subsequently treated with triethylamine (720 µL, 5.112 mmol) and di-*tert*-butyl dicarbonate (1.784 g, 8.179 mmol). After overnight stirring at room temperature, the volatiles were removed *in vacuo* and the residue was purified by silica gel

chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexane/diethyl ether 1:0 to 4:1 to afford the title compound (1.552 g, 100%) as a white solid.



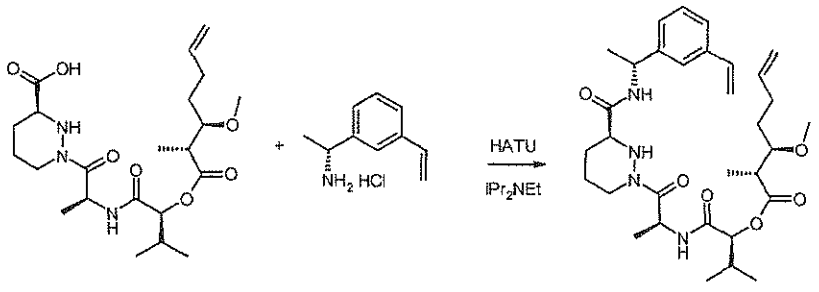
Compound 1i

Synthesis of Compound 1i: A solution of 1h (10.26 g, 0.0342 mol.) and tributyl(vinyl)stannane (32.5 g, 30mL, 0.103 mol.) in toluene (175 mL) was purged with nitrogen for 30 minutes before addition of bis(triphenylphosphine palladium(II) dichloride (2.38 g, 0.0034 mol). The stirred mixture was heated to 60 °C for 16 h before cooling to room temperature. The reaction mixture was filtered through hyflo-supercel then evaporated to give a dark colored oil. The oil was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 19:1 to yield the title compound (6.95 g, 82%) as a yellow oil.



Compound 1j

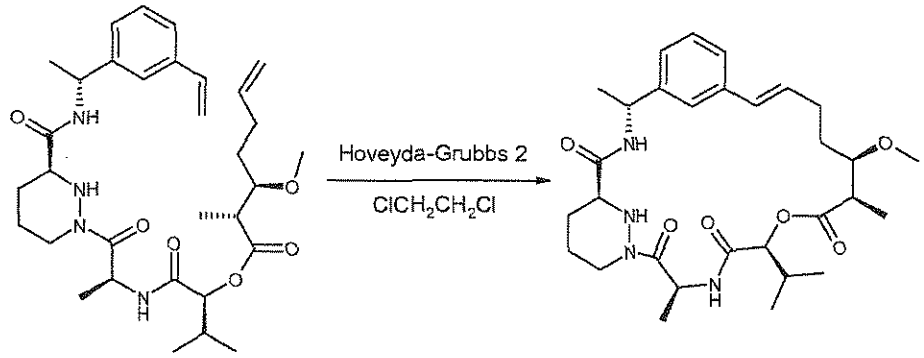
Synthesis of Compound 1j: A solution of 1i (6.95 g, 28.1 mmol.) in 1,4-dioxane (30mL) was prepared and a solution of hydrogen chloride in 1,4 dioxane (4M, 60 mL) was added. The reaction mixture was stirred at room temperature for 2 h then evaporated to dryness. The resultant solid was re-dissolved in toluene and evaporated. The solid was triturated with diethyl ether, which was removed by decanting. The solid was then dried under vacuum to give the title compound (4.96 g, 96%) as an off-white solid.



Compound 1k

Synthesis of Compound 1k: A solution of 1g (343 mg, 0.752 mmol), 1j (138 mg, 0.752 mmol) and *N,N*-diisopropylethylamine (0.52 mL, 3.00 mmol) in acetonitrile (25 mL) was prepared and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

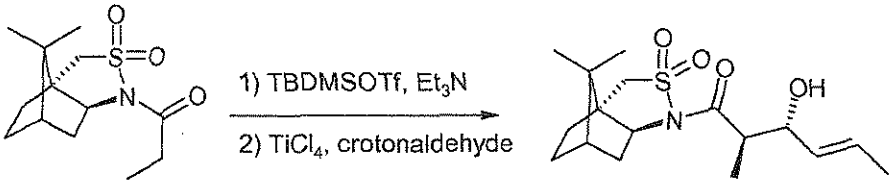
methanaminium (0.40 g,1.05 mmol) was added. The mixture was left to stir at room temperature for 18 h. The reaction mixture was evaporated then re-dissolved in ethyl acetate (25 mL) and water (25 mL). The layers were separated and the aqueous layer was extracted with further ethyl acetate (2 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated to give a brown gum. The gum was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1:3 to give the title compound (217 mg, 49%) as a colorless solid.



Compound 1

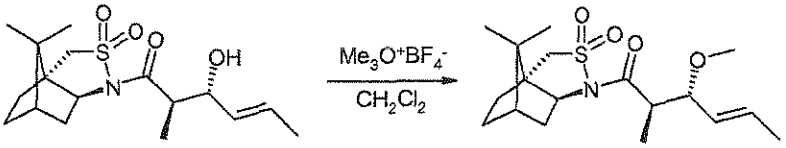
Synthesis of the title compound: A stirred solution of 1k (217 mg, 0.37 mmol) in 1,2-dichloroethane (125 mL) was prepared and Hoveyda-Grubbs 2nd generation catalyst (23 mg, 0.037 mmol) was added. The stirred solution was heated to reflux for 3 h. Further Hoveyda-Grubbs 2nd generation catalyst (46 mg, 0.074 mmol) was added and the reaction was heated to 85 °C for a further 2 h. The cooled reaction mixture was treated with silica gel. The mixture was evaporated then purified by silica gel chromatography using ethyl acetate to give an off-white solid (177 mg). This was re-purified by silica gel chromatography using a 5 g cartridge and ethyl acetate to give the title compound (67 mg, 32%) as a white solid. ^{1}H NMR (300 MHz, d_6-acetone) 0.93 (d, J = 7.1 Hz, 3H), 0.95 (d, J = 7.3 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H), 1.43 (d, J = 7.1 Hz, 3H), 1.47-1.69 (m, 3H), 1.70-1.91 (m, 3H), 1.92-2.17 (m, 3H), 2.32-2.48 (m, 1H), 3.02-3.13 (m, 1H), 3.35 (s, 3H), 3.40-3.65 (m, 3H), 4.27-4.43 (m, 2H), 4.80 (d, J = 5.3 Hz, 1H), 5.00-5.15 (m, 1H), 5.32-5.44 (m, 1H), 6.20-6.33 (m, 1H), 6.42 (d, J = 15.8 Hz, 1H), 7.10-7.32 (m, 3H), 7.34 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H). LCMS (m/z) 557.3 [M+H], Tr = 2.59 min.

EXAMPLE 2: Compound 2



Compound 2a

Synthesis of Compound 2a: A solution of 1-((1R,5S)-10,10-dimethyl-3,3-dioxo-3lambda*6*-thia-4-aza-tricyclo[5.2.1.0*1,5*]dec-4-yl)-propan-1-one (6.0 g, 22.1 mmol) in anhydrous dichloromethane (24 mL) was prepared and *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.0 mL, 22.1 mmol) was added, followed by anhydrous triethylamine (3.54 mL, 25.4 mmol).The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 15 h. This gave a dark solution that was evaporated to give an oil. The oil was dissolved in anhydrous dichloromethane (22 mL) and the solution was added dropwise to a solution of crotonaldehyde (3.66 mL, 44.2 mmol) and titanium tetrachloride (1 M in dichloromethane, 44.2 mL, 44.2 mmol) in dichloromethane (22 mL) at –78 °C under a nitrogen atmosphere. The reaction mixture was stirred at –78 °C for 1 h, before addition of ammonium chloride solution (30 mL). The stirred mixture was allowed to warm to room temperature before separating the layers. The aqueous layer was extracted with dichloromethane (2 x 25 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated to give a brown oil. The oil was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 4:1 to yield the title compound (6.7 g, 89%) as a colorless solid.



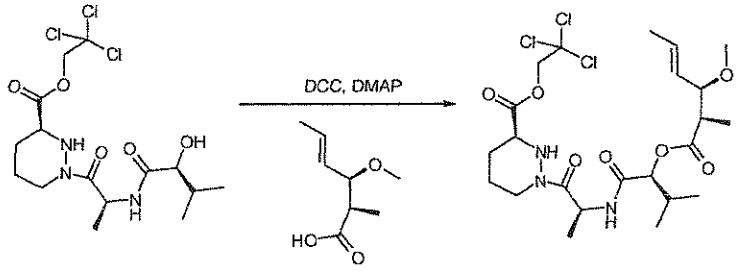
Compound 2b

Synthesis of Compound 2b: A solution of 2a (4.15 g, 12.1 mmol) in anhydrous dichloromethane (80 mL) was prepared and 1,8-bis(dimethylamino)naphthalene (7.78 g, 36.3 mmol) was added followed by trimethyloxonium tetrafluoroborate (3.6 g, 24.2 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was treated with methanol (3 mL) and stirred for 5 min before adding hydrochloric acid (2 M, 200 mL) and ethyl acetate (250 mL). The mixture was filtered to remove an insoluble solid and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered and evaporated to give the title compound (4.80 g, 100%) as a pale brown solid.



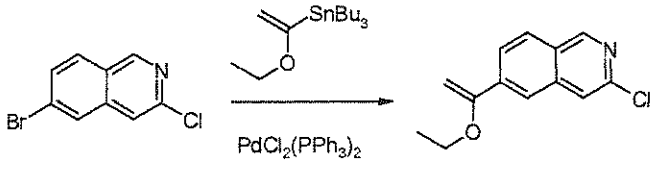
Compound 2c

Synthesis of Compound 2c: A solution of lithium hydroxide in water (2 M, 50 mL, 100 mmol) was added to a stirred solution of 2b (4.80 g, 12.1 mmol) in tetrahydrofuran (130 mL). The reaction mixture was heated to 60°C for 15 h. The reaction mixture was cooled to room temperature, before partially evaporating and adding hydrochloric acid (2 M, 150 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The extract was dried over sodium sulfate, filtered and evaporated to give a brown oil (3.5 g). The oil was purified by silica gel chromatography using *iso*-hexane/diethyl ether 1:1 to give the title compound (1.132 g, 59%) as a colorless oil.



Compound 2d:

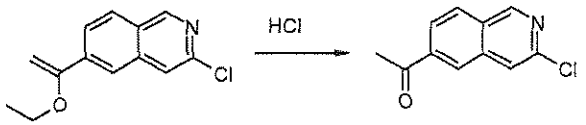
Synthesis of Compound 2d: Compound 2d was prepared in the same manner as compound 1f replacing 1c with 2c (148 mg, 0.94 mmol) to afford the title compound (340 mg, 76 %) as a white solid.



Compound 2e

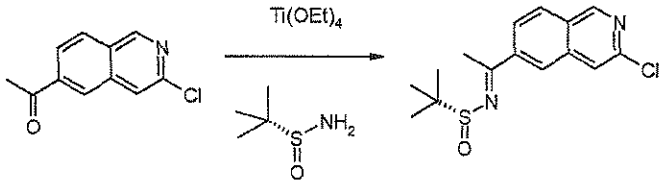
Synthesis of Compound 2e: A solution of 6-bromo-3-chloro-isoquinoline (Frontier Scientific, Logan, Utah USA) (8.0 g, 33 mmol) and tributyl-(1-ethoxy-vinyl)-stannane (14.88 g, 14 mL, 41.2 mmol) in toluene (100 mL) was degassed with nitrogen for 30 min. Bis(triphenylphosphine)palladium(II) dichloride (1.16 g, 1.65 mmol, 5 mol%) was added and the reaction mixture was heated at 60 °C for 20 h. The reaction mixture was cooled to room temperature, the mixture was filtered and the filtrate was evaporated. The residue was purified

by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 20:1 to 10:1 to afford the title compound (7.1 g, 92%) as a pale yellow solid.



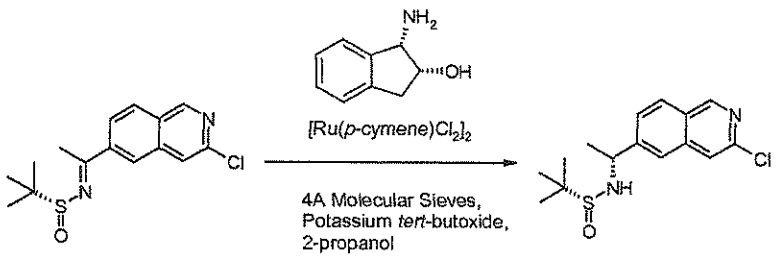
Compound 2f

Synthesis of Compound 2f: A solution of 2e (7.1 g, 30 mmol) in 1,4-dioxane (60 mL) and 2 M hydrochloric acid (30 mL) was stirred at room temperature for 30 min. The majority of the solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic extracts were combined, washed with water and brine, dried over sodium sulfate, filtered and evaporated. The residue was triturated with 5% ether in *iso*-hexane and the resulting solid was collected and dried to afford the title compound (6.0 g yield) as a white solid.



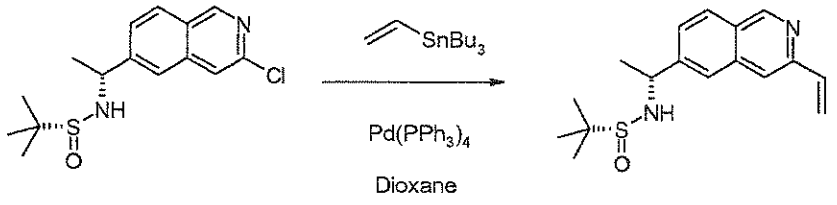
Compound 2g

Synthesis of Compound 2g: A solution of 2f (1.72 g, 8.3 mmol) in tetrahydrofuran (40 mL) was stirred under nitrogen. Titanium (IV) ethoxide (3.8 g, 3.45 mL, 16.6 mmol, tech. grade) was added followed by (R)-(+)-2-methyl-propanesulfinimide (1.11 g, 9.2 mmol) and the reaction mixture was stirred at 60°C under nitrogen for 18 h. Additional (R)-(+)-2-methyl-propanesulfinimide (190 mg, 0.2 equiv) was added and the reaction mixture was stirred at 65°C for a further 2 h. The reaction mixture was cooled to room temperature and ethyl acetate and brine were added. The suspension was filtered through celite and the filter pad was washed with ethyl acetate. The ethyl acetate layer was separated, washed with brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 7:3 to 3:7 to afford the title compound (2.2 g, 86%).



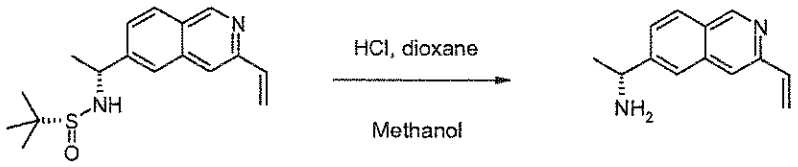
Compound 2h

Synthesis of Compound 2h: A mixture of (1S, 2R)-(-)-cis-1-amino-2-indanol (60 mg, 0.4 mmol), [Ru(*p*-cymen)Cl_2]$_2$ (122mg, 0.2 mmol) and powdered 4 Å molecular sieves (2g) was suspended in anhydrous 2-propanol (9 mL) and stirred under nitrogen. The suspension was heated at 90°C for 20 min. The reaction mixture was cooled to 40°C and a solution of 2g (1.23 g, 4 mmol) in 2-propanol (28 mL) was added followed by a solution of potassium *tert*-butoxide (122 mg, 1.1 mmol) in 2-propanol (10 mL). The reaction mixture was stirred for 2 h at 40°C and then allowed to cool. The mixture was poured directly onto a silica gel cartridge and eluted with ethyl acetate to give, after evaporation, the title compound as a brown gum (1.19 g, 96%).



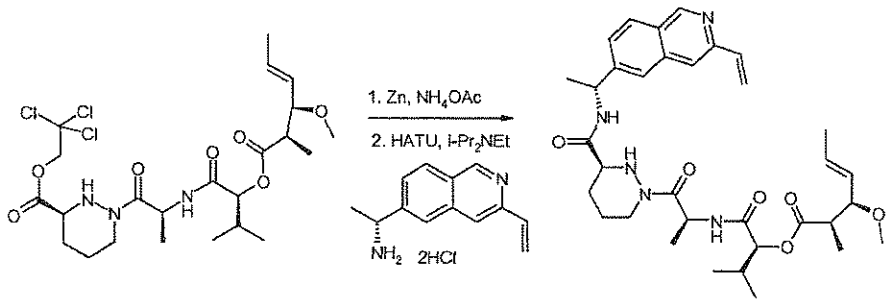
Compound 2i

Synthesis of Compound 2i: A mixture of 2h (1.66g, 2.11 mmol), tributyl(vinyl)tin (1.85 mL, 6.35 mmol) and palladium tetrakis(triphenylphosphine) (488 mg, 0.42 mmol in 1,4-dioxane (10.5 mL) was capped in a microwave vial. The reaction mixture was heated and stirred at 160°C for 40 min in a microwave reactor. A second reaction was carried under identical scale and conditions and the reactions combined and evaporated. The residue was purified by silica gel chromatography using a gradient of 25 to 100% ethyl acetate in *iso*-hexanes to afford the title compound as a brown gum (1g).



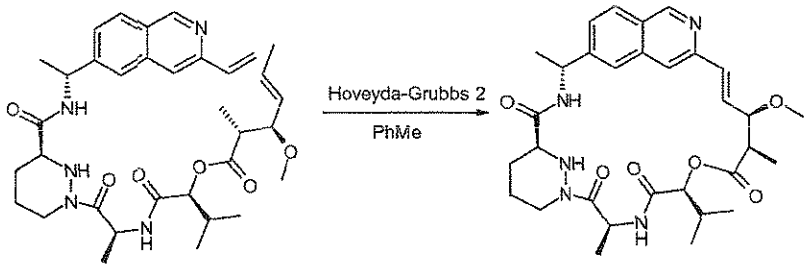
Compound 2j

Synthesis of Compound 2j: 2i was suspended in 4 M HCl in 1,4-dioxane (17 mL, 68 mmol) and methanol was added (34 mL). The reaction mixture was stirred for 90 min and then evaporated to give the title compound as the di-HCl salt. The residue was passed through an SCX cartridge eluting with methanol and then methanolic ammonia. The basic fraction was collected and evaporated to give the title compound as a beige solid (530 mg, 63% over 2 steps).



Compound 2k

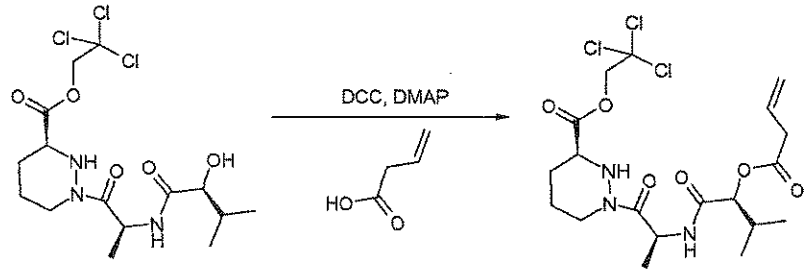
Synthesis of Compound 2k: Compound 2k was prepared in the same manner as compound 1k, by first replacing 1g with (S)-1-{(S)-2-[(S)-2-((E)-(2R,3R)-3-methoxy-2-methyl-hex-4-enoyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (340 mg, 0.59 mmol) and following the synthesis for compound 1g and then replacing (R)-1-(3-vinyl-phenyl)-ethylamine hydrochloride with 2j dihydrochloride (160 mg, 0.59 mmol) in the synthesis of compound 1k to give the title compound (240 mg, 66%, 2 steps) as a viscous light brown oil.



Compound 2

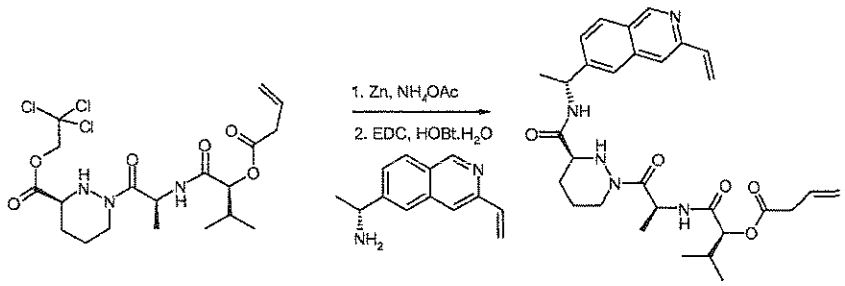
Synthesis of the title compound: A solution of 2k (300 mg, 0.48 mmol) in toluene (161 mL) was degassed with nitrogen for 10 min before adding Hoveyda Grubbs 2nd generation catalyst (61 mg, 0.1 mmol). The stirred solution was heated to 125°C for 2 h before a further amount of Hoveyda Grubbs 2nd generation catalyst (61 mg, 0.1 mmol) was added and heating continued for 4 h. The reaction was cooled to ambient temperature and concentrated to dryness. The residue was purified by silica gel chromatography using ethyl acetate/acetone 1/0 then 3/1 followed by preparative TLC using ethyl acetate/acetone 8/1 to yield the title compound (4 mg, 1%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 0.80-1.11 (m, 6H), 1.20-1.38 (m, 3H), 1.42-1.70 (m, 6H), 1.67-1.88 (m, 2H), 1.89-2.25 (m, 3H), 2.60-2.75 (m, 2H), 2.98-3.18 (m, 1H), 3.48 (s, 3H), 3.58-3.77 (m, 1H), 4.36-4.67 (m, 2H), 4.91 (s, 1H), 5.18-5.43 (m, 1H), 5.61-5.76 (m, 1H), 6.40-6.65 (m, 1H), 6.82-7.10 (m, 3H), 7.36-7.50 (m, 1H), 7.64 (s, 1H), 7.85-8.01 (m, 1H), 8.18 (s, 1H), 9.16 (s, 1H). LCMS (m/z) = 580.3 [M+H], Tr = 1.50 min.

EXAMPLE 3: Compound 3



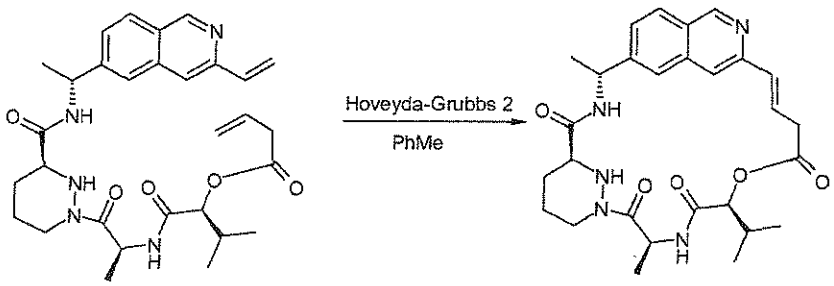
Compound 3a

Synthesis of Compound 3a: Compound 3a was prepared in the same manner as compound 1f by replacing 1c with 3-butenoic acid to afford the title compound (397 mg, 66 %) as a white solid.



Compound 3b

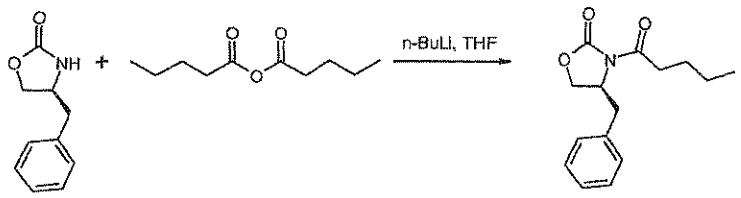
Synthesis of Compound 3b: To a solution of 3a (390 mg, 0.78 mmol) in tetrahydrofuran (17 mL) and water (9 mL) was added powdered zinc (1.11 g, 17.1 mmol) followed by ammonium acetate (899 mg, 11.7 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction was filtered through Celite, the filtrate was acidified to pH 2 with concentrated hydrochloric acid and extracted twice with ethyl acetate. The organic layers were dried through a hydrophobic frit and concentrated *in vacuo*, followed by co-evaporation from toluene (2 x). The ensuing residue was dissolved in anhydrous acetonitrile (15 mL) and 2j (211 mg, 0.78 mmol) was added followed by hydroxybenzotriazole monohydrate (119 mg, 0.78 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (210 mg, 1.1 mmol). The reaction mixture was stirred at room temperature for 16 h. Silica gel was added to the reaction mixture and concentrated *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1/1 then ethyl acetate to give the title compound (276 mg, 57%, 2 steps) as a white solid.



Compound 3

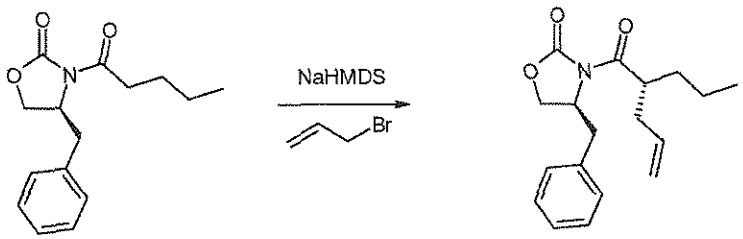
Synthesis of the title compound: To a refluxing solution of Hoveyda Grubbs 2nd generation catalyst (85 mg, 0.14 mmol) and 2, 6-dichlorobenzoquinone (8 mg, 0.05 mmol) in anhydrous toluene (150 mL) was added a solution of 3b (250 mg, 0.45 mmol) in toluene/dichloroethane (1:1, 9 mL) over 1 h. Following 1 h at reflux, a further amount of Hoveyda Grubbs 2nd generation catalyst (42 mg, 0.07 mmol) was added and heating continued for 3 h. The reaction was cooled to room temperature and evaporated to dryness. The residue was purified by silica gel chromatography using ethyl acetate then ethyl acetate/acetone 3/1 to yield a brown foam. This was purified further by preparative TLC using ethyl acetate/acetone 8/1 (2 x) to yield the title compound (2 mg, 1%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 0.73-1.20 (m, 9H), 1.40-2.08 (m, 5H), 2.15-2.61 (m, 4H), 3.14-4.15 (m, 6H), 4.78-5.63 (m, 3H), 6.67-7.03 (m, 2H), 7.38-7.58 (m, 2H), 7.83-8.04 (m, 2H), 9.17 (s, 1H). LCMS (m/z) = 522.2 [M+H], Tr = 1.33 min.

EXAMPLE 4 - Compound 4



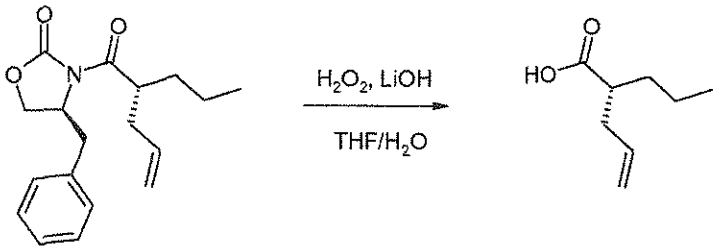
Compound 4a

Synthesis of Compound 4a: To a solution of (S)-4-benzyl-2-oxazolidinone (3.85 g, 21.7 mmol) in tetrahydrofuran (10 mL) at -78°C, was added 2.5 M butyllithium in hexanes (10 mL, 25 mmol) and the mixture stirred for 5 min. Valeric anhydride (5.15 mL, 26.1 mmol) was then added and the solution stirred at -78°C for 50 min before addition of brine (10 mL). The mixture was then allowed to warm to room temperature when more brine (20 mL) was added. The organics were extracted with ethyl acetate (2 x 50 mL) and the combined extract was dried over sodium sulfate, filtered and evaporated to give a crude oil. This was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 9:1 to yield the title compound (5.24 g, 92%).



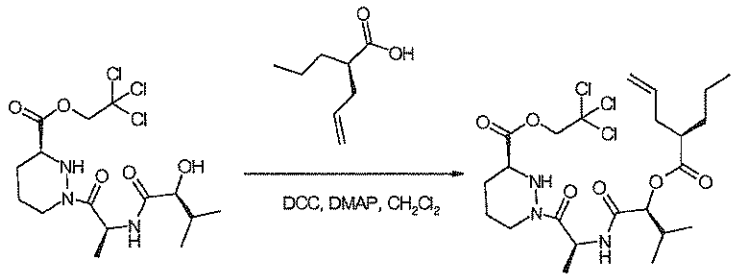
Compound 4b

Synthesis of Compound 4b: A solution of 4a (5.24 g, 20.0 mmol) in tetrahydrofuran (50 mL) was cooled to –78°C. 1 M sodium hexamethyldisilazane in tetrahydrofuran (32.1 mL, 32 mmol) was added dropwise and the internal temperature kept below -70°C. Upon complete addition, stirring was continued at -78°C for 1 h. After this time allyl bromide (6.98 mL, 80.2 mmol) was added dropwise and the internal temperature kept between -55°C to -40°C. Upon complete addition stirring was continued between -55°C and -40°C for 3 h, after which saturated ammonium chloride (20 mL) was added and the mixture allowed to warm to room temperature. The organics were extracted with ethyl acetate (2 x 100 mL), washed with brine, dried over sodium sulfate and evaporated to give a crude yellow oil. This was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1:0 then 95:5 then 9:1 to yield the title compound (2.95 g, 49%).



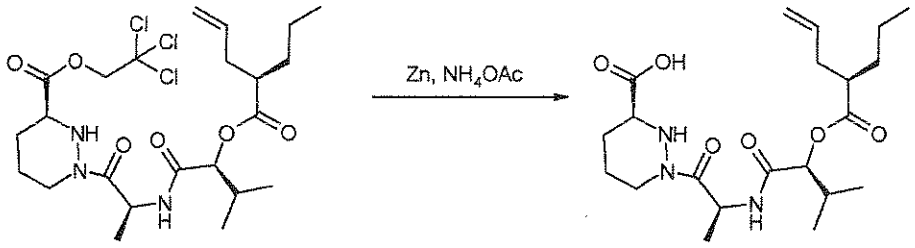
Compound 4c

Synthesis of Compound 4c: A solution of 4b (2.95 g, 9.79 mmol) in tetrahydrofuran (72 mL) and water (36 mL) was cooled to 0°C. 30% aqueous hydrogen peroxide (4.72 mL, 48.9 mmol) was added followed by a solution of lithium hydroxide (470 mg, 19.6 mmol) in water (7.2 mL). The mixture was stirred at 0°C and after 3.42 h a solution of sodium sulphite (11.3 g, 90 mmol) in water (36 mL) was added and the solution stirred at 0°C for 15 min. The solution was treated with saturated sodium hydrogen carbonate until pH = 9-10, then the aqueous phase was washed with ethyl acetate (3 x 100 mL) then acidified to pH = 1-2 with 1 M sulphuric acid and extracted with diethyl ether (3 x 100 mL). The diethyl ether extracts were dried over sodium sulfate, filtered and evaporated to give the title compound (649 mg, 47%) as a colorless oil.



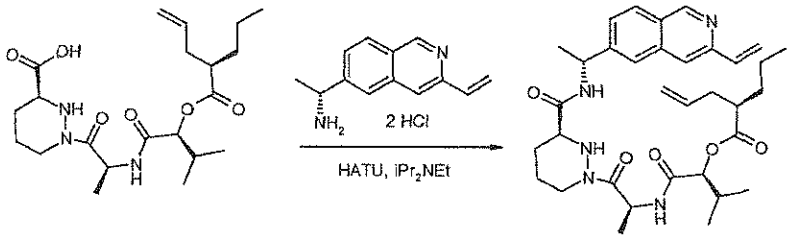
Compound 4d

Synthesis of Compound 4d: To a solution of 1e (790 mg, 1.82 mmol) in dichloromethane (9 mL) at room temperature, was added 4c (388 mg, 2.19 mmol), *N,N'*-dicyclohexylcarbodiimide (564 mg, 2.74 mmol) and 4-dimethylaminopyridine (223 mg, 1.82 mmol) and the reaction mixture stirred at room temperature for 3 h. After this time the reaction mixture was diluted with dichloromethane (50 mL) and washed with a saturated ammonium chloride solution. The aqueous phase was re-extracted with dichloromethane (2 x 50 mL) and the combined organics washed with brine (100 mL), dried over magnesium sulfate and evaporated to give a white residue. This was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1:0 to 1:1 to yield the title compound (916 mg, 90%).



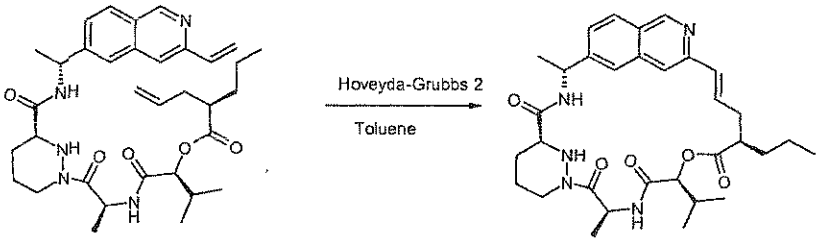
Compound 4e

Synthesis of Compound 4e: A solution of 4d (916 mg, 1.65 mmol) in tetrahydrofuran (41 mL) was prepared and powdered zinc (2.37 g, 36.2 mmol) was added followed by a solution of ammonium acetate (1.90 g, 24.7 mmol) in water (10.2 mL). The reaction mixture was stirred at room temperature for 24 h. The reaction was filtered through hyflo-supercel washing through with ethyl acetate and saturated aqueous potassium hydrogen sulfate. The mixture was treated with hydrochloric acid (1 M, 5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and evaporated to give a colorless gum. The residue was azeotroped with toluene (3 x 100 mL) to give the title compound (675 mg, 89%) as a white solid.



Compound 4f

Synthesis of Compound 4f: 4e (368 mg, 0.87 mmol) was dissolved in acetonitrile (5 mL) and 2j (180 mg, 0.77 mmol) was added followed by *N,N*-diisopropylethylamine (535 µL, 3.07 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (409 mg, 1.08 mmol). The reaction mixture was stirred at room temperature for 72 h. To the reaction mixture was added 2 M hydrochloric acid (15 mL) and the mixture was concentrated *in vacuo*. The residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was separated and re-extracted with ethyl acetate (100 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated to give a crude residue. The residue was purified by silica gel chromatography using ethyl acetate to give the title compound (440 mg, 95%) as an off-white solid.

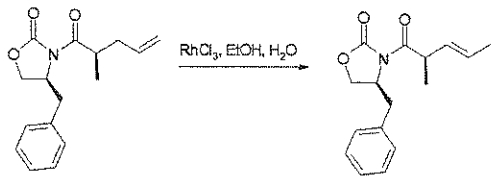


Compound 4

Synthesis of the title compound: A solution of 4f (440 mg, 0.73 mmol) in toluene (242 mL) was degassed with nitrogen for 15 min then Hoveyda-Grubbs 2nd generation catalyst (91 mg, 0.15 mmol) was added and the reaction mixture heated at 100-110°C for 2.5 h. After this time more Hoveyda-Grubbs 2nd generation catalyst (91 mg, 0.15 mmol) was added and the reaction mixture heated at 110°C for 1 h and allowed to cool to room temperature. The residue was purified by silica gel chromatography using a gradient of *iso*-hexane/ethyl acetate 1:1 to neat ethyl acetate. Impure product (160 mg) was further purified by silica gel chromatography using a gradient of dichloromethane/acetone 99:1 to 4:1. Pure product (4.4 mg) was obtained along with impure fractions which were further purified by reverse phase preparative HPLC where pure product (22.6 mg) was collected. After purification the title compound was collected (27 mg total, 6%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) 0.93-1.11 (m, 11H), 1.24-1.47 (m, 6H), 1.63-1.82 (m, 3H), 1.84-2.01 (m, 3H), 2.41-2.72 (m, 2H), 2.82 (td, J = 13.1, 3.1 Hz, 1H), 3.59-3.70 (m, 1H), 4.46 (dd, J = 9.8, 3.3 Hz, 1H), 4.70-4.79 (m, 2H), 5.17 (q, J = 6.9 Hz, 1H),

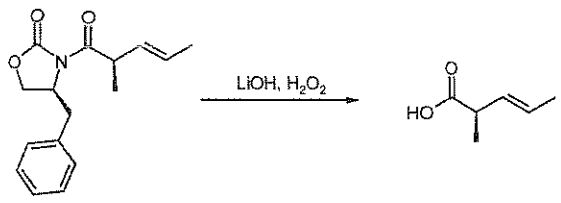
5.83-5.96 (m, 1H), 6.70 (d, *J* = 16.5 Hz, 1H), 6.85-6.99 (m, 1H), 7.59 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.71 (s, 1H), 7.96 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 8.54 (*br* d, *J* = 8.9 Hz, 1H), 9.10 (s, 1H). LCMS (m/z) 578.3 [M+H], Tr = 1.67 min.

EXAMPLE 5 - Compound 5



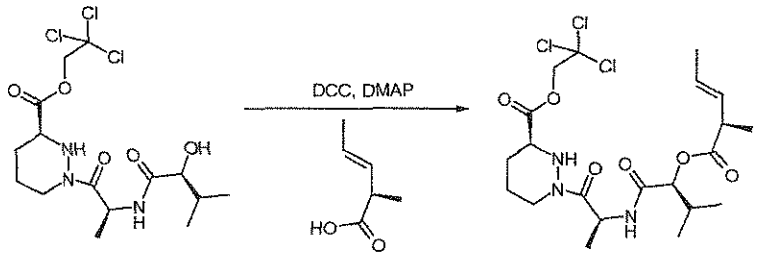
Compound 5a

Synthesis of Compound 5a: To (S)-4-benzyl-3-((R)-2-methyl-pent-4-enoyl)-oxazolidin-2-one (Prepared as in *JACS* 1990, *112 (8)* 2998-3017, 2.5 g, 9.16 mmol) in ethanol (13 mL) and water (1.5 mL) at room temperature was added rhodium trichloride hydrate (48 mg, 0.23 mmol). The reaction was heated to 80°C for 8 h, cooled and concentrated *in vacuo*. To the ensuing residue was added water and extracted with dichloromethane. The organic layer was dried through a hydrophobic frit and concentrated *in vacuo* to yield the title compound (2.2 g, 88%) as a brown oil.



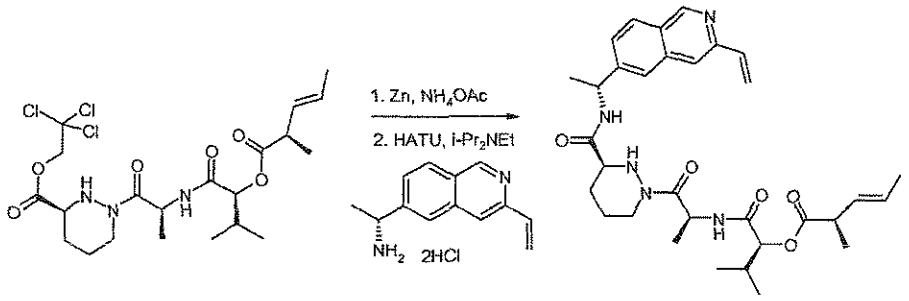
Compound 5b

Synthesis of Compound 5b: To 5a (2.2 g, 8.1 mmol) in tetrahydrofuran (60 mL) and water (20 mL) at 0°C was added lithium hydroxide (16 mL, 2.0 M solution in water, 32.2 mmol) and hydrogen peroxide (6.6 mL, 30% aqueous solution, 64.5 mmol). The reaction was stirred at 0°C for 16 h and then quenched by careful addition of aqueous sodium thiosulfate. The reaction mixture was concentrated to remove the tetrahydrofuran and then washed twice with dichloromethane. The aqueous layer was acidified to pH 1 with 2 M hydrochloric acid and extracted twice with diethyl ether. The combined organic layers were dried through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 5/1 to afford the title compound (530 mg, 57%) as a clear oil.



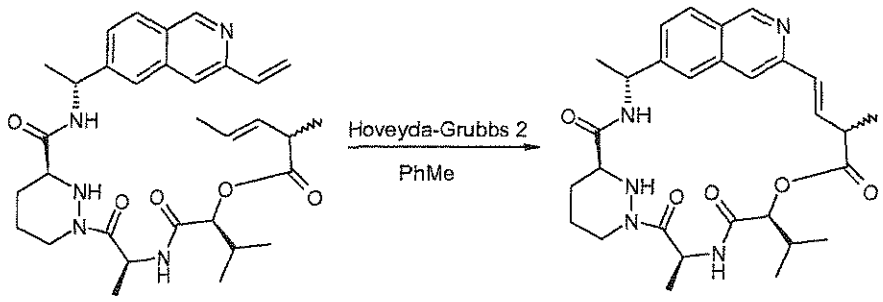
Compound 5c

Synthesis of Compound 5c: Compound 5c was prepared in the same manner as 1f replacing 1c with 5b (250 mg, 2.2 mmol), to afford the title compound (750 mg, 77 %) as a white foam.



Compound 5d

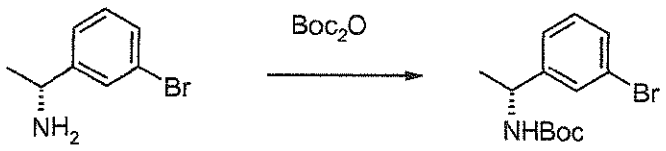
Synthesis of Compound 5d: To a solution of 5c (750 mg, 1.42 mmol) in tetrahydrofuran (35 mL) and water (20 mL) was added powdered zinc (2.03 g, 31.2 mmol) followed by ammonium acetate (1.64 g, 21.3 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction was filtered through Celite, the filtrate was acidified to pH 2 with concentrated hydrochloric acid and extracted twice with ethyl acetate. The organic layers were dried through a hydrophobic frit and concentrated *in vacuo*, followed by co-evaporation from toluene (2 x). The ensuing residue was dissolved in anhydrous acetonitrile (15 mL) and 2j (385 mg, 1.4 mmol) was added followed by *N,N*-diisopropylethylamine (743 µL, 4.3 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (755 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 3 h. Silica gel was added to the reaction mixture and concentrated *in vacuo*. The residue was purified by silica gel chromatography using ethyl acetate to give the title compound (580 mg, 71%, 2 steps) as a clear viscous oil.



Compound 5

Synthesis of the title compound: A solution of 5d (250 mg, 0.43 mmol) in toluene (144 mL) was degassed with nitrogen for 30 min before warming to 70°C and adding Hoveyda Grubbs 2nd generation catalyst (54 mg, 0.09 mmol). The stirred solution was heated to 125°C for 45 min. A further amount of Hoveyda Grubbs 2nd generation catalyst (50 mg, 0.08 mmol) was added and heating continued for 2 h. Another portion of Hoveyda Grubbs 2nd generation catalyst (27 mg, 0.04 mmol) was added and heating continued for 3 h. The reaction was cooled to room temperature and potassium isocyanoacetate (120 mg) in methanol (2 mL) was added. After stirring for 1 h, the reaction mixture was concentrated to approximately half its original volume, treated with silica gel and then evaporated to dryness. The residue was purified by silica gel chromatography using ethyl acetate/acetone 1/0 then 5/1 to yield a white solid. This was purified further by reverse phase preparative HPLC to yield the title compound (2 mg, 1%) as a white solid. ^{1}H NMR (300 MHz, d_4-MeOH, 2:1 diastereomeric mix, major diastereomer peaks quoted) 0.99 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 1.47 (d, J = 6.9 Hz, 3H), 1.56-1.64 (m, 6H), 1.65-1.79 (m, 1H), 1.83-2.00 (m, 3H), 2.09-2.25 (m, 1H), 2.73-2.87 (m, 1H), 3.41-3.52 (m, 1H), 3.63-3.71 (m, 1H), 4.38-4.48 (m, 1H), 5.12 (d, J = 8.5 Hz, 1H), 5.18 (q, J = 6.7 Hz, 1H), 5.82 (q, J = 7.1 Hz, 1H), 6.47 (dd, J = 16.0, 6.3 Hz, 1H), 6.67 (dd, J = 16.0, 1.0 Hz, 1H), 7.60-7.67 (m, 2H), 7.75 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 9.14 (s, 1H). LCMS (m/z) = 536.2 [M+H], Tr = 1.30 min.

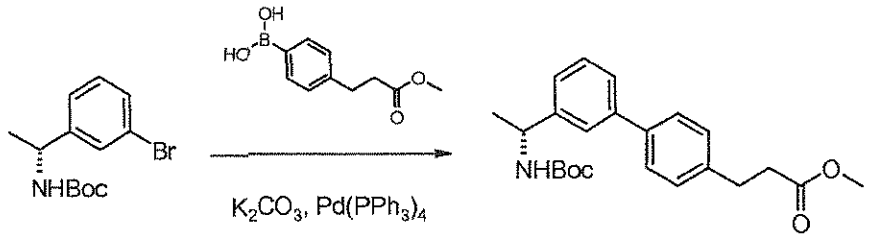
EXAMPLE 6 - Compound 6



Compound 6a

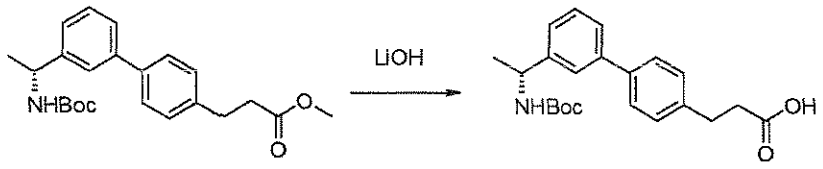
Synthesis of Compound 6a: A solution of (R)-bromo-α-methylbenzylamine (2.0 g, 10 mmol) in dichloromethane (20 mL) was treated with a solution of di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) in dichloromethane (20 mL) and the reaction mixture was stirred at room temperature for 1 h. The solution was washed with 2 M hydrochloric acid, water and brine, dried over

sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexane/ethyl acetate 20:1 to 6:1 to afford the title compound (2.51 g, 84%) as a white solid.



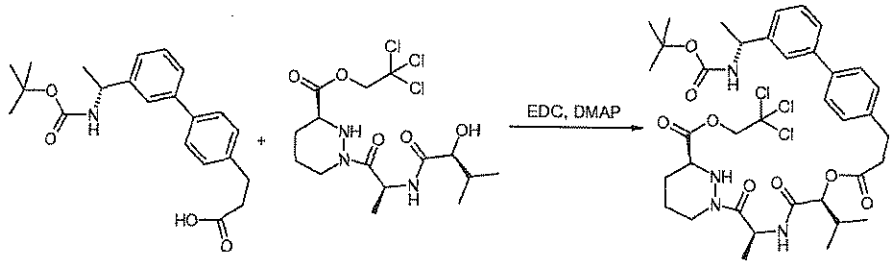
Compound 6b

Synthesis of Compound 6b: A mixture of 6a (900 mg, 3 mmol), 4-(2-methoxycarbonylethyl) phenylboronic acid (624 mg, 3 mmol) in 1,2-dimethoxyethane (10 mL) and potassium carbonate (828 mg, 6 mmol) in water (2 mL), was stirred at room temperature. Tetrakis(triphenylphosphine)palladium(0) (172 mg, 0.15 mmol) was added and the reaction mixture was heated at 100°C in a microwave reactor for 1 hour. The organic layer was separated. The organic layer was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 20:1 to 5:1 to afford the title compound (958 mg, 83%) as a white solid.



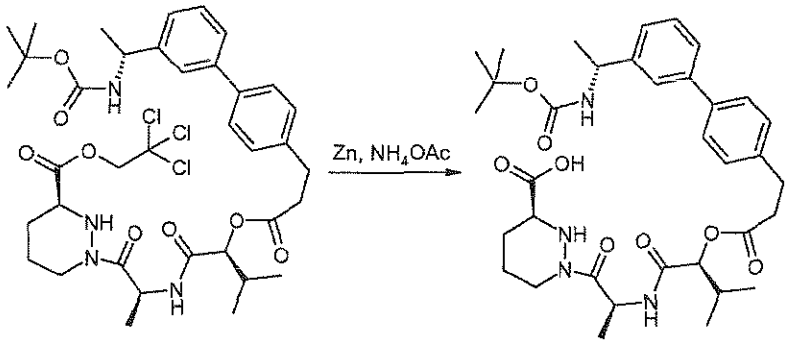
Compound 6c

Synthesis of Compound 6c: A solution of 6b (958 mg, 2.5 mmol) in tetrahydrofuran (15 mL) was stirred at 5°C. A solution of lithium hydroxide hydrate (300 mg, 5 mmol) in water (5 mL) was added and the reaction mixture was stirred at 5 °C for 1 hour and then at room temperature for 1 hour. The majority of the solvent was evaporated and water was added and 2 M hydrochloric acid was added to adjust the pH of the solution to pH 2. The mixture was extracted with ethyl acetate. The organic extracts were combined, washed with water and brine. The organic layer was filtered through a hydrophobic frit and the filtrate was evaporated to afford the title compound (883 mg, 96%) as a white solid.



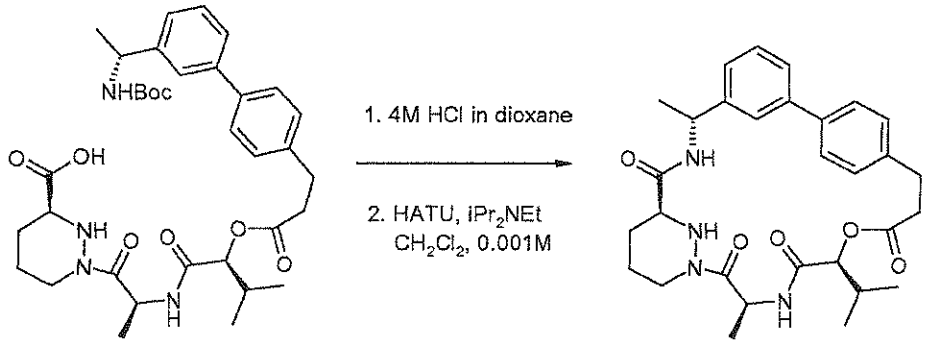
Compound 6d

Synthesis of Compound 6d: A solution of 6c (1.6 g, 4.3 mmol), 1e (1.86 g, 4.3 mmol) in dichloromethane (60 mL) was stirred at room temperature under nitrogen. *N*-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.25 g, 6.5 mmol) and 4-dimethylaminopyridine (525 mg, 4.3 mmol) was added and the reaction mixture was stirred at room temperature under nitrogen for 24 h. The reaction mixture was diluted with dichloromethane and the solution was washed with an aqueous citric acid solution (pH 2-3), water and brine. The organic layer was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 6:4 followed by silica gel chromatography using *iso*-hexanes/ethyl acetate 6:4 to afford the title compound (2.0 g, 60%) as a white foam.



Compound 6e

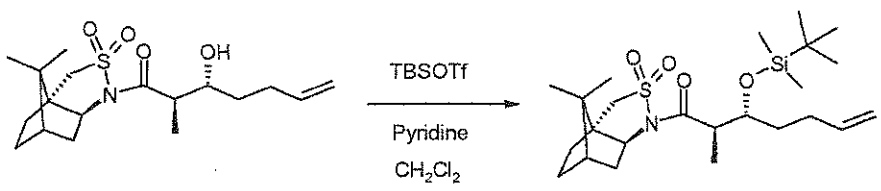
Synthesis of Compound 6e: A solution of 6d (1.96 g, 2.5 mmol) in tetrahydrofuran (50 mL) was stirred at room temperature under nitrogen. Zinc dust (3.58 g, 55 mmol) was added followed by a solution of ammonium acetate (2.9 g, 37.5 mmol) in water (25 mL) and the reaction mixture was stirred at room temperature under nitrogen for 24 hours. The reaction mixture was filtered through Celite and the filter pad was washed with ethyl acetate and 2 M hydrochloric acid. The filtrate was acidified to pH 2 with 2 M hydrochloric acid and sodium chloride was added to saturate the aqueous layer. The mixture was extracted with ethyl acetate (3 x). The organic extracts were combined, washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was co-evaporated with ethyl acetate (3 x), toluene (4 x) and dried to afford the title compound (1.56 g, 95%) as a white solid.



Compound 6

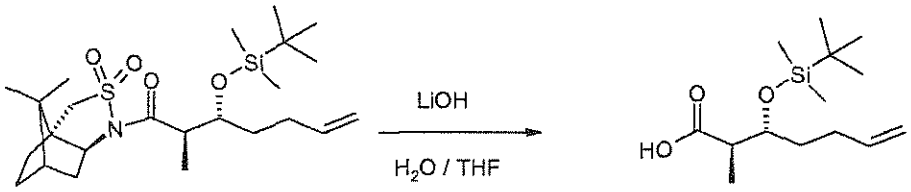
Synthesis of the title compound: A mixture of 6e (850 mg, 1.3 mmol) in 4M HCl in 1,4-dioxane (12 mL) was stirred at room temperature under nitrogen for 1 h. The solvent was evaporated and the residue was triturated with diethyl ether (3 x). The resulting solid was collected, washed with diethyl ether and dried to afford (S)-1-[(S)-2-((S)-2-{3-[3'-((R)-1-amino-ethyl)-biphenyl-4-yl]-propionyloxy}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid hydrochloride (1.3 mmol). A solution of (S)-1-[(S)-2-((S)-2-{3-[3'-((R)-1-amino-ethyl)-biphenyl-4-yl]-propionyloxy}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid hydrochloride (1.3 mmol) and *N,N-di*isopropylethylamine (671 mg, 0.9 mL, 5.2 mmol) in dichloromethane (1300 mL) was stirred at 0°C under nitrogen. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (988 mg, 2.6 mmol) was added and the reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated and the residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/acetone 7:3 to 1:1 followed by silica gel chromatography using ethyl acetate. The resulting solid was triturated with ether and the solid was collected and dried to afford the title compound (395 mg, 57%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 7.1 Hz, 3H), 1.54 (d, J = 6.9 Hz, 3H), 1.85-2.20 (m, 5H),2.65-3.10 (m, 5H), 3.53-3.59 (m, 1H), 4.38-4.25 (m, 1H), 4.64 (d, J = 12.5 Hz, 1H), 4.72 (d, J = 9.6 Hz, 1H), 5.05 (q, J = 6.9 Hz, 1H), 5.24 (q, J = 7.1 Hz, 1H), 4.82-4.90 (m, 2H), 7.23-7.30 (m, 3H), 7.37-7.55 (m, 5H). LCMS (m/z) 535.2 [M+H], Tr = 5.11 min.

EXAMPLE 7: (E)-(2R,5S,11S,14S,17R,18R)-18-Hydroxy-14-isopropyl-2,11,17-trimethyl-15-oxa-3,9,12,28-tetraaza-tricyclo[21.3.1.1*5,9*]octacosa-1(26),21,23(27),24-tetraene 4,10,13,16-tetraone – Compound 7



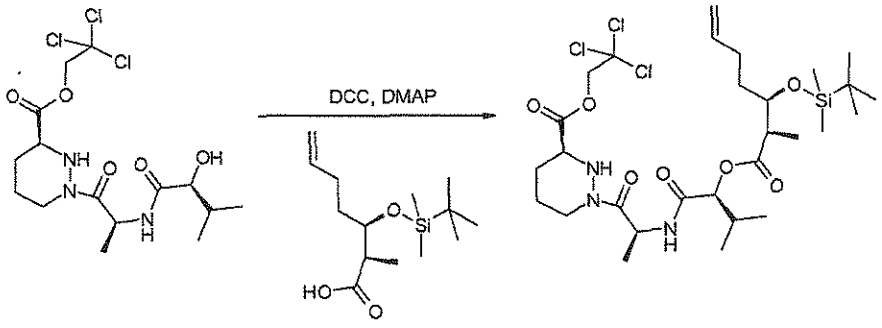
Compound 7a:

Synthesis of Compound 7a: A solution 1a (12.0 g, 0.034 mol) in anhydrous dichloromethane (520 mL) was cooled to 0°C before addition of pyridine (5.5 mL, 0.068 mol), then trifluoromethanesulfonic acid *tert*-butyldimethylsilyl ester (9 mL, 0.039 mol). The reaction was stirred at 0°C for 15 min then allowed to warm to room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (400 mL). The aqueous layer was back extracted with dichloromethane (200 mL). The organic layers were combined and washed with brine (200 mL) and then 2 M hydrochloric acid (200 mL). The solution was dried over sodium sulfate, filtered and evaporated to give the title product (15.29 g, 96%) as a white solid.



Compound 7b

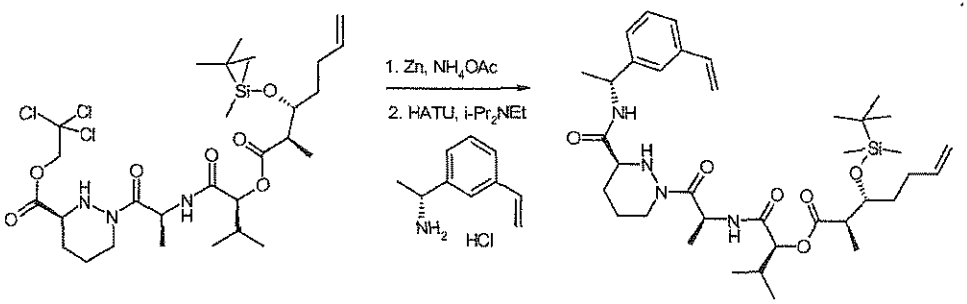
Synthesis of Compound 7b: A solution of 7a (15.29 g, 0.0325 mol) in tetrahydrofuran (300 mL) was prepared and an aqueous solution of lithium hydroxide (2 M, 120 mL) was added. The stirred mixture was heated to 60°C for 16 h. The reaction mixture was cooled to room temperature then treated with 2 M hydrochloric acid (250 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 200 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated to give an off-white solid. The solid was purified by silica gel chromatography using diethyl ether/*iso*-hexane 3:7 to yield the title product (7.18 g, 81%) as a colorless gum.



Compound 7c

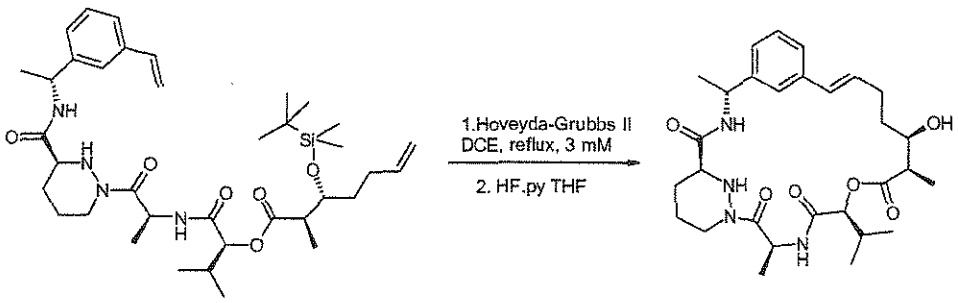
Synthesis of Compound 7c: To 1e (510 mg, 1.2 mmol) in anhydrous dichloromethane (4 mL) at room temperature and under an atmosphere of nitrogen was added 7b (385 mg, 1.41 mmol), dicyclohexylcarbodiimide (364 mg, 1.8 mmol) and 4-*N*,*N*-dimethylaminopyridine (142

mg, 1.2 mmol). The white suspension was stirred at room temperature for 20 h before adding silica gel and concentrating *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 2/1 to afford the title compound (700 mg, 86 %) as a viscous, clear oil.



Compound 7d

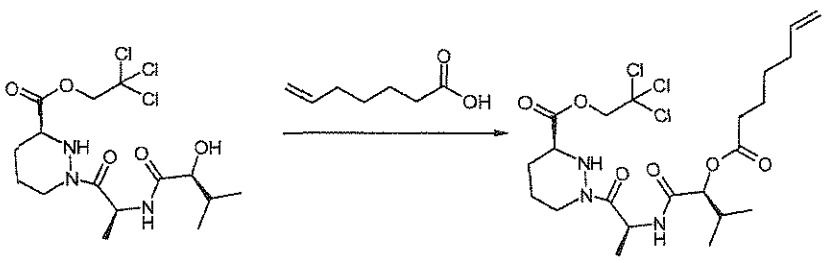
Synthesis of Compound 7d: To a solution of 7c (700 mg, 1.02 mmol) in tetrahydrofuran (22 mL) and water (13 mL) was added powdered zinc (1.46 g, 22.4 mmol) followed by ammonium acetate (1.2 g, 15.3 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction was filtered through Celite and concentrated *in vacuo* to remove the tetrahydrofuran. The ensuing solution was acidified to pH 1-2 with concentrated hydrochloric acid and extracted with dichloromethane (2 x). The organic layers were dried through a hydrophobic frit and concentrated *in vacuo*, followed by co-evaporation from toluene (2 x). The ensuing colorless viscous oil was dissolved in anhydrous acetonitrile (8 mL) and 1j (187 mg, 1.0 mmol) was added followed by *N,N*-diisopropylethylamine (900 µL, 5.1 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (542 mg, 1.4 mmol) The reaction mixture was stirred at room temperature for 15 h. Silica gel was added to the reaction mixture and concentrated *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1/1 to give the title compound (450 mg, 64%) as an off-white solid.



Compound 7

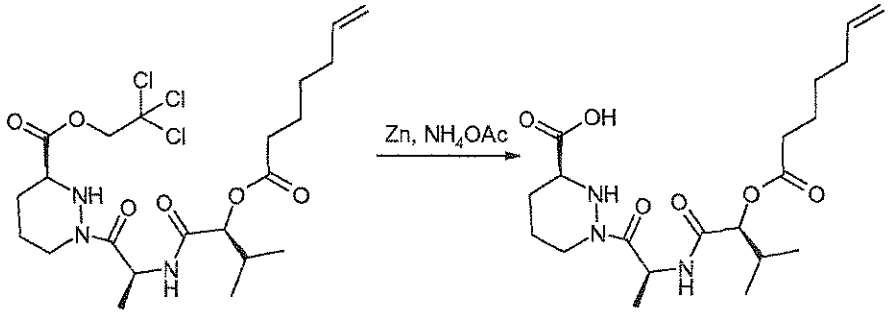
Synthesis of the title compound: A solution of 7d (450 mg, 0.66 mmol) in 1,2-dichloroethane (219 mL) was degassed with nitrogen for 15 min before adding Hoveyda Grubbs 2nd generation catalyst (41 mg, 0.07 mmol). The stirred solution was heated to 80°C for 2 h. The reaction was cooled, concentrated to approximately 20 mL, treated with silica gel and then evaporated to dryness. The residue was purified by silica gel chromatography using *iso*-hexane/ethyl acetate 1/1 then 1/3 to yield (E)-(2R,5S,11S,14S,17R,18R)-18-(*tert*-butyl-dimethyl-silanyloxy)-14-isopropyl-2,11,17-trimethyl-15-oxa-3,9,12,28-tetraaza-tricyclo[21.3.1.1*5,9*]octacosa-1(26),21,23(27),24-tetraene-4,10,13,16-tetraone (138 mg) as a brown foam. The foam (80 mg, 0.12 mmol) was dissolved in anhydrous tetrahydrofuran (6.5 mL) and transferred to a polypropylene vial. At ambient temperature hydrogen fluoride•pyridine (102 µL, 1.2 mmol) was added to the reaction mixture followed by stirring for 1 h. An additional amount of hydrogen fluoride•pyridine (600 µL, 7.1 mmol) was added, followed by stirring for 1 h. More hydrogen fluoride•pyridine (700 µL, 8.2 mmol) was added and after 1 h the reaction was quenched by the slow addition of the reaction mixture to a stirred solution of ethyl acetate/saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer further extracted with ethyl acetate (2 x). The combined organic layers were dried through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by silica gel chromatography using ethyl acetate/acetone 8/1 to afford the title compound (33 mg, 16%, 2 steps) as a white solid. ^{1}H NMR (500 MHz, CD_3CN) 0.92 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.26 (d, J = 7.3 Hz, 3H), 1.31 (d, J = 6.7 Hz, 3H), 1.41 (d, J = 6.7 Hz, 3H), 1.43-1.63 (m, 4H), 1.78-1.89 (m, 2H), 2.03-2.09 (m, 1H), 2.40-2.49 (m, 2H), 2.50-2.56 (m, 1H), 2.65-2.72 (m, 1H), 3.32 (td, J = 11.0, 2.4 Hz, 1H), 3.49-3.61 (m, 1H), 4.07 (d, J = 12.2 Hz, 1H), 4.31 (d, J = 12.8 Hz, 1H), 4.74 (d, J = 5.5 Hz, 1H), 4.97-5.04 (m, 1H), 5.18-5.25 (m, 1H), 6.27-6.34 (m, 1H), 6.38 (d, J = 15.9 Hz, 1H), 6.96-7.31 (m, 6H). LCMS (m/z) = 543.2 [M+H], Tr = 2.27 min.

EXAMPLE 8: (E)-(2R,5S,11S,14S)-14-Isopropyl-2,11-dimethyl-15-oxa-3,9,12,28-tetraaza-tricyclo[21.3.1.1*5,9*]octacosa-1(27),21,23,25-tetraene-4,10,13,16-tetraone - Compound 8



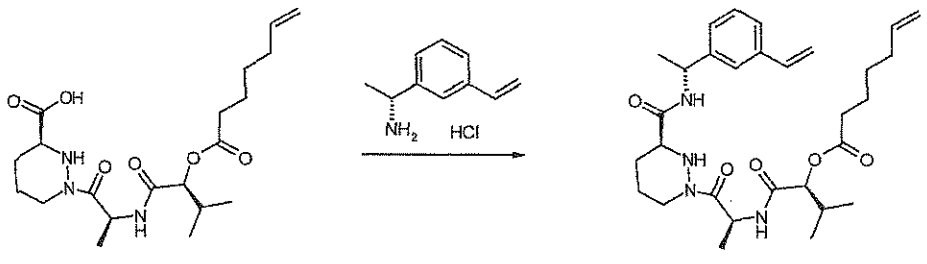
Compound 8a

Synthesis of Compound 8a: To a solution of 1e (791 mg, 1.83 mmol) in dichloromethane (9 mL) at room temperature, was added hept-6-enoic acid (0.296 mL, 2.19 mmol), *N,N'*-dicyclohexylcarbodiimide (564 mg, 2.74 mmol) and 4-*N,N*-dimethylaminopyridine (223 mg, 1.82 mmol) and the reaction mixture was stirred at room temperature for 2 h. After this time the reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous ammonium chloride solution. The aqueous phase was re-extracted with dichloromethane (2 x 50 mL) and the combined organics washed with brine (100 mL) and dried over magnesium sulfate and evaporated to give a white residue. The residue was purified by silica gel chromatography using a gradient of *iso*-hexane/ethyl acetate 1:1 to neat ethyl acetate to yield the title compound (774 mg, 81%).



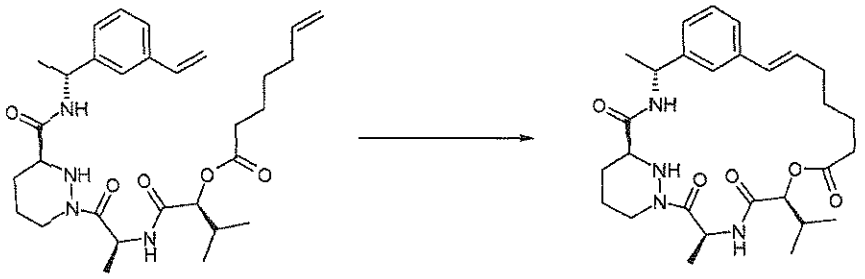
Compound 8b

Synthesis of Compound 8b: A solution of 8a (650 mg, 1.20 mmol) in tetrahydrofuran (29 mL) was prepared and powdered zinc (1.72 g, 26.3 mmol) was added followed by a solution of ammonium acetate (1.38 g, 18.0 mmol) in water (7.0 mL). The reaction mixture was stirred at room temperature for 72 h. The reaction was filtered through hyflo-supercel washing through with ethyl acetate and saturated aqueous potassium hydrogen sulfate. The mixture was treated with hydrochloric acid (1 M, 3 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, washed with brine, filtered and evaporated to give a colorless gum. The residue was azeotroped with toluene (3 x 100 mL) to give the title compound (492 mg, quantitative yield) as a white solid.



Compound 8c

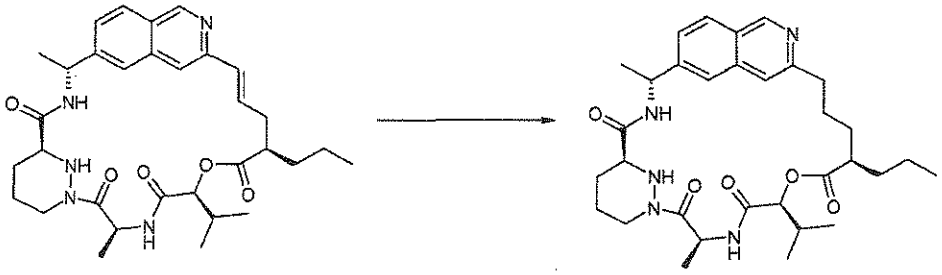
Synthesis of Compound 8c: To 8b (257 mg, 0.63 mmol) dissolved in acetonitrile (2 mL) was added 1j (122 mg, 0.83 mmol) followed by *N,N*-diisopropylethylamine (435 µL, 2.5 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (333 mg, 0.88 mmol). The reaction mixture was stirred at room temperature for 48 h. The mixture had evaporated to dryness over the 48 hours so this residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was separated and re-extracted with ethyl acetate (100 mL). The organic layers were combined, dried over magnesium sulfate, filtered and evaporated to give a crude residue. The residue was purified by silica gel chromatography using a gradient of *iso*-hexane/ethyl acetate 7:3 to 1:1 to neat ethyl acetate to give the title compound (194 mg, 57%).



Compound 8

Synthesis of the title compound: A solution of 8c (194 mg, 0.36 mmol) in 1,2-dichloroethane was degassed with nitrogen for 15 min then Hoveyda-Grubbs 2nd generation catalyst (23 mg, 0.04 mmol) was added and the reaction mixture heated at 80°C for 2.3 h. After this time the reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by silica gel chromatography using a gradient of *iso*-hexane/ethyl acetate 1:9 to neat ethyl acetate. Impure product (74 mg) was obtained which was further purified by preparatory reverse phase HPLC where the title compound was collected (28 mg, 15%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD). 0.96 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.41-1.51 (m, 8H), 1.59-1.82 (m, 4H), 1.85-1.96 (m, 2H), 2.02-2.26 (m, 3H), 2.32-2.57 (m, 2H), 2.80 (td, J = 12.9, 2.2 Hz, 1H), 3.50 (dd, J = 11.0, 2.5 Hz, 1H), 4.39 (*br* d, J = 13.2 Hz, 1H), 4.76 (d, J = 8.0 Hz, 1H), 4.99 (q, J = 6.9 Hz, 1H), 5.46 (q, J = 7.1 Hz, 1H), 6.19 (m, 1H), 6.40 (d, J = 15.8 Hz, 1H), 7.11-7.17 (m, 1H), 7.20-7.30 (m, 3H). LCMS (m/z) 513.2 [M+H], Tr = 2.58 min.

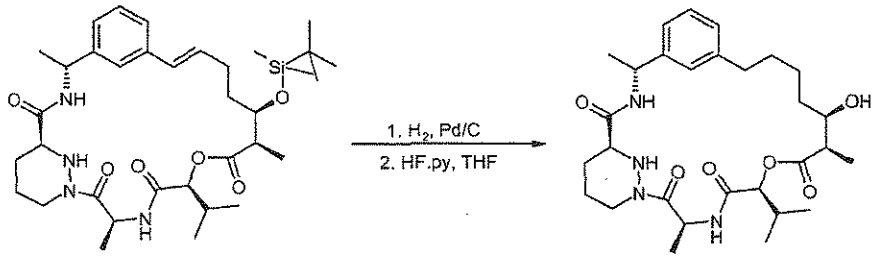
EXAMPLE 9 - Compound 9



Compound 9

To a solution of compound 4 (16.6 mg, 0.0287 mmol) in ethyl acetate (10 mL) was added 10% palladium on carbon (5 mg) and stirred under a hydrogen atmosphere for 1.5 h. Then additional 10% palladium on carbon (5 mg) was added and stirring continued under a hydrogen atmosphere for 24 h. The reaction mixture was filtered through Celite to remove the catalyst and evaporated then purified by preparatory reverse phase preparative HPLC to yield the title compound (5.3 mg, 32%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) 0.89-1.05 (m, 9H), 1.29-1.46 (m, 2H), 1.59 (dd, *J* = 7.1, 1.6 Hz, 6H), 1.65-1.99 (m, 7H), 2.09-2.18 (m, 1H), 2.43-2.58 (m, 1H), 2.74-3.06 (m, 3H), 3.57-3.68 (m, 1H), 4.43 (dd, *J* = 13.4, 2.7 Hz, 1H), 4.59 (*br* s, 3H), 4.66 (d, *J* = 7.4 Hz, 1H), 5.15 (q, *J* = 6.9 Hz, 1H), 5.66-5.78 (m, 1H), 7.58 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.69 (s, 1H), 7.70 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 8.40 (*br* d, *J* = 8.7 Hz, 1H), 9.08 (s, 1H). LCMS (m/z) 580.3 [M+H], Tr = 1.53 min.

EXAMPLE 10: (2R,5S,11S,14S,17R,18R)-18-Hydroxy-14-isopropyl-2,11,17-trimethyl-15-oxa-3,9,12,28-tetraaza-tricyclo[21.3.1.1*5,9*]octacosa-1(26),23(27),24-triene-4,10,13,16-tetraone - Compound 10

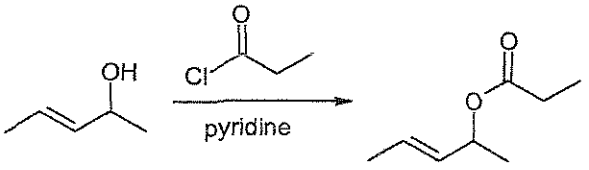


Compound 10

To (E)-(2R,5S,11S,14S,17R,18R)-18-(*tert*-butyl-dimethyl-silanyloxy)-14-isopropyl-2,11,17-trimethyl-15-oxa-3,9,12,28-tetraaza-tricyclo[21.3.1.1*5,9*]octacosa-1(26),21,23(27),24-tetraene-4,10,13,16-tetraone (50 mg, 0.08 mmol) in ethyl acetate (10 mL) at room temperature was added 10% palladium on carbon (50 mg). The system was purged with hydrogen gas and stirred vigorously for 16 h. The reaction mixture was filtered through Celite and the filter pad

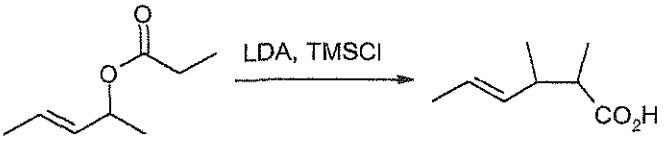
washed with methanol. The filtrate was concentrated *in vacuo*. The ensuing residue was dissolved in anhydrous tetrahydrofuran (5 mL) and transferred to a polypropylene vial. At room temperature hydrogen fluoride•pyridine (1.3 mL, 15.2 mmol) was added to the reaction mixture followed by stirring for 3 h. The reaction was diluted with ethyl acetate and quenched by cautious addition of saturated aqueous ammonium chloride. The organic layer was separated, dried through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by silica gel chromatography using ethyl acetate/acetone 5/1 to afford the title compound as a white solid. This was further purified by triturating with diethyl ether, filtering and drying the solid *in vacuo* (20 mg, 48 %, 2 steps). ^{1}H NMR (300 MHz, CD_3CN) 0.90-1.00 (m, 6H), 1.24-1.30 (m, 6H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.32-2.08 (m, 11H), 2.45-2.81 (m, 4H), 3.23-3.36 (m, 1H), 3.47-3.59 (m, 1H), 3.67 (d, *J* = 10.3 Hz, 1H), 4.02 (d, *J* = 11.8 Hz, 1H), 4.29 (d, *J* = 13.8 Hz, 1H), 4.75 (d, *J* = 5.4 Hz, 1H), 4.95-5.08 (m, 1H), 5.16-5.29 (m, 1H), 7.03-7.29 (m, 6H). LCMS (m/z) = 545.3 [M+H], Tr = 2.15 min.

EXAMPLE 11 - Compound 11



Compound 11a

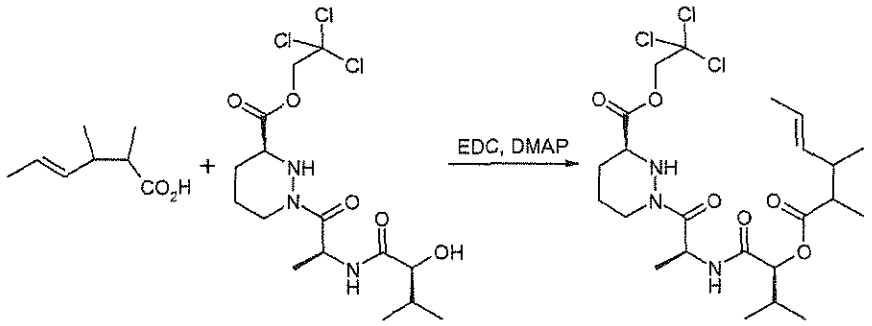
Synthesis of Compound 11a: A cooled (0°C) solution of (E)-pent-3-en-2-ol (1.024 g, 11.887 mmol) in dichloromethane (30 mL) was subsequently treated with pyridine (1.222 g, 1.3 mL, 15.452 mmol) and propionyl chloride (1.430 g, 1.3 mL, 15.452 mmol). After stirring for 1.5 h at 0°C the reaction was quenched with saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane and then the organics were combined, filtered through a phase separator and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexane/Et_2O 1:0 to 9:1 to afford the title compound (787 mg, 46%) as a colorless oil.



Compound 11b:

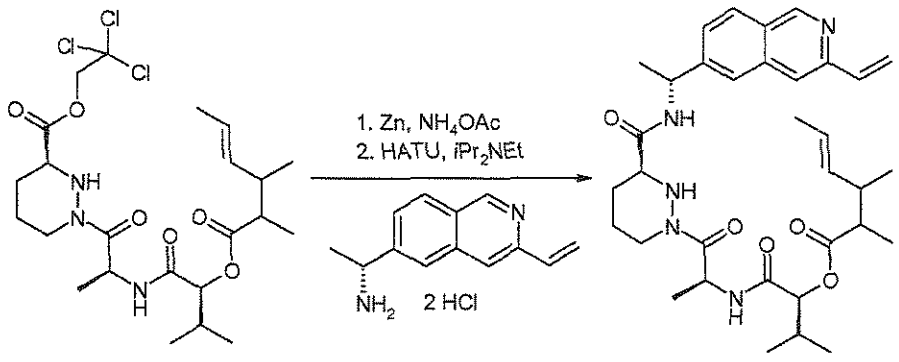
Synthesis of Compound 11b: A cooled (0°C) solution of *N,N*-diisopropylamine (672.0 mg, 930 µL, 6.641 mmol) in tetrahydrofuran (15 mL) was treated with *n*-butyl lithium (2.5 M in hexanes, 2.4 mL, 6.088 mmol). After stirring at 0°C for 20 min this solution was cooled to -78°C

and subsequently treated with chlorotrimethylsilane (841.7 mg, 990 µL, 7.748 mmol) and a solution of 11a (787.0 mg, 5.534 mmol) in tetrahydrofuran (10 mL). The reaction mixture was slowly warmed to room temperature. After 16 h, the reaction was quenched with 1 M hydrochloric acid (40 mL) and the pH was adjusted to 2 with 2 M hydrochloric acid. The aqueous layer was extracted with ethyl acetate (2 x 40 mL), the organics were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexane/ethyl acetate 1:0 to 4:1 to afford the title compound (375 mg, 48%) as a colorless oil.



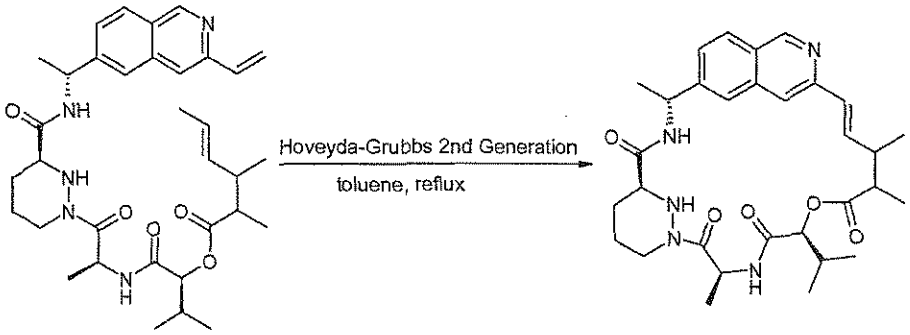
Compound 11c

Synthesis of Compound 11c: Compound 11c was prepared in the same manner as Compound 1f using 11b and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride instead of 1c and *N,N'*-dicyclohexyl carbodiimide in 60% yield.



Compound 11d

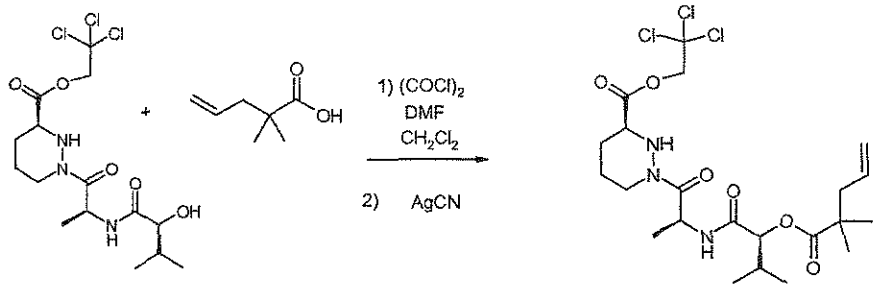
Synthesis of Compound 11d: Compound 11d was prepared in the same manner as compound 1k, by first using 11c instead of 1f in the preparation of 1g and then, using (R)-1-(3-vinyl-isoquinolin-6-yl)-ethylamine dihydrochloride instead of (R)-1-(3-vinyl-phenyl)-ethylamine hydrochloride following the procedure described for the synthesis of 1k from 1g, in 81% yield.



Compound 11

Synthesis of the title compound: Compound 11 was prepared in the same manner as compound 1 using 11d instead of 1k and using toluene instead of dichloroethane in 8% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 0.97-1.07 (m, 7H), 1.25 (d, J = 7.1 Hz, 3H), 1.31 (d, J = 7.1 Hz, 3H), 1.55-1.63 (m, 6H), 1.65-1.78 (m, 1H), 1.83-2.00 (m, 3H), 2.14 (*app* sextet, J = 6.7 Hz, 1H), 2.69-2.79 (m, 1H), 2.80-2.90 (m, 1H), 3.65 (*app* t, J = 8.0 Hz, 1H), 4.45 (*br* d, J = 13.6 Hz, 1H), 4.78 (dd, J = 6.0, 19.6 Hz, 2H), 5.15 (*app* pentet, J = 6.2 Hz, 1H), 5.83 (dq, J = 7.1, 19.9 Hz, 1H), 6.65 (dd, J = 6.7, 17.2 Hz, 1H), 6.79-6.93 (m, 1H), 7.53-7.61 (m, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.96 (d, J = 4.7 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 9.10 (s, 1H). LCMS (m/z) 564.1 [M+H], 596.1 [M+Na], Tr = 3.73 min.

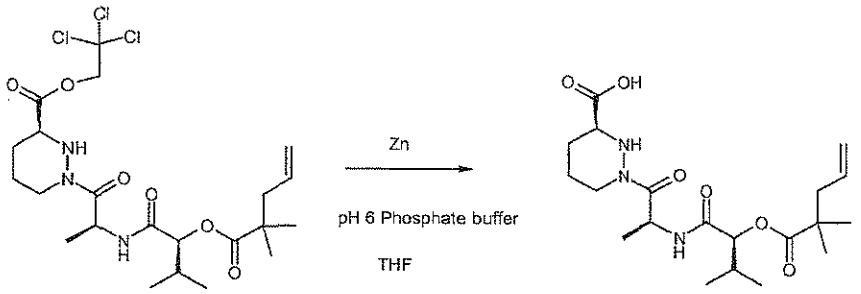
EXAMPLE 12 - Compound 12



Compound 12a

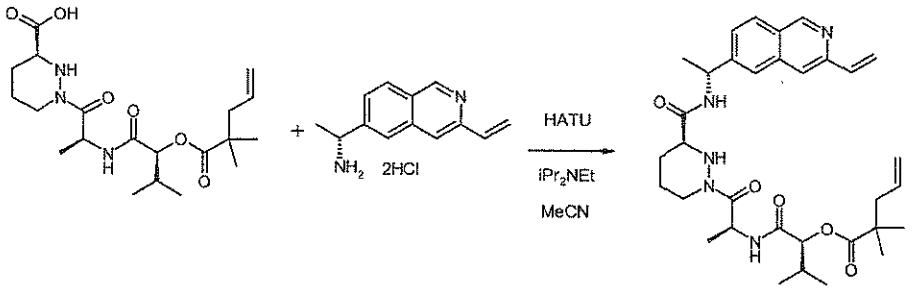
Synthesis of Compound 12a: A solution of 2,2-dimethyl-4-pentenoic acid (202 mg, 1.58 mmol) in dichloromethane (5 mL) was prepared and oxalyl chloride (411 µL, 4.74mmol) was added followed by dimethylformamide (5 µL). The mixture effervesced vigorously and was stirred at room temperature for 1 h before evaporating to give a solid (241mg). The solid was dissolved in toluene (10 mL) and 1e (433 mg, 1.0 mmol) was added followed by silver cyanide (310 mg, 2.25 mmol). The flask was covered with foil to exclude light, before heating to 80°C for 10 min. It was left at room temperature overnight. The reaction was heated to 80°C for a further 4.5 h then allowed to cool. It was filtered and evaporated to give a pale yellow gum. The

gum was purified by silica gel chromatography using ethyl acetate/*iso*-hexane 1:3 then ethyl acetate/*iso*-hexane 1:1 to yield the title compound (200 mg, 37%) as a colorless oil.



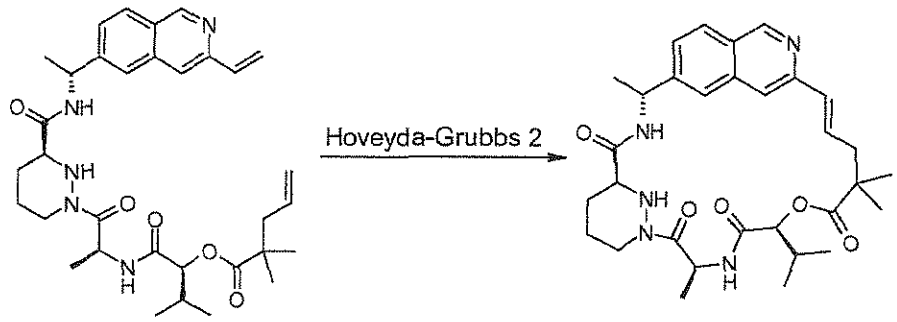
Compound 12b

Synthesis of Compound 12b: A solution of 12a (100 mg, 0.184 mmol) in tetrahydrofuran (10 mL) was prepared and zinc powder (360 mg, 5.52 mmol) was added, followed by pH 6 phosphate buffer (1 M, 2 mL). The reaction was stirred at room temperature for 18 h and further zinc powder (120 mg, 1.84 mmol) was added. The reaction was stirred at room temperature for a further 48 h. The reaction mixture was filtered to remove a suspended solid. The solid was washed with tetrahydrofuran (15 mL) and pH 6 buffer (5 mL) and this was added to the filtrate. The solution was evaporated and the residue purified by C18 chromatography using a gradient acetonitrile/water 0:1 to 1:3 to 1:1. This yielded the title product (69 mg, 91%) as a colorless oil.



Compound 12c

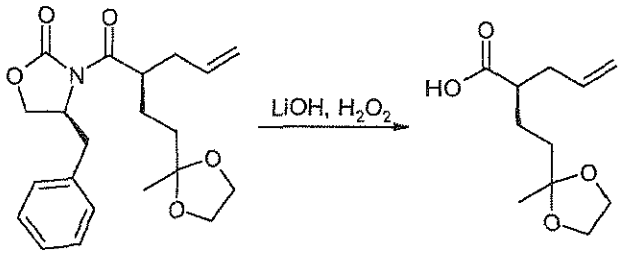
Synthesis of Compound 12c: A solution of 12b (94 mg, 0.23 mmol) in anhydrous acetonitrile (5 mL) was prepared and cooled to 0°C before adding 2j (54 mg, 0.23 mmol.), *N,N*-diisopropylethylamine (160 µL, 0.92 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium (122 mg, 0.32 mmol). The reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was evaporated onto silica gel and purified by silica gel chromatography using ethyl acetate to give the title product (119 mg, 87%) as a colorless solid.



Compound 12

Synthesis of the title compound: A solution of 12c (119 mg, 0.20 mmol) in toluene (65 mL) was prepared and Hoveyda-Grubbs 2nd generation catalyst (12.5 mg, 0.02 mmol) was added. The reaction mixture was heated to 110°C under a nitrogen atmosphere for 2 h. A further quantity of Hoveyda-Grubbs 2nd generation catalyst (6 mg, 0.01 mmol) was added and the reaction was stirred at 110°C for a further 1 h. The reaction mixture was cooled to room temperature then filtered, before adsorbing onto silica gel. The material was purified by silica gel chromatography using a gradient of ethyl acetate/acetone 1:0 to 9:1. The resultant gum was triturated with diethyl ether and dried under vacuum to yield a white solid (29 mg). This solid was further purified by preparatory reverse phase preparative HPLC to yield the title product (17 mg, 15%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) 1.08 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.18 (s, 3H), 1.38 (s, 3H), 1.59 (d, J = 3.3 Hz, 3H), 1.61 (d, J = 3.1 Hz, 3H), 1.83-2.00 (m, 3H), 2.32-2.43 (m, 1H), 2.75-2.82 (m, 2H), 3.60-3.70 (m, 1H), 4.40-4.50 (m, 1H), 5.15 (q, J = 6.9 Hz, 1H), 6.65 (d, J = 16.3 Hz, 1H), 7.57 (dd, J = 8.5,1.6 Hz, 1H), 7.70 (s, 1H), 8.00 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 9.10 (s, 1H). LCMS (m/z) 564.1 [M+H], Tr = 3.57 min.

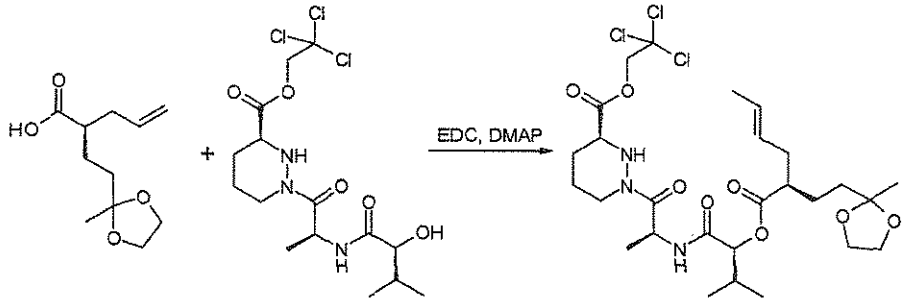
EXAMPLE 13 - Compound 13



Compound 13a

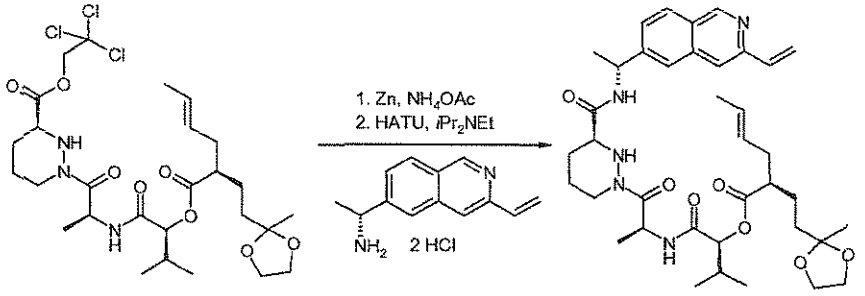
Synthesis of Compound 13a: A cooled (0°C) solution of (S)-4-benzyl-3-{(R)-2-[2-(2-methyl-[1,3]dioxolan-2-yl)-ethyl]-pent-4-enoyl}-oxazolidin-2-one (939.7 mg, 2.516 mmol) as prepared in WO 2001/024797 in tetrahydrofuran/water (45 mL, 2:1) was subsequently treated with hydrogen peroxide (30% in water, 1.3 mL, 12.580 mmol) and lithium hydroxide (211.1 mg, 5.032 mmol). After 2.5 h at 0°C, the reaction was quenched with sodium hydrogen sulphite (1.4

g). After 0.5 h, the volatiles were removed *in vacuo* and the residue diluted with water. The aqueous layer was extracted with dichloromethane (2 x) then acidified to pH ~2 and extracted with dichloromethane (3 x). These last organics were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to provide the title compound (538 mg, quant.) as a colorless oil.



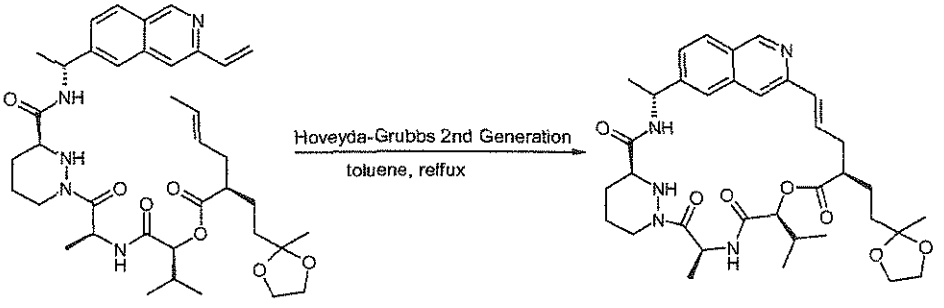
Compound 13b

Synthesis of Compound 13b: Compound 13b was prepared in the same manner as compound 1f using 13a and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride instead of 1c and *N,N'*-dicyclohexyl carbodiimide in 58% yield.



Compound 13c

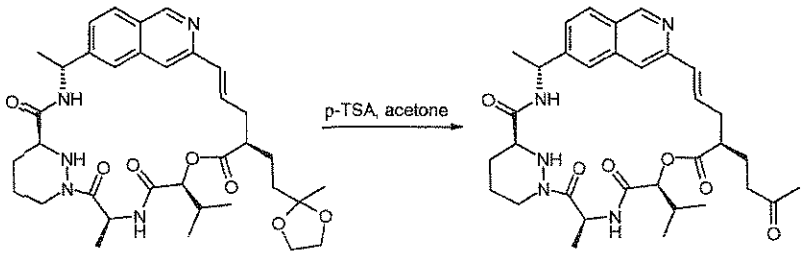
Synthesis of Compound 13c: Compound 13c was prepared in the same manner as Compound 1k, by first using 13b instead of 1f in the synthesis of 1g, and then using (R)-1-(3-vinyl-isoquinolin-6-yl)-ethylamine dihydrochloride instead of (R)-1-(3-vinyl-phenyl)-ethylamine hydrochloride following the procedure described for the synthesis of 1k from 1g, in 73% yield .



Compound 13

Synthesis of the title compound: Compound 13 was prepared in the same manner as compound 1 using 13c instead of 1k and using toluene instead of dichloroethane in 32% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 0.88-1.00 (m, 1H), 1.06 (2d, J = 6.9 Hz, 6H), 1.22-1.42 (m, 4H), 1.52-1.63 (m, 7H), 1.65-1.81 (m, 3H), 1.84-1.99 (m, 3H), 2.16 (*app* pentet, J = 6.9 Hz, 1H), 2.38-2.50 (m, 1H), 2.51-2.61 (m, 1H), 2.62-2.74 (m, 1H), 2.83 (dt, J = 2.7, 13.8 Hz, 1H), 3.59-3.72 (m, 1H), 4.46 (*br* dd, J = 3.3, 13.6 Hz, 1H), 4.69-4.79 (m, 4H), 5.16 (q, J = 7.1 Hz, 1H), 5.89 (q, J = 6.9 Hz, 1H), 6.71 (d, J = 16.3 Hz, 1H), 6.84-6.98 (m, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.71 (s, 1H), 7.96 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 9.10 (s, 1H). LCMS (m/z) 651.2 [M+H], Tr = 3.68 min.

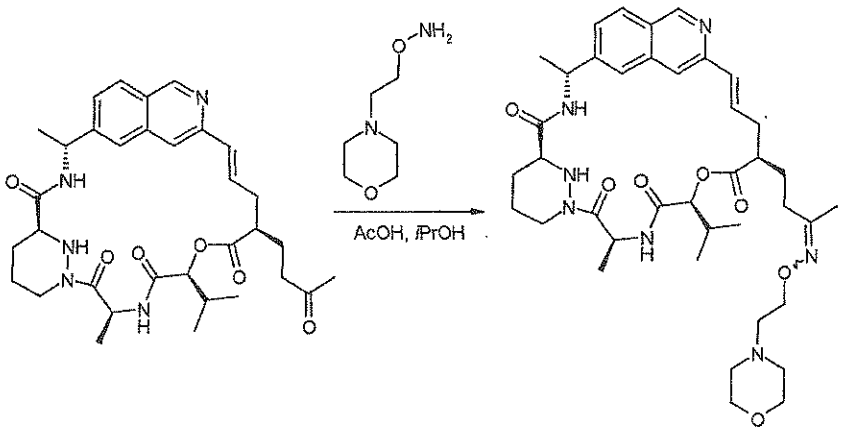
EXAMPLE 14 - Compound 14



Compound 14

A solution of 13 (183.7 mg, 0.282 mmol) in acetone (10 mL) was treated with *para*-toluene sulfonic acid (27 mg, 0.141 mmol). After stirring at room temperature for 2.5 h, the reaction was quenched with a saturated solution of sodium bicarbonate and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). Organics were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Isolute cartridge eluted with a continuous gradient of *iso*-hexane/acetone 1:0 to 2:3 and then triturated with *iso*-hexane/acetone to provide the title compound (49.3 mg, 28%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) 1.04 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 1.53-1.62 (m, 7H), 1.64-1.79 (m, 1H), 1.84-2.03 (m, 5H), 2.10-2.23 (m, 4H), 2.39-2.53 (m, 1H), 2.54-2.73 (m, 4H), 2.82 (dt, J = 2.9, 13.1 Hz, 1H), 3.59-3.70 (m, 1H), 4.46 (*br* dd, J = 4.0, 12.7 Hz, 1H), 5.17 (q, J = 6.9 Hz, 1H), 5.91 (, J = 7.1 Hz, 1H), 6.71 (d, J = 16.3 Hz, 1H), 6.86-7.00 (m, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.71 (s, 1H), 7.98 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 9.10 (s, 1H). LCMS (m/z) 606.1 [M+H], Tr = 3.26 min.

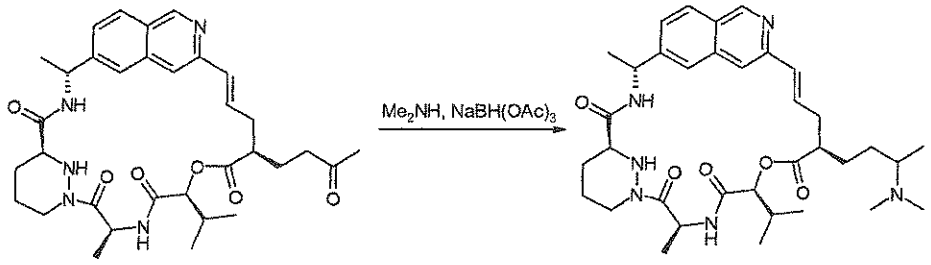
EXAMPLE 15 - Compound 15



Compound 15

A stock solution of O-(2-morpholin-4-yl-ethyl)-hydroxylamine (18 mg, 0.125 mmol) and acetic acid (a drop) in 2 mL isopropanol was prepared. To solid Compound 14 (16.4 mg, 0.027 mmol) was added 1 mL of the stock solution and after stirring at room temperature for 18 h the compound was purified by reverse phase HPLC to provide a mixture of geometric isomers of the oxime (1:1, 13.3 mg, 67%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) 1.00-1.10 (m, 6H), 1.54-1.64 (m, 5H), 1.65-1.78 (m, 1H), 1.81-2.04 (m, 8H), 2.09-2.22 (m, 1H), 2.23-2.33 (m, 1H), 2.34-2.90 (m, 12H), 3.53-3.76 (m, 6H), 4.18 (dt, *J* = 5.8, 8.5 Hz, 2H), 4.41-4.51 (m, 1H), 4.68-4.82 (m, 2H), 5.16 (q, *J* = 7.3 Hz, 1H), 5.82-5.96 (m, 1H), 6.71 (d, *J* = 15.8 Hz, 1H), 6.84-7.00 (m, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.71 (s, 1H), 7.98 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 8.53 (*br* dd, *J* = 3.1, 9.4 Hz, 1H), 9.10 (s, 1H). LCMS (m/z) 734.7 [M+H], Tr = 1.08 min.

EXAMPLE 16 - Compound 16

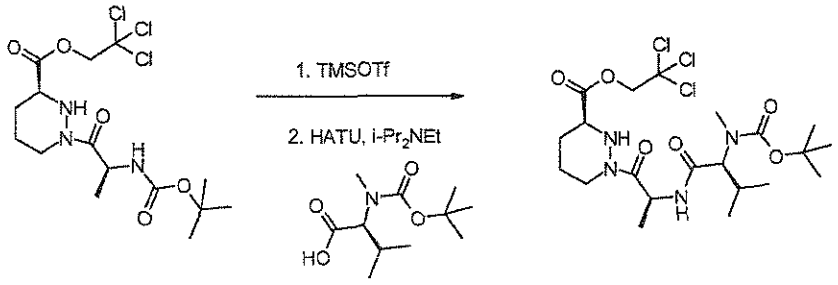


Compound 16

A solution of sodium triacetoxyborohydride (203.5 mg, 0.96 mmol) in methanol (1 mL) and acetic acid (100 µL) was subsequently treated with a 2 M solution of dimethylamine in methanol (480 µL, 0.96 mmol) and compound 14 (5.8 mg, 0.0096 mmol). After stirring for a month at room temperature, the reaction mixture was directly loaded onto the reverse phase preparative HPLC which was eluted with a gradient of water/CH_3CN 95:5 to 0:100. This

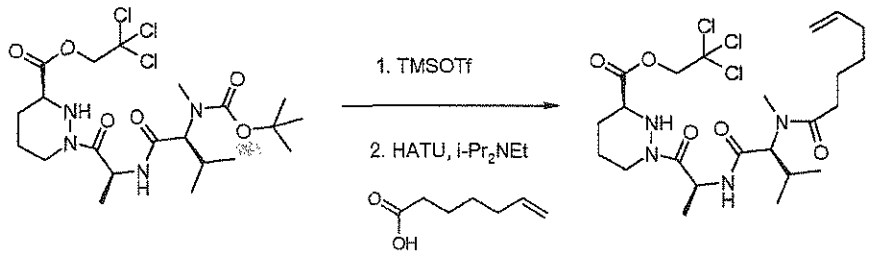
provided the title compound (1.1 mg, 18%) as a white solid and as a 1:1 mixture of diastereomers. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87-0.97 (m, 1H), 1.01-1.09 (m, 6H), 1.24 (d, J = 6.4 Hz, 3H), 1.55-1.63 (m, 6H), 1.64-1.80 (m, 2H), 1.84-2.02 (m, 4H), 2.10-2.24 (m, 1H), 2.41-2.72 (m, 7H), 2.73-2.90 (m, 3H), 3.60-3.69 (m, 1H), 4.41-4.51 (m, 1H), 5.17 (q, J = 7.1 Hz, 1H), 5.85-5.95 (m, 1H), 6.71 (d, J = 16.0 Hz, 1H), 6.85-6.99 (m, 1H), 7.56-7.63 (m, 1H), 7.71 (s, 1H), 7.98 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 9.06-9.13 (m, 1H). LCMS (m/z) 635.0 [M+H], Tr = 0.94 min.

Example 17: (E)-(2R,5S,11S,14S)-14-Isopropyl-2,11,15-trimethyl-3,9,12,15,28-pentaaza-tricyclo[21.3.1.1*5,9*]octacosa-1(27),21,23,25-tetraene-4,10,13,16-tetraone - Compound 17



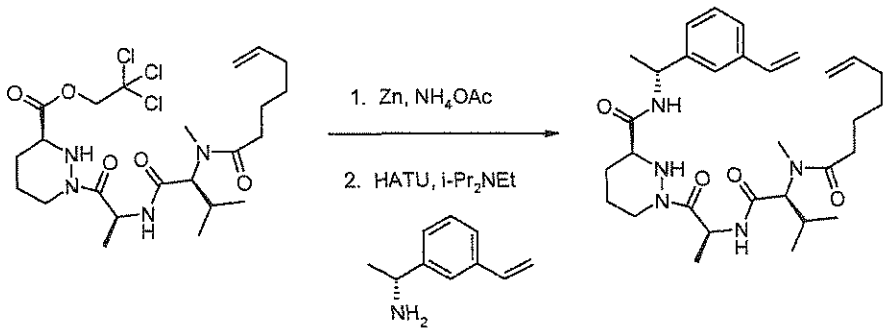
Compound 17a

Synthesis of Compound 17a: A solution of 1d (1.08 g, 2.5 mmol) in dichloromethane (35 mL) was stirred at 0°C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (682 mg, 0.55 mL, 3.1 mmol) was added and the reaction mixture was stirred at 0°C for 45 minutes. *N,N*-diisopropylethylamine (1.29 g, 1.73 mL, 10 mmol) was added and the solvent was evaporated to afford crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (2.5 mmol), which was used in the next step. A solution of crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (2.5 mmol) in acetonitrile (30 mL) was stirred at 0°C under nitrogen. (S)-2-(*tert*-Butoxycarbonyl-methyl-amino)-3-methyl-butyric acid (635 mg, 2.75 mmol) and *N,N-d*iisopropylethylamine (1.29 g, 1.7 mL, 10 mmol) was added followed by 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (1.33 g, 3.5 mmol) and the reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with water, 2 M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, water and brine, and then dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso-h*exane/ethyl acetate 1:1 to neat ethyl acetate to afford the title compound (950 mg, 70%) as a white solid.



Compound 17b

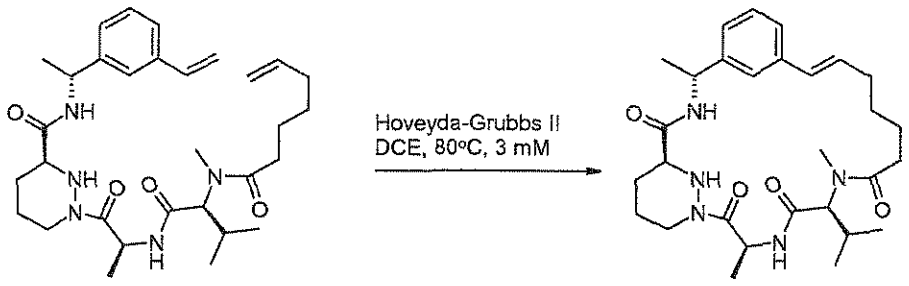
Synthesis of Compound 17b: A solution of 17a (950 mg, 1.74 mmol) in dichloromethane (25 mL) was stirred at 0°C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (577 mg, 0.47 mL, 2.6 mmol) was added and the reaction mixture was stirred at 0°C for 1 h. Additional trimethylsilyl trifluoromethanesulfonate (0.2 mL, 1.1 mmol) was added and the reaction mixture was stirred at 0°C for 2 h. *N,N*-diisopropylethylamine (903 mg, 1.2 mL, 7 mmol) was added and the solvent was evaporated and the residue was dried to afford crude (S)-1-[(S)-2-((S)-3-methyl-2-methylamino-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (1.74 mmol), which was used in the next step. A solution of crude (S)-1-[(S)-2-((S)-3-methyl-2-methylamino-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (1.74 mmol) in acetonitrile (20 mL) was stirred at 0°C under nitrogen. Hept-6-enoic acid (268 mg, 0.3 mL, 2.1 mmol) and *N,N-d*iisopropylethylamine (903 mg, 1.2 mL, 7 mmol) were added. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (912 mg, 2.4 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated and the residue was diluted with ethyl acetate. The solution was washed with saturated sodium hydrogen carbonate solution, water, 2 M hydrochloric acid, water and brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso-h*exane/ethyl acetate 3:1 to 1:1 to afford the title compound (710 mg, 74%) as a white solid.



Compound 17c

Synthesis of Compound 17c: A solution of 17b (710 mg, 1.3 mmol) in tetrahydrofuran (30 mL) was stirred at room temperature under nitrogen. Zinc dust (1.86 g, 28.6 mmol) was

added followed by a solution of ammonium acetate (1.50 g, 19.5 mmol) in water (20 mL) and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was filtered through Celite and the filter pad was washed with ethyl acetate and potassium hydrogen sulfate solution (pH ~2). The filtrate was acidified to pH 2 with 2 M hydrochloric acid and the mixture was extracted with ethyl acetate. The organic extracts were combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was co-evaporated with toluene and dried to afford (S)-1-{(S)-2-[(S)-2-(hept-6-enoyl-methyl-amino)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid (468 mg, 85%) as a gum. A solution of (S)-1-{(S)-2-[(S)-2-(hept-6-enoyl-methyl-amino)-3-methyl-butyrylamino]propionyl}-hexahydropyridazine-3-carboxylic acid (468 mg, 1.1 mmol) in acetonitrile (25 mL) was stirred at room temperature under nitrogen. 1j (200 mg, 1.1 mmol) and *N,N*-diisopropylethylamine (710 mg, 1.0 mL, 5.5 mmol) was added followed by 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (585 mg, 1.54 mmol) and the reaction mixture was stirred at room temperature for 72 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with 2 M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexane/ethyl acetate 1:1 to ethyl acetate to afford the title compound as a white solid (300 mg, 49%).

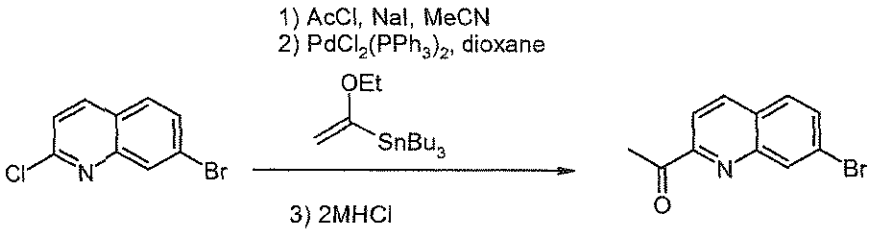


Compound 17

Synthesis of the title compound: A solution of 17c (276 mg, 0.5 mmol) in 1,2-dichloroethane (150 mL) was stirred at room temperature under nitrogen. Hoveyda-Grubbs 2nd generation catalyst (32 mg, 0.05 mmol) was added and the reaction mixture was heated at 80°C under nitrogen for 3 hours. The reaction mixture was cooled to room temperature, silica gel was added and the reaction mixture was evaporated. The residue was purified by silica gel chromatography using a gradient of ethyl acetate to ethyl acetate/acetone 7:3. The residue was triturated with ether and the resulting solid was collected, washed with ether and dried to afford the title compound (112 mg, 43%) as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 0.82 (d, J =

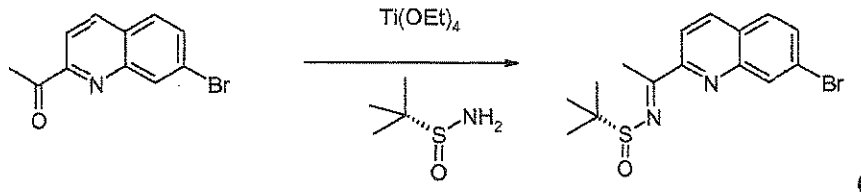
6.7 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 1.34 (d, *J* = 7.1 Hz, 3H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.40-1.90 (m, 10H), 2.60-2.75 (m, 2H), 2.86-2.92 (m, 4H), 3.28-3.36 (m, 1H), 3.93 (d, *J* = 12.0 Hz, 1H), 4.33-4.38 (m, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.85-4.99 (m, 2H), 6.16-6.51 (m, 3H), 7.12-7.30 (m, 6H). LCMS (m/z) 526.3 [M+H], Tr = 2.16 min.

EXAMPLE 18 - Compound 18



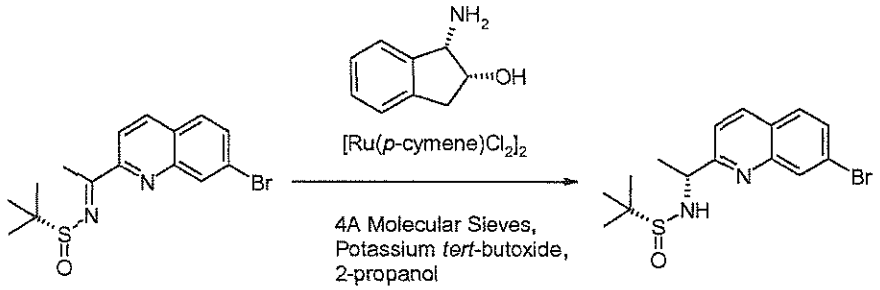
Compound 18a

Synthesis of Compound 18a: To a stirred slurry of 7-bromo-2-chloro-quinoline (Fluorochem, 8.10g, 33.4 mmol) and sodium iodide (50.0g, 334 mmol) in acetonitrile (27 mL) was added acetyl chloride (3.56 mL, 50.0 mmol) slowly. The flask was stoppered, sealed and heated at 80°C for 3 h before being allowed to cool. The mixture was treated sequentially with 10% w/w aqueous potassium carbonate solution (80 mL), 5% w/w aqueous sodium sulfite solution (80 mL) and saturated aqueous sodium thosulfate solution (80 mL) and the mixture extracted with dichloromethane (2 x). The combined organic extracts were dried over sodium sulfate, filtered and evaporated to give a crude 7-bromo-2-iodo-quinoline. To the quinoline was added tributyl(1-ethoxyvinyl)stannane (13.6 mL, 40.1 mmol), 1,4-dioxane (67 mL) and bis(triphenylphosphine)palladium(II) dichloride (2.37 g, 3.34 mmol) and the reaction mixture heated at 100°C for 5 h before being allowed to cool. 2 M aqueous hydrochloric acid (67 mL) was added and the reaction stirred for 1 h. The mixture was filtered and the solids washed with ethyl acetate and the filtrate evaporated to remove organics. The residue was extracted with ethyl acetate (3 x) and the combined organic extracts were dried over sodium sulfate, filtered and evaporated. The product was purified on silica gel doped with 10% w/w potassium carbonate, eluting with a gradient of 0 to 6% ethyl acetate in *iso*-hexanes to afford the title compound (5.5 g, 66%) as a white solid.



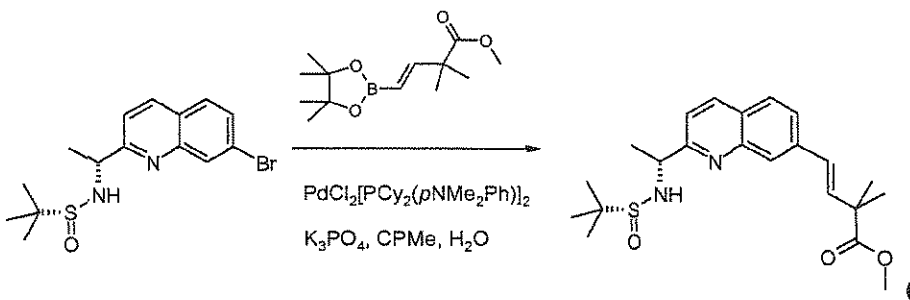
Compound 18b

Synthesis of Compound 18b: To a solution of 18a (1.42 g, 5.68 mmol) in tetrahydrofuran (28 mL) was added titanium (IV) ethoxide (2.6 g, 2.35 mL, 11.4 mmol) followed by (R)-(+)-2-methyl-propanesulfinimide (825 mg, 6.82 mmol). The reaction mixture was stirred at 60°C under nitrogen for 6 h and allowed to cool. Brine was added followed by ethyl acetate and the suspension filtered through celite and the filter pad was washed with ethyl acetate. The ethyl acetate layer was separated, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography eluting with 10-25% ethyl acetate in *iso*-hexanes to afford the title compound (448 mg, 22%).



Compound 18c

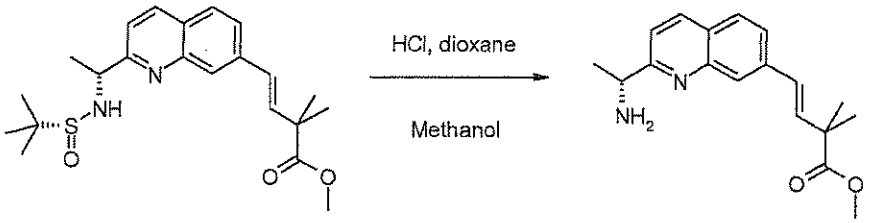
Synthesis of Compound 18c: A mixture of (1S, 2R)-(-)-*cis*-1-amino-2-indanol (19 mg, 0.13 mmol), $[Ru(p\text{-cymen})Cl_2]_2$ (39mg, 0.064 mmol) and powdered 4 Å molecular sieves (0.7 g) was suspended in anhydrous 2-propanol (3 mL) and stirred under nitrogen. The suspension was heated at 90°C for 30 min. The reaction mixture was cooled to 40°C and a solution of 18b (448 mg, 1.27 mmol) in 2-propanol (9 mL) was added followed by a solution of potassium *tert*-butoxide (36 mg, 0.32 mmol) in 2-propanol (3 mL). The reaction mixture was stirred for 2 h at 40°C and then allowed to cool. The mixture was poured directly onto a silica gel cartridge and eluted with ethyl acetate. After concentration the residue was further purified on silica eluting with ethyl acetate in *iso*-hexanes (1:1 to 1:0) to afford the title compound (287 mg, 64%).



Compound 18d

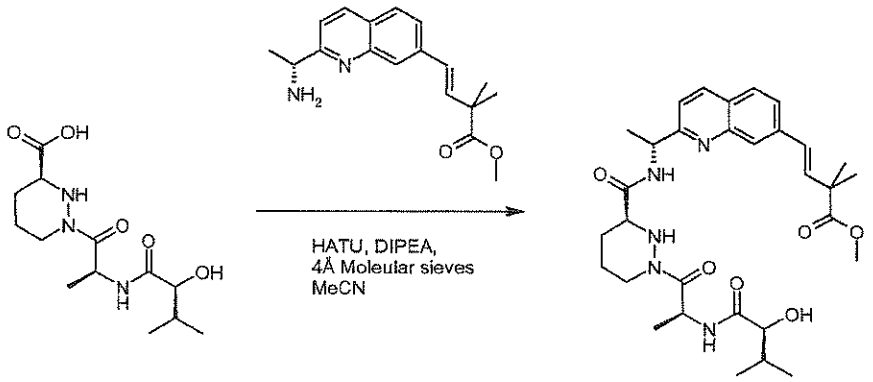
Synthesis of Compound 18d: A mixture of 18c (207 mg, 0.583 mmol), (E)-2,2-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-3-enoic acid methyl ester (170 mg, 0.670 mmol), bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine] palladium(II) chloride (24 mg,

0.029 mmol) and potassium phosphate tribasic (371 mg, 1.75 mmol) was suspended in cyclopentylmethyl ether (3 mL) and water (1.5 mL) and the mixture stirred and heated at 80°C under nitrogen for 5 h. The reaction mixture was allowed to cool and diluted with ethyl acetate and water. The aqueous layer was separated and washed with further ethyl acetate and the combined organic extracts dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of ethyl acetate in *iso*-hexanes (1:1 to 3:1) to afford the title compound as a yellow oil (201 mg, 86 %).



Compound 18e

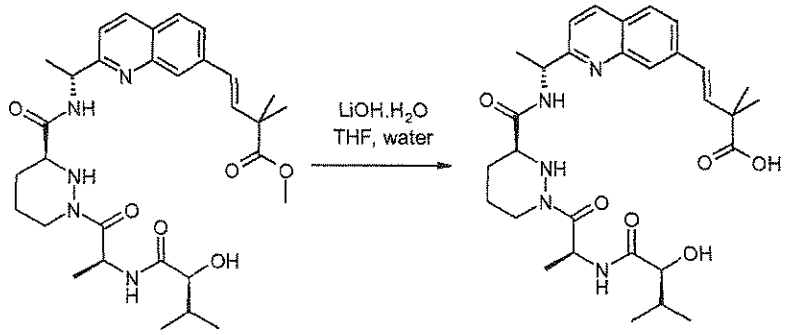
Synthesis of Compound 18e: 18d (193 mg, .48 mmol) was suspended in 4 M HCl in 1,4-dioxane (5 mL, 20 mmol) and methanol was added (10 mL). The reaction mixture was stirred for 2 h and then evaporated. The residue was triturated with ether to give the title compound as a yellow solid (166 mg).



Compound 18f

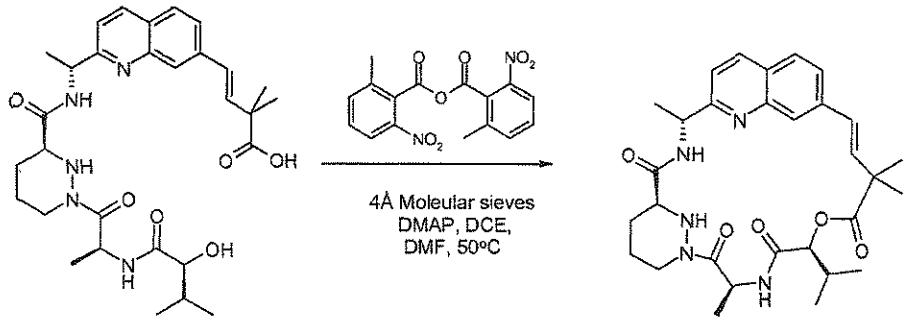
Synthesis of Compound 18f: (S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (166 mg, 0.48 mmol), 18e (190 mg, 0.48 mmol), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (256 mg, 0.67 mmol) and powdered 4Å molecular sieves were suspended in acetonitrile (9.6 mL) under nitrogen. To the stirred mixture was added *N,N*-diisopropylethylamine (186 mg, 250 µL, 1.44 mmol) and the reaction mixture stirred for 20 h. The mixture was filtered through a phase separator and the filtrate evaporated, dissolved in dichloromethane and washed successively with saturated sodium bicarbonate solution, water and saturated ammonium chloride solution, and then dried over sodium sulfate, filtered and evaporated. The residue was purified by silica

gel chromatography using a gradient of ethyl acetate in *iso*-hexanes (1:1 to 1:0) to afford the title compound as a yellow gum (77 mg, 28 % over 2 steps).



Compound 18g

Synthesis of Compound 18g: To 18f (117 mg, 0.201 mmol) in tetrahydrofuran (4 mL) was added, with stirring, water (0.8 mL) and lithium hydroxide monohydrate (9.2 mg, 0.221 mmol). The reaction mixture was stirred for 1 h and then further lithium hydroxide monohydrate (36 mg, 0.857 mmol) was added and the mixture stirred for a further 19.5 hours. The reaction mixture was evaporated and the residue azeotroped with toluene. The residue was purified by preparative HPLC using a gradient of 20 to 100% acetonitrile in water to give 18g as a white solid (60 mg, 53 %).

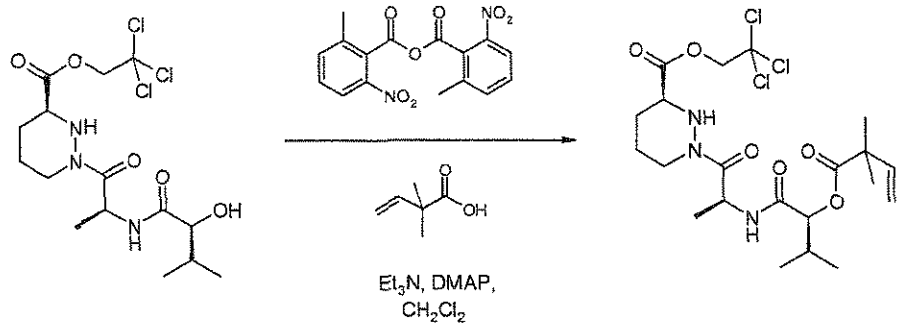


Compound 18

Synthesis of the title compound: A slurry of 2-methyl-6-nitrobenzoic anhydride (177 mg, 0.500 mmol), DMAP (92 mg, 0.750 mmol) and powdered 4Å molecular sieves (1 g) in 1,2-dichloroethane (33 mL) was stirred under nitrogen at 50°C. 18g (57 mg, 0.100 mmol) was dissolved in *N,N*-dimethylformamide (5 mL) and the solution added to the slurry over 5 h *via* syringe pump. After the addition was complete the original flask containing the acid was washed with further *N,N*-dimethylformamide (1 mL) and the washings transferred to the reaction vessel over 30 min. The reaction mixture was stirred at 50°C for a further hour and then allowed to cool. The residue was purified by preparative HPLC using a gradient of 5 to 100%

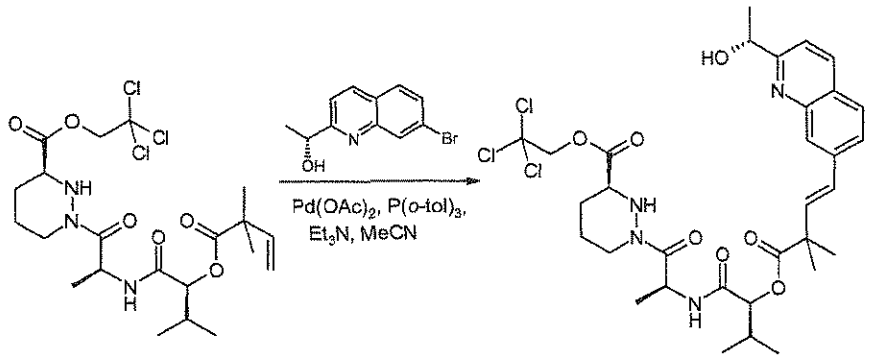
acetonitrile in water to give the title compound as a white solid (24.5 mg, 45 %).^{1}H NMR (300 MHz, CD3OD) δ 1.00 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H), 1.43 (s, 3H), 1.54 (s, 3H), 1.59 (d, J = 7.6 Hz, 3H), 1.64 (d, J = 7.4 Hz, 3H), 1.96 (m, 1H), 2.17 (m, 1H), 2.28 (m, 1H), 2.71 (m, 1H), 3.61 (m, 1H), 4.43 (m, 1H), 5.10 (m, 1H), 5.24 (d, J = 8.9 Hz, 1H), 5.81 (q, J = 7.1 Hz, 1H), 6.46 (ABq, $\Delta\delta_{AB}$ = 0.18, J_{AB} = 16.3 Hz, 2H), 7.45 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.3 Hz, 1H), 7.79 (s, 1H), 7.85 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 9.41 (*br* d, J = 5.6 Hz, 1H). LCMS (m/z) 550.2 [M+H], Tr 2.05 min.

EXAMPLE 19 - Compound 19



Compound 19a

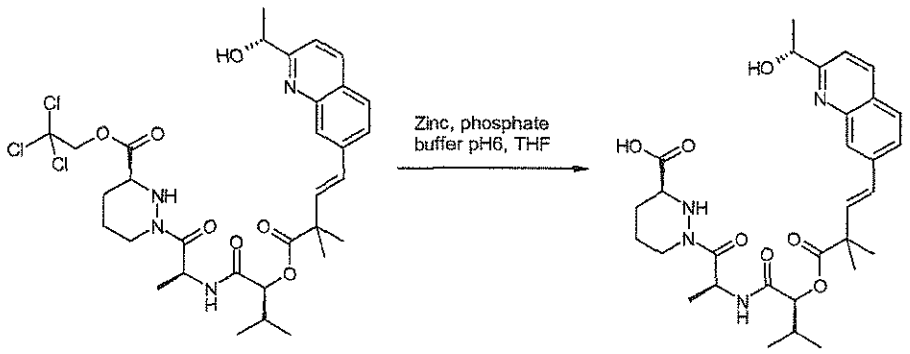
Synthesis of Compound 19a: 1e (1.08 g, 2.50 mmol), 2-methyl-6-nitrobenzoic anhydride (1.46 g, 4.25 mmol), 4-dimethylaminopyridine (122 mg, 1.00 mmol) and powdered 4Å molecular sieves were suspended in dry dichloromethane (11 mL) and the mixture stirred under nitrogen. Triethylamine (633 mg, 871 µL, 6.25 mmol) and a solution of 2,2-dimethyl-but-3-enoic acid (390 mg, 3.43 mmol) in dry dichloromethane (1.5 mL) were added and the reaction mixture stirred for 17 h. The suspension was passed through a phase separator cartridge and the filtrate evaporated. The residue was purified by silica gel chromatography using a gradient of ethyl acetate in *iso*-hexanes (1:4 to 2:3) to afford the title compound as a brown gum (735 mg, 56 %).



Compound 19b

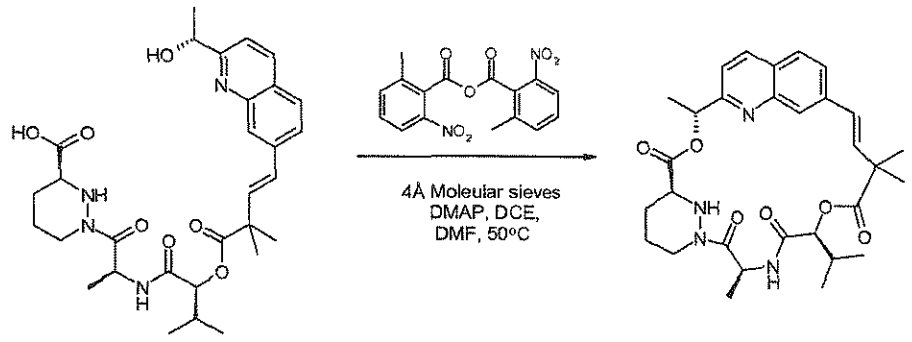
Synthesis of Compound 19b: 19a (124 mg, 0.235 mmol), (R)-1-(7-bromo-quinolin-2-yl)-ethanol (65 mg, 0.258 mmol), palladium acetate (8 mg, 0.035 mmol), tri(*o*-tolyl)phosphine (22

mg, 0.071 mmol) and triethylamine (48 mg, 66 µL, 0.47 mmol) were suspended in acetonitrile (2.35 mL). The reaction mixture was heated and stirred at 120°C for 2 h in a microwave reactor. The residue was evaporated and suspended in ethyl acetate and saturated ammonium chloride solution. The organic layer was separated and washed with saturated ammonium chloride solution then water and the combined aqueous washes back-extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of ethyl acetate in *iso*-hexanes (1:1 to 3:1) to afford the title compound as a yellow gum (38 mg, 23%).



Compound 19c

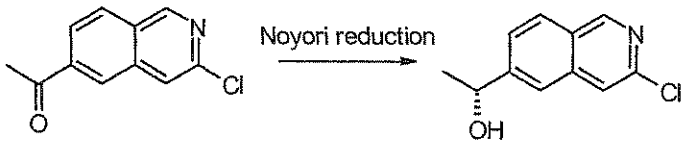
Synthesis of Compound 19c: To a solution of 19b (58 mg, 0.083 mg) in tetrahydrofuran (5 mL) was added zinc (218 mg, 3.33 mmol) and pH 6 phosphate buffer (1 mL). The reaction mixture was rapidly stirred for 18 h. Zinc (218 mg, 3.33 mol) was added and the reaction heated to 40°C for 1 h and allowed to cool. The mixture was filtered through a phase separator washing with tetrahydrofuran and pH 6 phosphate buffer. The filtrate was diluted with ethyl acetate and water and the aqueous phase extracted with further ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and evaporated. The aqueous phase was evaporated to *ca.* half volume and extracted with ethyl acetate (5 x) and the combined organic extracts dried over sodium sulfate, filtered and combined with the rest of the product and evaporated to give a yellow gum (51 mg).



Compound 19

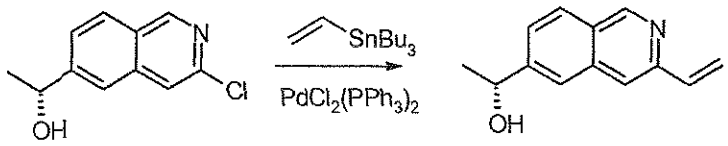
Synthesis of the title compound: A slurry of 2-methyl-6-nitrobenzoic anhydride (143 mg, 0.415 mmol), 4-dimethylaminopyridine (76 mg, 0.623 mmol) and powdered 4Å molecular sieves (1 g) in 1,2-dichloroethane (27 mL) was stirred under nitrogen at 50°C. 19c (51 mg, 0.083 mmol) was dissolved in *N,N*-dimethylformamide (3 mL) and the solution added to the slurry over 3.5 h *via* syringe pump. After the addition was complete the original flask containing the acid was washed with further *N,N*-dimethylformamide (1 mL) and the washings transferred to the reaction vessel over 10 min. The reaction mixture was stirred at 50°C for a further hour and then allowed to cool. The residue was purified by preparative HPLC using a gradient of 10% to 100% acetonitrile in water. The residue was further purified by silica gel chromatography using a gradient of 50% to 60% ethyl acetate in *iso*-hexanes (1:1 to 3:2) to give the title compound as a colorless gum (1.7 mg, 4% over 2 steps). ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 1.41 (s, 3H), 1.52 (s, 3H), 1.65 (d, J = 7.1 Hz, 3H), 1.68 (m, 2H), 1.73 (d, J = 6.7 Hz, 3H), 1.89 – 2.03 (m, 2H), 2.15 (m, 1H), 2.76 (m, 1H), 3.82 (m, 1H), 4.39 (*br* d, J = 13.4 Hz, 1H), 5.08 (d, J = 9.8 Hz, 1H), 5.81 (q, J = 7.1 Hz, 1H), 5.93 (q, J = 6.9 Hz, 1H), 6.34 (ABq, $\Delta\delta_{AB}$ = 0.11, J_{AB} = 16.6 Hz, 2H), 7.41 (d, J = 8.5 Hz, 1H), 7.67 (s, 1H), 7.75 (dd, J = 8.7, 1.3 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H). LCMS (m/z) 551.2 [M+H], Tr 2.22 min.

EXAMPLE 20 - Compound 20



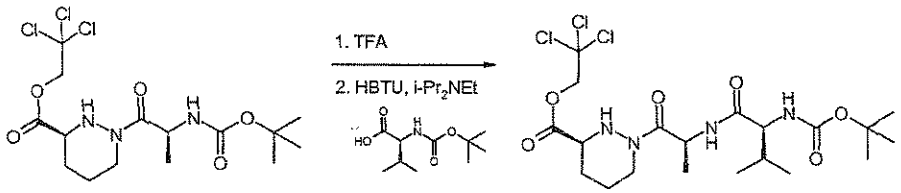
Compound 20a

Synthesis of Compound 20a: Dichloro(*p*-cumene)ruthenium(II) dimer (3 mg, 0.005 mmol) and (1R,2R)-(-)-*N*-p-tosyl-1,2-diphenylethylenediamine (4.4 mg, 0.012 mmol) were suspended in degassed water (2 mL) and the mixture was degassed with nitrogen for 15 min. The mixture was stirred at 70°C under nitrogen for 90 min. The resulting yellow solution was cooled to room temperature. 2f (206 mg, 1 mmol), sodium formate (340 mg, 5 mmol) and degassed tetrahydrofuran (1 mL) were added and the reaction mixture was degassed with nitrogen for 5 min. The reaction mixture was vigorously stirred at 40°C for 2.5 h. The reaction mixture was cooled to room temperature and was extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 4:1 to 2:1 to afford the title compound (193 mg, 92%) as a white solid.



Compound 20b

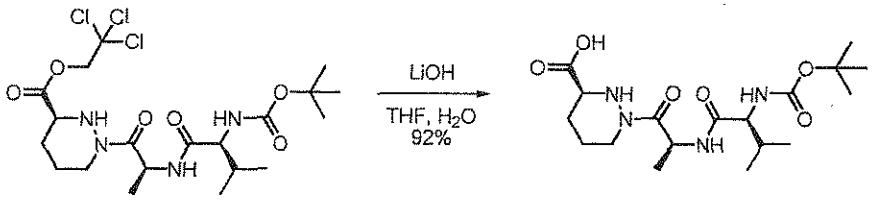
Synthesis of Compound 20b: 1,4-Dioxane (5 mL) was degassed with nitrogen, 20a (208 mg, 1 mmol), tributyl(vinyl)tin (951 mg, 0.9 mL, 3 mmol) and bis(triphenylphosphine)palladium(II) dichloride (70 mg, 0.1 mmol) were added and the reaction mixture was heated at 150°C in a microwave reactor for 1 h. Additional tributyl(vinyl)tin (0.3 mL, 1 mmol) and bis(triphenylphosphine)palladium(II) dichloride (70 mg, 0.1 mmol) were added and the reaction mixture was heated at 150°C in a microwave reactor for 1 h. The reaction mixture was cooled to room temperature and the mixture was filtered through filter aid and the filter pad was washed with ethyl acetate. The filtrate was evaporated and the residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 4:1 to 2:1 followed by silica gel chromatography using *iso*-hexanes/ethyl acetate 3:1 to afford the title compound (100 mg, 50%) as a white solid.



Compound 20c

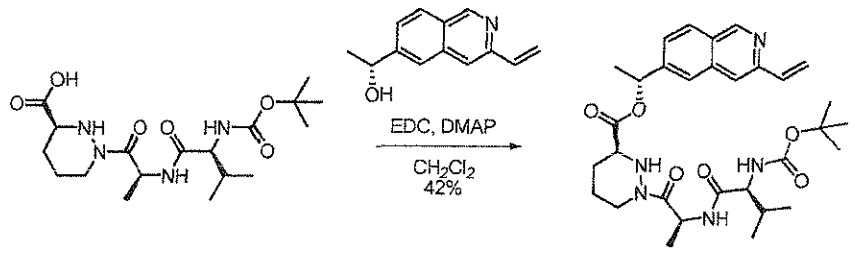
Synthesis of Compound 20c: A solution of 1d (6.88 g, 15.9 mmol) in dichloromethane (200 mL) was prepared and trifluoroacetic acid (50 mL) was added. The reaction mixture was stirred at room temperature for 2 h. TLC showed the reaction to be complete. The solution was evaporated to give a brown oil. This was azeotroped with toluene (50 mL) and the resultant oil was dried under vacuum to give (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester trifluoroacetic acid salt (7.8 g) as a brown gum. A solution of ((S)-1-carbamoyl-2-methylpropyl)-carbamic acid tert-butyl ester in acetonitrile (300 mL) was cooled to 0°C before adding *N,N*-diisopropylethylamine (13.8 mL, 79.7 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (6.33 g, 16.7 mmol). The reaction was stirred at 0°C for 15 min before adding a solution of the (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester trifluoroacetic acid salt (ca. 15.9 mmol) in acetonitrile (85 mL). The reaction was stirred at 0°C for a further 20 min and then allowed to warm to room temperature and stirred for 15 h. The reaction mixture was evaporated then re-dissolved in ethyl acetate (250 mL). The solution was washed with water (150 mL) then dried over sodium sulfate, filtered and evaporated to give a red oil. This was

purified by silica gel chromatography using *iso*-hexane/ethyl acetate 7:3 then *iso*-hexane/ethyl acetate 1:1 to yield the title compound (8.2 g, 92%) as a pale orange amorphous solid.



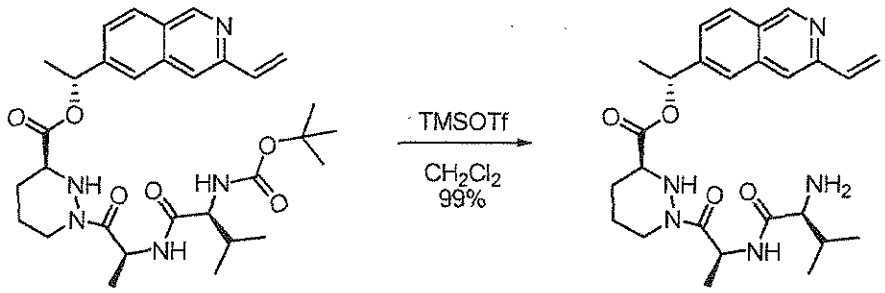
Compound 20d

Synthesis of Compound 20d: To a solution of 20c (530 mg, 1.00 mmol) in tetrahydrofuran (3 mL) and water (2 mL) was added lithium hydroxide (26 mg, 1.1 mmol) at 23°C under an argon atmosphere. After 19 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel flash column chromatography (12 g Combiflash HP Gold Column, 0-20% methanol/dichloromethane gradient) to afford the title compound (339 mg, 92%) as a colorless solid.



Compound 20e

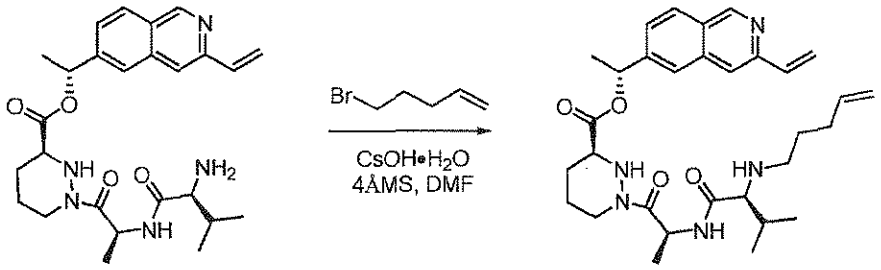
Synthesis of Compound 20e: To a solution of 20d (339 mg, 0.920 mmol) and 20bl (183 mg, 0.920 mmol) in dichloromethane (4.6 mL) were added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (211 mg, 1.10 mmol) and 4-dimethylaminopyridine (56.2 mg, 0.46 mmol) at 23°C under an argon atmosphere. After 21 h, the reaction mixture was purified directly by silica gel flash column chromatography (24 g Combiflash HP Gold Column, 0-100% ethyl acetate/hexanes gradient) to afford the title compound (224 mg, 42%) as a light tan solid.



Compound 20f

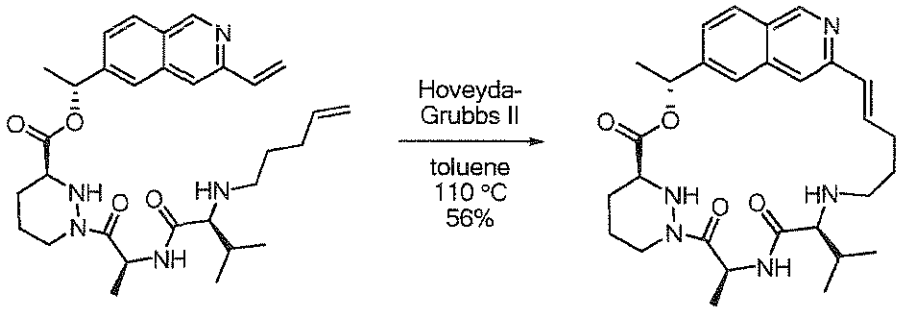
Synthesis of Compound 20f: To a solution of 20e (224 mg, 0.390 mmol) in dichloromethane (2.0 mL) was added trimethylsilyl trifluoromethanesulfonate (128 mg, 0.58 mmol) at 0°C under an argon atmosphere. After 2 h, the reaction mixture was concentrated

under reduced pressure to afford the title compound (188 mg, 99%) as a light yellow oil, which was used without further purification.



Compound 20g

Synthesis of Compound 20g: To a solution of 20f (94 mg, 0.195 mmol) in dimethylformamide (1.00 mL) were added cesium hydroxide monohydrate (98.5 mg, 0.585 mmol) and activated 4Å molecular sieves (53 mg) at 23°C under an argon atmosphere. After 10 min, 5-bromopent-1-ene (29 mg, 0.195 mmol) was added. After 4 d, the reaction mixture was diluted with brine (20 mL) and was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (12 g Combiflash HP Gold Column, 0–20% methanol/dichloromethane gradient) to afford the title compound (5.7 mg, 5%) as a light yellow solid.

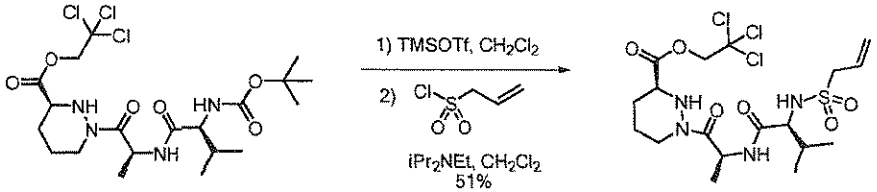


Compound 20

Synthesis of the title compound: To a solution of 20g (5.7 mg, 11 µmol) in toluene (3.7 mL) was added the Hoveyda-Grubbs 2nd Generation Catalyst (1.0 mg, 1.7 µmol) at 23°C under an argon atmosphere, and the resulting mixture was heated to 110°C. After 1.25 h, the reaction mixture was allowed to cool to 23°C, and was concentrated under reduced pressure. The crude residue was purified by preparatory HPLC (Gemini 5u C18 110Å column, 5-100% MeCN/H_2O, 0.1% trifluoroacetic acid modifier) to afford the title compound (3.7 mg, 56%) as a white solid trifluoroacetic acid salt. ^{1}H NMR (CD_3OD, 400MHz): δ 9.21 (s, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.84 (s, 1H), 7.79 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.57 – 6.45 (m, 1H), 5.99 (q, J = 6.7 Hz, 1H), 5.30 (q, J = 7.0 Hz, 1H), 4.31 (br-d, J = 12.0 Hz, 1H), 3.69 – 3.61 (m, 2H), 2.91 (br-t, J = 8.1 Hz, 2H), 2.68 (td, J = 12.8, 3.2 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.42 –

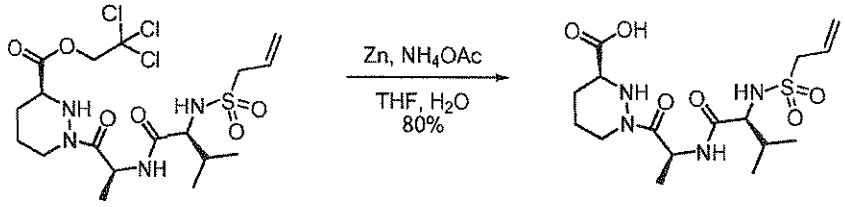
2.31 (m, 1H), 2.15 – 2.03 (m, 1H), 1.99 – 1.78 (m, 4H), 1.74 – 1.59 (m, 2H), 1.60 (d, J = 6.7 Hz, 3H), 1.56 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H). HPLC t_R (min), 4.169, purity %: 99%. (Phenomenex Kinetex 2.6u C18 100 Å, 100 × 4.60 mm 2.6 micron column, 8.5 min, 1.5 ml/min, 2–98% MeCN/H_2O, 0.1% trifluoroacetic acid modifier gradient). LCMS (ESI) m/z 522.2 $[M + H]^+$, t_R = 1.68 min. (Gemini 5u C18 110Å, 50 × 4.60 mm 5 micron column, 3.5 min, 2 ml/min, 5–100% MeCN/H_2O, 0.1% acetic acid modifier gradient).

EXAMPLE 21 - Compound 21



Compound 21a

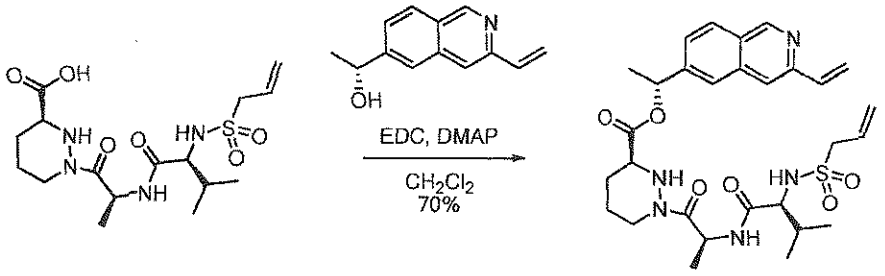
Synthesis of Compound 21a: To a solution of 20c (500 mg, 0.945 mmol) in dichloromethane (4.7 mL) was added trimethylsilyl trifluoromethanesulfonate (314 mg, 0.1.41 mmol) at 0°C under an argon atmosphere. After 1 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with dichloromethane (4.7 mL) and *N,N*-diisopropylethylamine (657 µL, 3.78 mmol) and prop-2-ene-1-sulfonyl chloride (140 mg, 0.992 mmol) were sequentially added at 23°C under an argon atmosphere. After 17 h, the reaction mixture was diluted with dichloromethane (50 mL) and the resulting mixture was washed with saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and was concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (24 g Combiflash HP Gold Column, 0–100% ethyl acetate/hexanes gradient) to afford the title compound (256.4 mg, 51%) as an orange oil.



Compound 21b

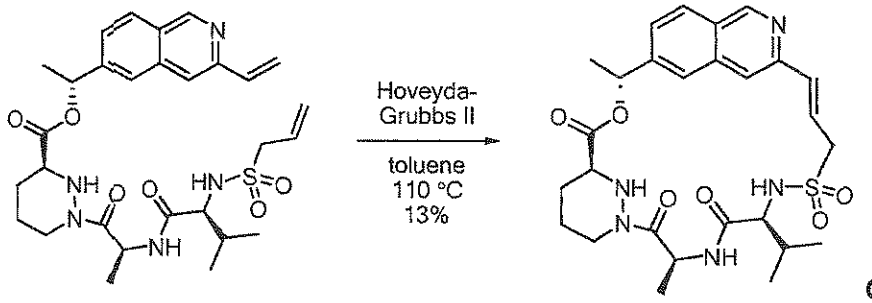
Synthesis of Compound 21b: To a solution of 21a (256 mg, 0.478 mmol) in tetrahydrofuran (8.0 mL) were added zinc powder (625 mg, 9.57 mmol) followed by a solution of ammonium acetate (552 mg, 7.17 mmol) in water (5.31 mL) at 23°C under an argon atmosphere. After 17 h, the reaction mixture was warmed to 45°C. After 7 h, the reaction mixture was allowed to cool to room temperature and was filtered through a pad of celite

washing with water (10 mL). The filtrate was concentrated under reduced pressure to remove tetrahydrofuran and the residue was partitioned between water (25 mL) and ethyl acetate (25 mL). The layers were split and the aqueous layer was acidified to pH = 2 with 12 N aqueous hydrogen chloride solution. The aqueous layer was extracted with ethyl acetate (4 × 50 mL), and the combined organic extracts were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure. Residual acetic acid was removed azeotropically via addition of toluene (5 mL) followed by concentration under reduced pressure (3 x) to afford the title compound (156 mg, 80%) as a white solid.



Compound 21c

Synthesis of Compound 21c: To a solution of 21b (156 mg, 0.390 mmol) and 20b (92.3 mg, 0.464 mmol) in dichloromethane (1.95 mL) were added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (105 mg, 0.546 mmol) and 4-dimethylaminopyridine (23.8 mg, 195 µmol) at 23°C under an argon atmosphere. After 21 h, the reaction mixture was purified directly by silica gel flash column chromatography (24 g Combiflash HP Gold Column, 0–100% ethyl acetate/hexanes gradient) to afford the title compound (155 mg, 70%) as a colorless oil.

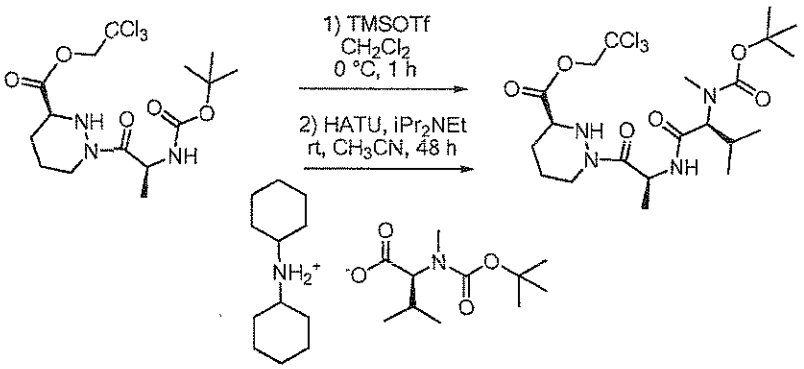


Compound 21

Synthesis of the title compound: To a solution of 21c (150 mg, 256 µmol) in toluene (51 mL) was added the Hoveyda-Grubbs 2nd Generation Catalyst (16 mg, 25 µmol) at 23°C under an argon atmosphere, and the resulting mixture was heated to 110°C. After 2 h, the reaction mixture was quenched with ethyl vinyl ether (500 µL) and the resulting mixture was allowed to cool to 23°C. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel flash column chromatography (12 g Combiflash HP Gold Column, 0–100% ethyl acetate/hexanes gradient) to afford the title compound (18.6 mg, 13%)

as a tan solid. ^{1}H NMR (CD_3OD, 400MHz): δ 9.37 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.14 (s, 1H), 7.97 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 15.8 Hz, 1H), 6.75 – 6.64 (m, 1H), 6.22 (q, *J* = 6.7 Hz, 1H), 5.62 – 5.52 (m, 1H), 4.40 (dd, *J* = 13.3, 3.3 Hz, 1H), 4.21 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.10 (dd, *J* = 13.4, 7.5 Hz, 1H), 4.06 (d, *J* = 4.5 Hz, 1H), 3.72 (dd, *J* = 11.5, 2.5 Hz, 1H), 2.79 (td, *J* = 12.8, 3.2 Hz, 1H), 2.19 (app-sextet, *J* = 7.0 Hz, 1H), 2.04 – 1.88 (m, 2H), 1.87-1.66 (m, 2H), 1.72 (d, *J* = 6.7 Hz, 3H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H). HPLC t_R (min), 2.882, purity %: 98%. (Synergi 4u hydro-RP, 50 × 4.60 mm 4 micron column, 7 min, 2ml/min, 5–100% MeCN/H_2O, 0.05% trifluoroacetic acid modifier gradient). LCMS (ESI) *m/z* 558.44 $[M + H]^+$, t_R = 1.88 min. (Gemini 5u C18 110Å, 50 × 4.60 mm 5 micron column, 3.5 min, 2ml/min, 5–100% MeCN/H_2O, 0.1% acetic acid modifier gradient). R_f = 0.25 (ethyl acetate) UV.

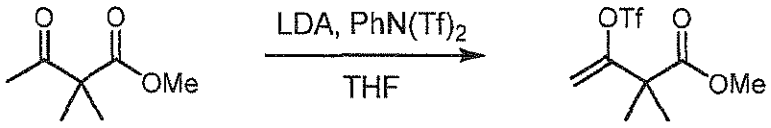
EXAMPLE 22 - Compound 22



Compound 22a

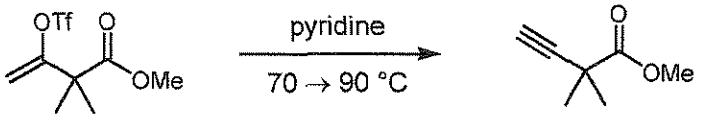
Synthesis of Compound 22a: A solution of 1d (865 mg, 2 mmol) in DCM (20 mL) was cooled in an ice water bath. Trimethylsilyl trifluoromethanesulfonate (667 mg, 3 mmol) was added dropwise at 0°C under argon, and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was evaporated to dryness and the resulting crude residue was dissolved in dry acetonitrile (25 mL) under argon. Reaction mixture was stirred at 0°C, (*S*)-2-(*tert*-butoxycarbonyl(methyl)amino)-3-methylbutanoic acid dicyclohexylamine salt (908 mg, 2.2 mmol) and *N,N*-diisopropylethylamine (1.034 g, 8 mmol) were added followed by 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (1.065 g, 2.8 mmol). Reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated, the residue was dissolved in ethyl acetate (100 mL) and the solution was washed twice with 20% water solution of citric acid (100 mL), water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and evaporated. The residue was purified by silica gel

chromatography (gradient from 0-40% ethyl acetate+methanol (4/1) in hexane) to afford the title compound as a white solid after evaporation (617 mg, 56%).



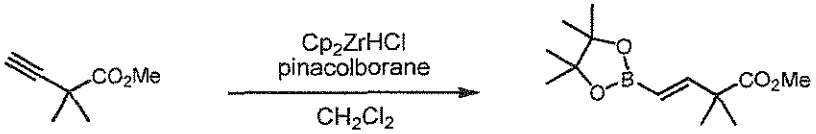
Compound 22b

Synthesis of Compound 22b: Under argon, a solution of diisopropylamine (2.51 g, 24.8 mmol) in tetrahydrofuran (150 mL) was cooled in an ice water bath. A solution of *n*-butyllithum in hexanes (2.5 M, 9.7 mL, 24 mmol) was added dropwise over 2 min, and the resulting solution was stirred for 10 additional min. The solution was then cooled to -78°C in a CO_2:acetone bath, and methyl 2,2-dimethyl-3-oxobutanoate (3.2 g, 22 mmol) was added dropwise over 30 sec. The solution was stirred for an additional 15 min, and *N*-phenyl-bis(trifluoromethanesulfonimide) (8.4 g, 23.5 mmol) was added as a solution in tetrahydrofuran (20 mL) via cannula over 5 min, washing with an additional portion of tetrahydrofuran (10 mL). The resulting solution was stirred for 10 min and was removed from the cold bath. After stirring an additional 1 h, the reaction mixture was concentrated *in vacuo* and diluted with diethyl ether (150 mL). The organic phase was washed with 1M aqueous sodium hydroxide (1 x 100 mL, 1 x 30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford the title compound (6.2 g, 100%) as an amber liquid that was used without further purification.



Compound 22c

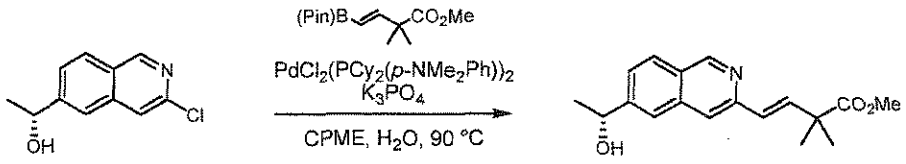
Synthesis of Compound 22c: A solution of 22b (6.2 g, 22 mmol) in anhydrous pyridine (11 mL, 140 mmol) was heated to 70°C. After 18.5 h, the temperature was increased to 90°C. After stirring for a total of 72 h, the reaction mixture was partitioned between a stirred mixture of diethyl ether (100 mL) and 3 M aqueous HCl (100 mL). The phases were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate (75 mL), dried over magnesium sulfate, filtered, and concentrated to afford the title compound (2.7 g, 97%) as a slightly brown liquid that was used without further purification.



Compound 22d

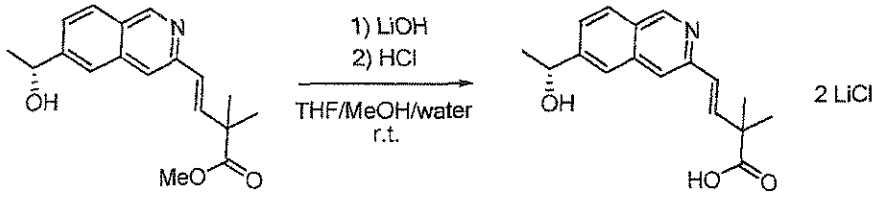
Synthesis of Compound 22d: Under argon, bis(cyclopentadienyl) zirconium chloride hydride (290 mg, 1.1 mmol) was cooled in an ice water bath. A solution of 22c (1.4 g, 11.1

mmol) and pinacolborane (2.4 mL, 16.5 mmol) in dichloromethane (3 mL) was added by cannula, washing with an additional portion of dichloromethane (2 mL). The resulting mixture was removed from the cold bath and was stirred for 72 h at room temperature. The reaction was then diluted with ethyl acetate (50 mL), quenched with dropwise water (5 mL), and was further diluted with water (50 mL). The organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (30 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude residue that was purified by silica gel chromatography (5% to 15% ethyl acetate in hexanes) to afford the title compound (1.6 g, 57%) as a colorless oil that crystallized on standing at -15°C.



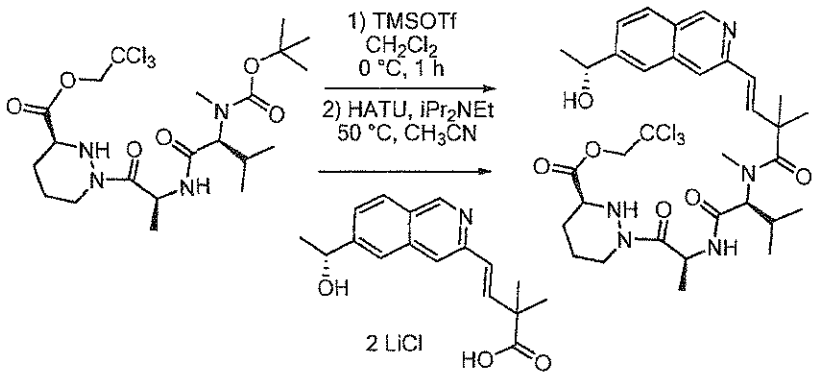
Compound 22e

Synthesis of Compound 22e: Under argon, 20a (880 mg, 4.23 mmol), 22d (1.24 g, 4.88 mmol), $PdCl_2(PCy_2(p\text{-}NMe_2Ph))_2$ (173 mg, 0.21 mmol) and K_3PO_4 (2.64 g, 12.4 mmol) were dissolved in cyclopentyl methyl ether (11.9 mL) and water (5.1 mL). The resulting biphasic mixture was vigorously stirred in an oil bath at 90°C for 3.5 h, at which time the reaction was cooled to ambient temperature and was diluted with ethyl acetate (50 mL) and water (40 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a crude residue that was purified by silica gel chromatography (25 to 60% ethyl acetate in hexanes) to afford the title compound as a yellow oil (1.07 g, 85%).



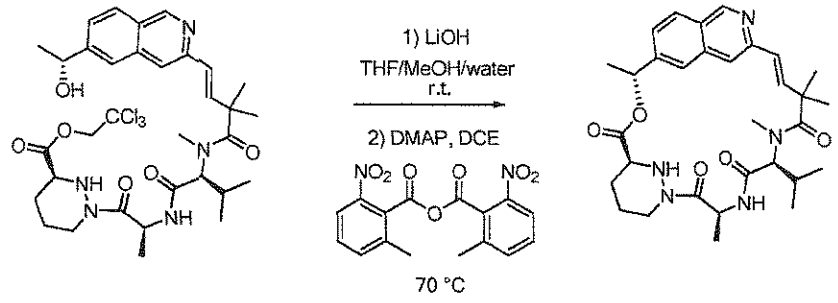
Compound 22f

Synthesis of Compound 22f: To a solution of 22e (600 mg, 2 mmol) in tetrahydrofuran (8 mL) was added methanol (4 mL), water (4 mL) and lithium hydroxide (96 mg, 4 mmol). The resulting mixture was stirred at room temperature for 10 h and quenched with 1 M HCl (4.2 mL, 4.2 mmol). The resulting solution was concentrated to a crude residue which was co-distilled twice with tetrahydrofuran (20 mL), twice with dry acetonitrile (20 mL) and twice with dry toluene (20 mL). The resulting white solid was dried under high vacuum overnight and it was used without further purification (735 mg, quantitative yield).



Compound 22g

Synthesis of Compound 22g: A solution of 17a (230 mg, 0.42 mmol) in dichloromethane (10 mL) was cooled in an ice water bath. Trimethylsilyl trifluoromethanesulfonate (128 mg, 0.575 mmol) was added dropwise at 0°C under argon, and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was evaporated to dryness and the resulting crude residue was dissolved in dry acetonitrile (20 mL) under argon. Reaction mixture was stirred at 0°C, 22f (128 mg, 0.38 mmol) and *N,N-d*iisopropylethylamine (198 mg, 1.53 mmol) were added followed by 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (218 mg, 0.58 mmol). Reaction mixture was stirred at 50°C for 5 days. The solvent was evaporated, the residue was dissolved in ethyl acetate (50 mL) and the solution was washed twice with 20% water solution of citric acid (50 mL), water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (gradient from 0-40% ethyl acetate+methanol (4/1) in hexane) to afford after evaporation the title compound as a white solid (88 mg, 32%).

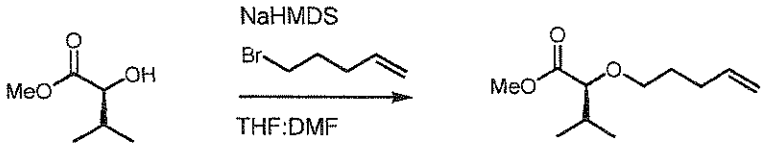


Compound 22

Synthesis of the title compound: To a solution of 22g (45 mg, 0.06 mmol) in tetrahydrofuran (2 mL) was added methanol (1 mL), water (1 mL) and lithium hydroxide (2.9 mg, 0.12 mmol). The mixture was stirred for 2 h at ambient temperature and was quenched with aqueous 1 M HCl (0.14 mL, 0.14 mmol). The resulting solution was concentrated to a crude residue which was co-distilled twice with tetrahydrofuran (5 mL), twice with dry acetonitrile (5 mL) and twice with dry toluene (5 mL). The resulting white solid was dried under high vacuum

overnight and it was used without further purification (40 mg, quantitative yield). Into oven dried, argon purged flask were placed 2-methyl-6-nitrobenzoic anhydride (83 mg, 0.24 mmol), 4-dimethylformamide (88 mg, 0.72 mmol) and dry 1,2-dichloroethane (100 mL). The resulting solution was heated at 70°C, and the crude product from the previous step was added dropwise via syringe as a solution in dry *N,N*-dimethylformamide (5 mL) over 12 h. An additional portion of dry *N,N*-dimethylformamide (2 x 1 ml) was used to complete the quantitative transfer. After stirring for additional 8 h at 70°C, the reaction mixture was transferred to separatory funnel and washed with water (100 mL, 5 mL of brine was added to support the separation). The aqueous phase was extracted with dichloromethane (50 mL). Combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (100 mL) and was washed with water (100 mL, 5 mL of brine was added to support the separation). The aqueous phase was extracted with ethyl acetate (50 mL). Combined organic extracts were washed with water (100 mL, 5 mL of brine was added to support the separation). Resulting aqueous phase was extracted with ethyl acetate (50 mL). Combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient from 0-40% ethyl acetate+methanol (4/1) in hexane) to afford after evaporation the title compound (6 mg, 18%) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD): δ 9.05 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H), 6.76 (d, *J* = 16.2 Hz, 1H), 6.28 (d, *J* = 16.2 Hz, 1H), 5.93 (m, 1H), 5.27 – 5.22 (m, 1H), 5.14 (m 1H), 4.82 (m 1H), 4.29 (m 1H), 3.70 (m, 1H), 3.38 (m, 1H), 2.77 (s, 3H), 2.63 (m, 1H), 2.09 (m, 2H), 1.93 (m, 2H), 1.86 (m, 1H), 1.79 (m, 2H), 1.59 (t, *J* = 7.4 Hz, 6H), 1.45 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 3H). LC/MS (*m/z*) 564 (100%) [M + H]$^+$; R_T = 3.14 min.; purity >95% (Phenomenex Gemini 5 micron C18, 30 x 4.6 mm, 5 to 100% acetonitile in water over 6 min, 2 mL/min, 0.05% formic acid modifier). TLC Rf = 0.43, 5% methanol in dichloromethane.

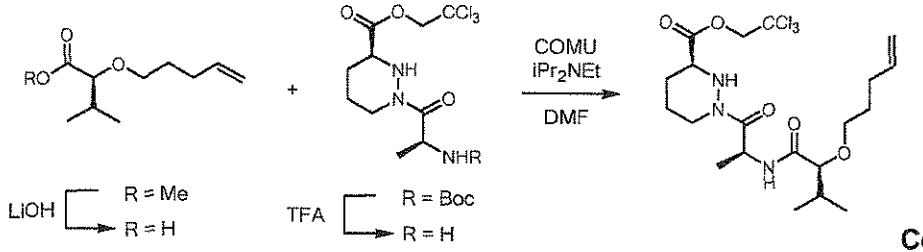
EXAMPLE 23 - Compound 23



Compound 23a

Synthesis of Compound 23a: Under argon, (S)-methyl 2-hydroxy-3-methylbutanoate (578 mg, 4.37 mmol) was dissolved in tetrahydrofuran (3.7 mL) and *N,N*-dimethylformamide (2.5 mL). The solution was cooled in an ice water bath. Sodium bis(trimethylsilyl)amide was

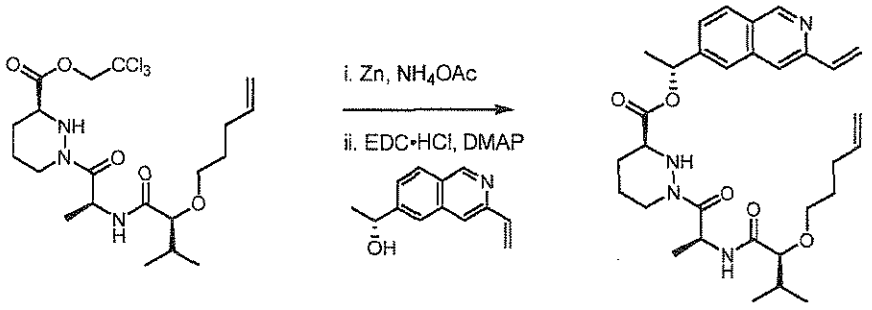
added as a 1.0 M solution in tetrahydrofuran (3.7 mL, 3.7 mmol) dropwise over 1.5 min. After an additional 3.5 min, 5-bromopent-1-ene was added in one portion. The reaction was stirred for 2 min and was removed from the cold bath. After 2 h, the reaction was quenched with saturated aqueous ammonium chloride (10 mL) and was diluted with ethyl acetate (20 mL), water (10 mL), and 0.1 N HCl (5 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phase was dried over sodium sulfate, filtered, and concentrated to afford a crude residue that was purified by silica gel chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (290 mg, 33%) as a colorless liquid.



Compound 23b

Synthesis of Compound 23b: To a solution of 23a (155 mg, 0.774 mmol) in tetrahydrofuran (3 mL) was added water (1 mL) and lithium hydroxide monohydrate (165 mg, 3.93 mmol). The reaction was stirred 18 h at which time methanol (1 mL) was added. The reaction was stirred for an additional 24 h and was then concentrated by 50% *in vacuo* and diluted with water (20 mL), ethyl acetate (20 mL) and 3 N aqueous HCl (15 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phase was dried over anhydrous sodium sulfate filtered, and concentrated to afford (S)-3-methyl-2-pent-4-enyloxy-butyric acid (115 mg, 80%) which was used without further purification. Under argon, 1d (240 mg, 0.55 mmol) was dissolved in dichloromethane (10 mL). The solution was cooled in an ice water bath and trimethylsilyl trifluoromethanesulfonate (209 mg, 0.94 mmol) was added. The reaction was stirred for 1 h and was quenched by the addition of *N,N*-diisopropylethylamine (296 mg, 2.3 mmol). The mixture was concentrated *in vacuo* and dissolved in methanol. After stirring for 10 min, the solution was concentrated *in vacuo* and was twice dissolved in and concentrated from toluene (10 mL portions). The resulting crude residue was used without further purification. (S)-3-methyl-2-pent-4-enyloxy-butyric acid (0.62 mmol) and (S)-1-[(S)-2-((S)-2-amino-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloroethyl ester (ca. 0.55 mmol) were dissolved in *N,N*-dimethylformamide (5 mL). *N,N*-diisopropylethylamine (192 mg, 1.5 mmol) was added, and the solution was cooled in an ice water bath. (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (320 mg,

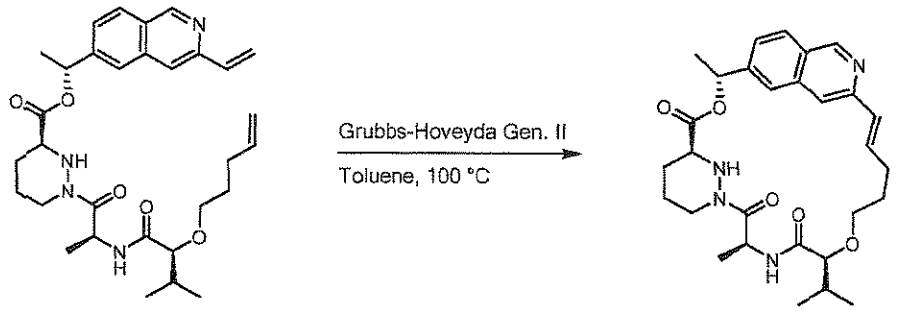
0.75 mmol) was added in one portion, and the reaction was stirred for 15 min. The reaction was then removed from the cold bath and let warm to ambient temperature. After stirring overnight, the reaction was diluted with ethyl acetate (30 mL) and saturated aqueous sodium bicarbonate (30 mL). The phases were separated, and the organic phase was washed with a mixture of 0.2 N aqueous HCl (30 mL) and brine (5 mL) followed by half-saturated brine (30 mL) and brine (30 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude residue that was purified by silica gel chromatography (30% to 60% ethyl acetate in hexanes) to afford the title compound (157 mg, 57%) as an amorphous residue.



Compound 23c

Synthesis of Compound 23c: To a solution of 23b (157 mg, 0.31 mmol) in tetrahydrofuran(5.3 mL) was added water (2.6 mL), ammonium acetate (365 mg, 4.7 mmol) and zinc dust (460 mg, 7.0 mmol). The resulting mixture was stirred vigorously at room temperature for 24 h, and the reaction was then heated to 50°C. After an additional 3.5 h, additional zinc powder (240 mg, 3.7 mmol) was added. The reaction was stirred at 50°C for 2 h and was then cooled to 35°C and stirred for an additional 18.5 h. The mixture was filtered through Celite with ethyl acetate (50 mL) and was washed with a mixture of 2 N aqueous HCl (30 mL) and brine (15 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic phase was dried over sodium sulfate, filtered, and concentrated. The resulting crude residue was twice taken up in and concentrated from toluene (10 mL), and the crude (S)-1-[(S)-2-((S)-3-methyl-2-pent-4-enyloxy-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid was used without further purification. (S)-1-[(S)-2-((S)-3-Methyl-2-pent-4-enyloxy-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (74 mg, 0.37 mmol) and 4-dimethylaminopyridine (45.5 mg, 0.37 mmol) were dissolved in dichloromethane (5 mL). *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (78 mg, 0.41 mmol) was added in one portion. The reaction was stirred 44 h at room temperature and was diluted with ethyl acetate (50 mL), water (25 mL), saturated aqueous sodium bicarbonate (25 mL), and brine (25 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and

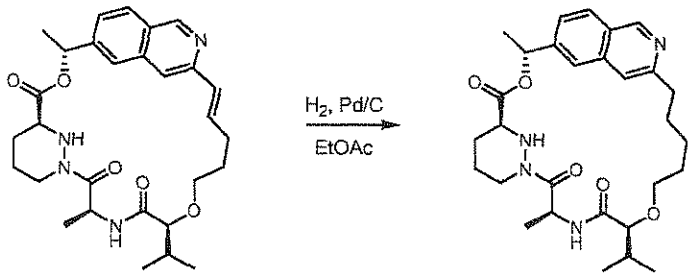
concentrated to afford a crude residue that was purified by silica gel chromatography (50 to 80 to 100% ethyl acetate in hexanes) to afford the title compound (118 mg, 69% over 2 steps) as a white foam.



Compound 23

Synthesis of the title compound: 23c (53 mg, 0.096 mmol) was dissolved in toluene (30 mL) under argon. The solution was sparged with argon with stirring for 10 min. Grubbs-Hoveyda second generation metathesis catalyst (9.0 mg, 0.014) was then added as a solution in argon-sparged toluene (2.0 mL). The reaction was heated to 100°C in a preheated oil bath and was stirred for 35 min. The reaction was concentrated *in vacuo* to ~6.5 mL final volume and was loaded directly onto a silica gel column. Elution with 60% to 85% to 100% ethyl acetate in hexanes provided 30 mg of impure material that was re-purified by reverse-phase HPLC (C18, 15% to 100% acetonitrile in water, 0.1% trifluoroacetic acid) to provide the title compound (17.8 mg, 35%) as its trifluoroacetic acid salt as an amorphous solid. ^{1}H NMR (400 MHz, CD_3OD) δ 9.56 (s, 1H), 8.53 (s, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.20 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.60 – 7.45 (m, 1H), 6.73 (d, *J* = 16.1 Hz, 1H), 6.21 (q, *J* = 6.7 Hz, 1H), 5.93 – 5.79 (m, 1H), 4.49 – 4.36 (m, 1H), 3.84 – 3.73 (m, 1H), 3.61 (d, *J* = 6.7 Hz, 1H), 3.59 – 3.45 (m, 2H), 2.86 – 2.70 (m, 2H), 2.44 – 2.31 (m, 1H), 2.18 – 1.89 (m, 4H), 1.88 – 1.61 (m, 7H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.04 – 0.95 (m, 6H) ppm. LCMS (m/z) 523.3 [M + H], R_T 2.72 min.

EXAMPLE 24 - Compound 24

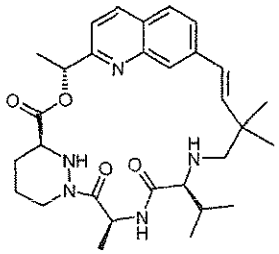


Compound 24

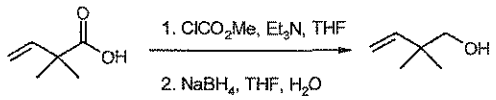
The trifluoroacetic acid salt of Compound 23 (7.9 mg, 0.012 mmol) was dissolved in ethyl acetate (0.80 mL). 10% palladium on carbon (5.6 mg) was added in one portion, and the

reaction vessel was flushed with hydrogen. The reaction mixture was stirred for 2.5 h under 1 atm hydrogen gas and was then filtered through a pad of Celite with ethyl acetate. The filtrate was concentrated and the resulting crude residue was purified by reverse-phase HPLC (C18, 15% to 100% acetonitrile in water, 0.1% trifluoroacetic acid) to provide the title compound (4.2 mg, 60%) as its trifluoroacetic acid salt as an amorphous solid following lyophilization. ^{1}H NMR (400 MHz, CD_3OD) δ 9.63 (s, 1H), 8.42 (d, *J* = 8.8 Hz, 1H), 8.26 (s, 1H), 7.96 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 6.16 (q, *J* = 6.5 Hz, 1H), 5.79 – 5.68 (m, 1H), 3.91 – 3.83 (m, 1H), 3.46 – 3.40 (m, 1H), 3.40 (d, *J* = 5.7 Hz, 1H), 3.26 – 3.09 (m, 4H), 2.06 – 1.89 (m, 6H), 1.84 (m, 1H), 1.73 – 1.59 (m, 7H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.52 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H) ppm. LCMS (m/z) 525.4 [M + H], R_T 2.51 min.

Example 25. Compound 25.



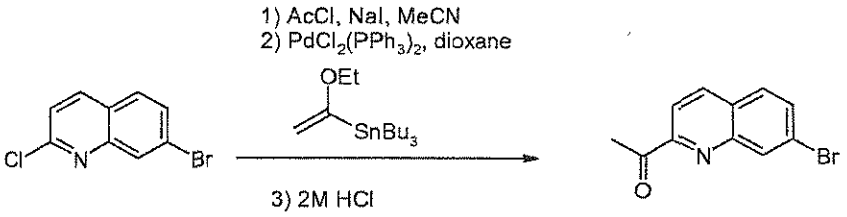
Compound 25a. 2,2-Dimethyl-but-3-en-1-ol



A solution of 2,2-dimethyl-but-3-enoic acid (570 mg, 5 mmol) and triethylamine (505 mg, 0.7 mL, 5 mmol) in tetrahydrofuran (15 mL) was stirred at –5 °C under nitrogen. A solution of methyl chloroformate (473 mg, 0.4 mL, 5 mmol) in tetrahydrofuran (5 mL) was added and the reaction mixture was stirred at –5 °C for 30 min. The reaction mixture was filtered, the residue was washed with tetrahydrofuran and the filtrate was evaporated. The residue was dissolved in tetrahydrofuran (5 mL), water (5 mL) was added and the reaction mixture was stirred at 0°C. Sodium borohydride (190 mg, 5 mmol) was added portion-wise and the reaction mixture was stirred at 0°C for 15 min and then at room temperature for 30 min. Saturated ammonium chloride solution (25 mL) was added and the mixture was extracted with diethyl ether. The organic extracts were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/diethyl ether 10:1 to 5:1 to afford the title compound (569 mg, 95%) as an oil. ^{1}H

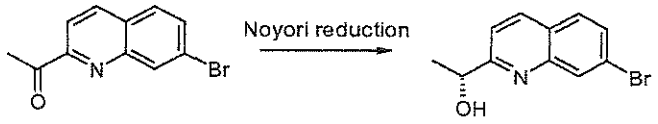
NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 6H), 1.33 (t, J = 6.5 Hz, 1H), 3.36 (d, J = 6.5 Hz, 2H), 5.09 (dd, J = 17.4, 1.3 Hz, 1H), 5.12 (dd, J = 10.9, 1.3 Hz, 1H), 5.79 (dd, J = 17.4, 10.9 Hz, 1H).

Compound 25b: 1-(7-Bromo-quinolin-2-yl)-ethanone



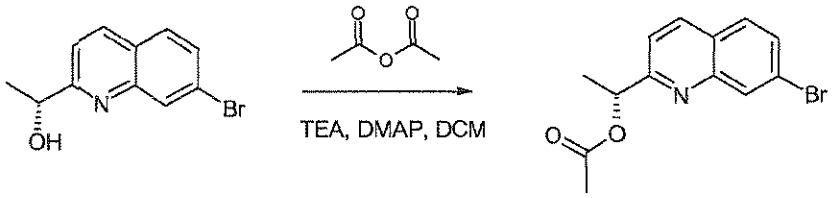
To a stirred slurry of 7-bromo-2-chloro-quinoline (obtained from AstaTech, Inc.), (8.10 g, 33.4 mmol) and sodium iodide (50.0 g, 334 mmol) in acetonitrile (27 mL) was slowly added acetyl chloride (3.56 mL, 50.0 mmol). The flask was stoppered and sealed and heated at 80°C for 3 h before being allowed to cool. The mixture was treated sequentially with 10% w/w aqueous potassium carbonate solution (80 mL), 5% w/w aqueous sodium sulfite solution (80 mL) and saturated aqueous sodium thiosulfate solution (80 mL) and the mixture extracted with dichloromethane (2 x). The combined organic extracts were dried over sodium sulfate, filtered and evaporated to give a crude 7-bromo-2-iodo-quinoline. To the quinoline was added tributyl(1-ethoxyvinyl)tin (13.6 mL, 40.1 mmol), 1,4-dioxane (67 mL) and bis(triphenylphosphine)palladium(II) dichloride (2.37 g, 3.34 mmol) and the reaction mixture heated at 100°C for 5 h before being allowed to cool. 2 M aqueous hydrochloric acid (67 mL) was added and the reaction stirred for 1 h. The mixture was filtered and the solids washed with ethyl acetate and the filtrate evaporated to remove organics. The residue was extracted with ethyl acetate (3 x) and the combined organic extracts were dried over sodium sulfate, filtered and evaporated. The product was purified on silica gel doped with 10% w/w potassium carbonate eluting with a gradient of 0% to 6% ethyl acetate in *iso*-hexanes to afford the title compound (5.5 g, 66%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 3H), 7.72-7.80 (m, 2H), 8.21 (ABq, $\Delta\delta_{AB}$ = 0.11, J_{AB} = 8.5 Hz, 2H), 8.42 (s, 1H). LCMS (m/z) 250.1/252.1 [M+H], Tr = 2.90 min.

Compound 25c: (R)-1-(7-Bromo-quinolin-2-yl)-ethanol.



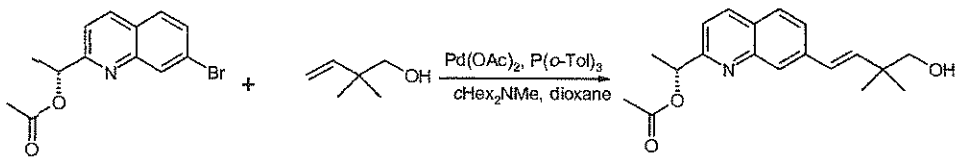
Dichloro (*p*-cymene) ruthenium(II) dimer (61 mg, 0.100 mmol) and (1R,2R)-(-)-*N*-p-tosyl-1,2-diphenylethylenediamine (88 mg, 0.012 mmol) was suspended in degassed water (40 mL) and the mixture was degassed with nitrogen for 5 min. The mixture was stirred at 70°C under nitrogen for 90 min. The resulting turbid orange mixture was allowed to cool to room temperature. 1-(7-Bromo-quinolin-2-yl)-ethanone (5.00 g, 20 mmol) in degassed tetrahydrofuran (40 mL) was added followed by sodium formate (6.8 g, 100 mmol) and the reaction mixture was degassed with nitrogen for 5 min. The reaction mixture was vigorously stirred at 40°C for 4 h and allowed to cool. It was then diluted with ethyl acetate and water and the organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of 0% to 30% ethyl acetate in *iso*-hexanes to afford the title compound (4.96 g, 98%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, J = 6.7 Hz, 3H), 4.85 (d, J = 4.5 Hz, 1H), 5.04-5.07 (m, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 8.7, 1.6 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.28 (d, J = 1.6 Hz, 1H). LCMS (m/z) 252.1/254.1 [M+H], Tr = 1.74 min.

Compound 25d: Acetic acid (R)-1-(7-bromo-quinolin-2-yl)-ethyl ester



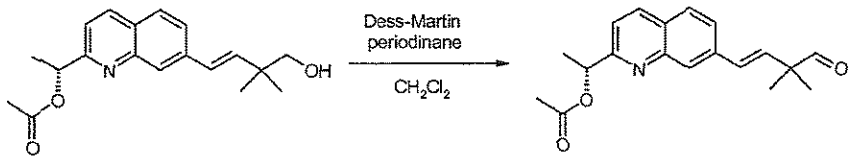
To a solution of 25c (1.00 g, 3.97 mmol) and triethylamine (1.65 mL, 11.9 mmol) in anhydrous dichloromethane at 0°C, was added acetic anhydride (0.75 mL, 7.93 mmol) and 4-(dimethylamino)pyridine (24 mg, 0.197 mmol). The reaction mixture was stirred and allowed to warm to room temperature. After 1.5 h water (100 mL) was added and the layers separated. The aqueous phase was re-extracted with dichloromethane (2 x 100 mL) and the combined organics were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a crude residue. This was purified by silica gel chromatography using *iso*-hexanes (66 mL) then *iso*-hexanes/ethyl acetate 95:5 (300 mL), then *iso*-hexanes/ethyl acetate 9:1 (1066 mL) to yield 25d (1.16 g, 99%) as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 1.65 (d, J = 6.7 Hz, 3H), 2.16 (s, 3H), 5.98 (q, J = 6.7 Hz,1H), 7.63 (d, J = 8.5 Hz, 1H), 7.72 (dd, J = 8.7, 1.8 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 8.23 (d, J = 1.8 Hz, 1H), 8.37 (d, J = 8.5 Hz, 1H). LCMS (m/z) 293.9/296.0 [M+H], Tr = 2.58 min.

Compound 25e. Acetic acid (R)-1-[7-((E)-4-hydroxy-3,3-dimethyl-but-1-enyl)-quinolin-2-yl]-ethyl ester



A solution of 2,2-dimethyl-but-3-en-1-ol (40 mg, 0.4 mmol) and 25d (118 mg, 0.4 mmol) in 1,4-dioxane (5 mL) was stirred at room temperature under nitrogen. Palladium(II) acetate (18 mg, 0.08 mmol) and tri(*o*-tolyl)phosphine (24 mg, 0.08 mmol) were added followed by a solution of *N,N*-dicyclohexylmethylamine (125 mg, 0.14 mL, 0.64 mmol) in 1,4-dioxane (1 mL) and the reaction mixture was heated at 100°C for 90 min. Additional palladium(II) acetate (9 mg, 0.04 mmol), tri(o-tolyl)phosphine (12 mg, 0.04 mmol) were added and the reaction mixture was heated at 100°C for 3 h. The reaction mixture was cooled to room temperature. Ethyl acetate was added and the mixture was washed with saturated sodium hydrogen carbonate solution and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 3:1 to 1:1 to afford 25e (85 mg, 68%) as a gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.43 (t, J = 6.3 Hz, 1H), 1.69 (d, J = 6.7 Hz, 3H), 2.18 (s, 3H), 3.50 (d, J = 6.3 Hz, 2H), 6.06 (q, J = 6.7 Hz, 1H), 6.52 (ABq, $\Delta\delta_{AB}$ = 0.18, J_{AB} = 16.0 Hz, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.6 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 8.03 (*br* s, 1H), 8.11 (d, J = 8.5 Hz, 1H). LCMS (m/z) 314.1 [M+H], Tr = 2.21 min.

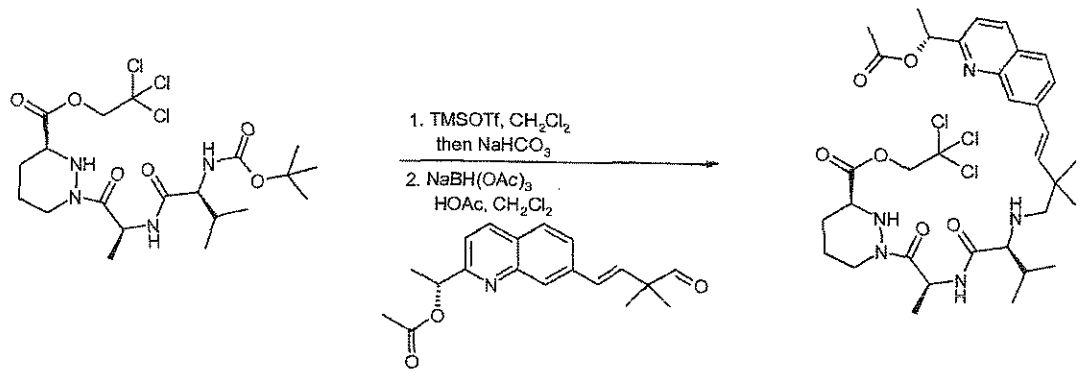
Compound 25f. Acetic acid (R)-1-[7-((E)-3,3-dimethyl-4-oxo-but-1-enyl)-quinolin-2-yl]-ethyl ester



A solution of 25e (78 mg, 0.25 mmol) in dichloromethane (5 mL) was stirred 0°C under nitrogen. Dess-Martin periodinane (106 mg, 0.25 mmol) was added and the reaction mixture was stirred at 0°C for 60 min. Additional Dess-Martin periodinane (22 mg, 0.05 mmol) was added and the reaction mixture was stirred at 0°C for 30 min and then at room temperature for 15 min. The reaction mixture was diluted with dichloromethane and the mixture was washed with saturated sodium hydrogen carbonate solution, water and brine. The organic solution was

filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 4:1 to 1:1 to afford 25f (85 mg, 68%) as a gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 6H), 1.69 (d, J = 6.7 Hz, 3H), 2.18 (s, 3H), 6.06 (q, J = 6.7 Hz, 1H), 6.40 (d, J = 16.3 Hz, 1H), 6.65 (d, J = 16.3 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.2 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 8.04 (*br* s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 9.52 (s, 1H). LCMS (m/z) 312.1 [M+H], Tr = 2.65 min.

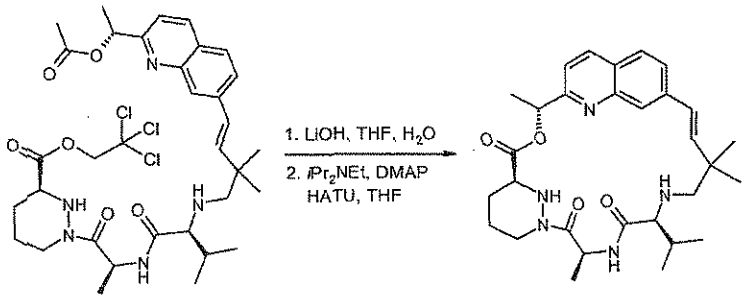
Compound 25g. (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enylamino}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



A solution of 20c (133 mg, 0.25 mmol) in dichloromethane (5 mL) was stirred at 0°C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (111 mg, 0.09 mL, 0.5 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 1 h. Cold saturated aqueous sodium hydrogen carbonate solution (10 mL) was added and the mixture was stirred at 0°C for 15 min. Dichloromethane was added and the organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford (S)-1-[(S)-2-((S)-2-amino-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (0.25 mmol) which was used without further purification. A solution of (S)-1-[(S)-2-((S)-2-amino-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (0.25 mmol) and 25f (66 mg, 0.21 mmol) in dichloromethane (5 mL) was stirred at room temperature for 10 min. Sodium triacetoxyborohydride (55 mg, 0.26 mmol) and acetic acid (1 drop) was added and the reaction mixture was stirred at room temperature for 4 h. Additional sodium triacetoxyborohydride (13 mg, 0.25 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate and the solution was washed with saturated sodium hydrogen carbonate solution, water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The

residue was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 1:1 to 0:1 to afford 25g (84 mg, 46%) as a gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.20 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.31 (s, 3H), 1.69 (d, J = 6.7 Hz, 3H), 1.70-2.15 (m, 6H), 2.18 (s, 3H), 2.52-2.63 (m, 2H), 2.82-2.86 (m, 2H), 3.66-3.73 (m, 1H), 3.83 (d, J = 11.4 Hz, 1H), 4.45-4.50 (m, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.95 (d, J = 12.0 Hz, 1H), 5.28-5.38 (m, 1H), 6.06 (q, J = 6.7 Hz, 1H), 6.52 (ABq, $\Delta\delta_{AB}$ = 0.14, J_{AB} = 16.0 Hz, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H). LCMS (m/z) 726.1/728.1 [M+H], Tr = 2.08 min.

Compound 25.

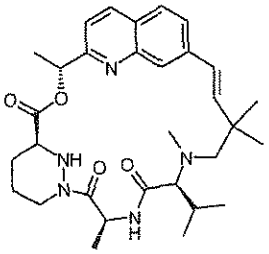


A solution of 25g (80 mg, 0.11 mmol) in tetrahydrofuran (3 mL) was stirred at 0 °C under nitrogen. A solution of lithium hydroxide monohydrate (18.5 mg, 0.44 mmol) in water (1 mL) was added and the reaction mixture was stirred at 0 °C for 4 h. Hydrochloric acid (1 M, 0.45 mL) was added and the solvent was evaporated. The residue was co-evaporated with tetrahydrofuran/toluene (1:1, 4 x) and the residue was triturated with diethyl ether (2 x) and dried to afford (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-hydroxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enylamino}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (0.11 mmol) as a white solid which was used crude in the next reaction. LCMS (m/z) 554.2 [M+H], Tr = 1.03 min.

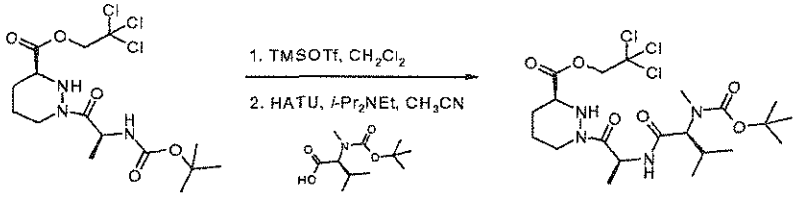
A mixture of crude (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-hydroxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enylamino}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (0.11 mol), *N,N*-diisopropylethylamine (84 mg, 0.65 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) in tetrahydrofuran (130 mL) was stirred at room temperature under nitrogen. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (133 mg, 0.35 mmol) was added and the reaction mixture was stirred at room temperature for 2.5 h. The solvent was evaporated and the residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The organic solution was separated and

washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using ethyl acetate. The residue was triturated with diethyl ether and the resulting solid was dried to afford Compound 25 (21 mg, 30%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ □0.80 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 1.11 (s, 3H), 1.25 (s, 3H), 1.62 (d, J = 7.1 Hz, 3H), 1.67-1.71 (m, 3H), 1.74 (d, J = 6.7 Hz, 3H), 1.88-2.05 (m, 2H), 2.64 (d, J = 8.5 Hz, 1H), 2.70-2.80 (m, 3H), 3.80-3.85 (m, 1H), 4.35-4.40 (m, 1H), 5.89-5.99 (m, 2H), 6.42 (ABq, $\Delta\delta_{AB}$ = 0.15, J_{AB} = 16.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 1H), 7.61 (dd, J = 8.5, 1.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 8.01 (*br* s, 1H), 8.22 (d, J = 8.5 Hz, 1H). LCMS (m/z) 536.2 [M+H], Tr = 1.47 min.

Example 26: Compound 26.



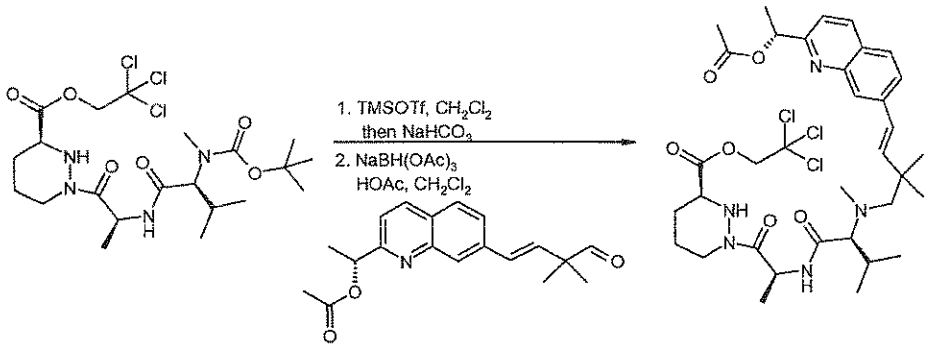
Compound 26a. (S)-1-{(S)-2-[(S)-2-(*tert*-Butoxycarbonyl-methyl-amino)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



A solution of 1d (1.08 g, 2.5 mmol) in dichloromethane (35 mL) was stirred at 0 °C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (682 mg, 0.55 mL, 3.1 mmol) was added and the reaction mixture was stirred at 0 °C for 45 min. *N,N*-diisopropylethylamine (1.29 g, 1.73 mL, 10 mmol) was added and the solvent was evaporated to afford crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (2.5 mmol), which was used in the next step. A solution of crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (2.5 mmol) in acetonitrile (30 mL) was stirred at 0 °C under nitrogen. (S)-2-(*tert*-Butoxycarbonyl-methyl-amino)-3-methyl-butyric acid (635 mg, 2.75 mmol, obtained from Sigma-Aldrich Inc.) and *N,N*-diisopropylethylamine (1.29 g, 1.7 mL, 10 mmol) was added followed by 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl

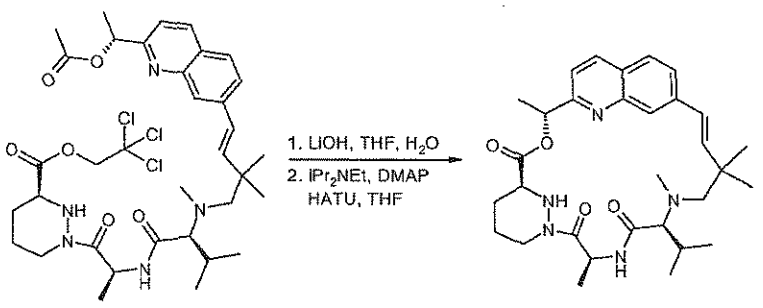
uronium hexafluorophosphate methanaminium (1.33 g, 3.5 mmol) and the reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with water, hydrochloric acid (2 M), water, saturated sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:1 to 0:1 to afford the title compound (756 mg, 55%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.28 (d, J = 6.7 Hz, 3H), 1.49-1.54 (m, 9H), 1.65-2.30 (m, 5H), 2.82 (s, 3H), 2.82-2.94 (m, 1H), 3.62-4.18 (m, 3H), 4.30-4.45 (m, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.95 (d, J = 12.0 Hz, 1H), 5.29-5.39 (m, 1H), 6.62-6.77 (m, 1H). LCMS (m/z) 545.2/547.1 [M+H], Tr = 3.02 min.

Compound 26b. (S)-1-{(S)-2-[(S)-2-({(E)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enyl}-methyl-amino)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



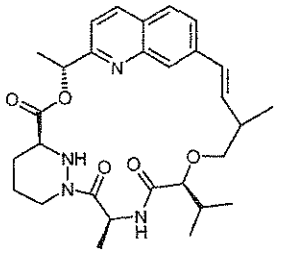
Compound 26b was prepared in the same manner as compound 25g using 26a instead of 20c in 42% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 6.5 Hz, 3H), 1.16 (s, 3H), 1.19 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H), 1.69 (d, J = 6.7 Hz, 3H), 1.70-2.15 (m, 5H), 2.17 (s, 3H), 2.40 (s, 3H), 2.57-2.62 (m, 3H), 2.82-2.89 (m, 1H), 3.66-3.73 (m, 1H), 3.83 (d, J = 11.4 Hz, 1H), 4.43-4.48 (m, 1H), 4.72 (d, J = 11.8 Hz, 1H), 4.94 (d, J = 11.8 Hz, 1H), 5.27-5.37 (m, 1H), 6.06 (d, J = 6.7 Hz, 1H), 6.50 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 16.5 Hz, 2H), 6.77 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.6 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.95 (*br* s, 1H), 8.11 (d, J = 8.3 Hz, 1H). LCMS (m/z) 740.2/742.3 [M+H], Tr = 2.44 min.

Compound 26.

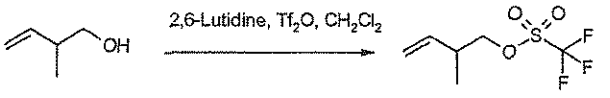


Compound 26 was prepared in the same manner as compound 25 using 26b instead of 25g in 11% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ □0.86 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H), 1.14 (s, 3H), 1.23 (s, 3H), 1.44 (d, J = 7.1 Hz, 3H), 1.67-1.72 (m, 2H), 1.75 (d, J = 6.9 Hz, 3H), 1.81-2.25 (m, 3H), 2.51 (s, 3H), 2.79-2.91 (m, 4H), 3.69-3.73 (m, 1H), 4.25-4.30 (m, 1H), 5.47 (q, J = 6.7 Hz, 1H), 5.97 (q, J = 6.7 Hz, 1H), 6.54 (ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 16.0 Hz, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.95 (*br* s, 1H), 8.21 (d, J = 8.5 Hz, 1H). LCMS (m/z) 550.3 [M+H], Tr = 1.50 min.

Examples 27 and 28, Compound 27 and 28



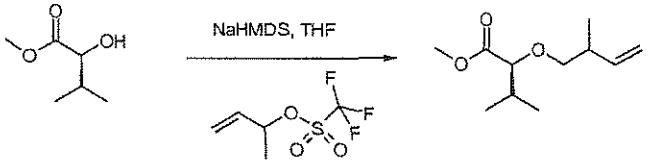
Compound 27a. Trifluoro-methanesulfonic acid 2-methyl-but-3-enyl ester



A solution of 2-methyl-but-3-en-1-ol (840 mg, 10 mmol) and 2,6-lutidine (1.5 g, 1.6 mL, 14 mmol) in dichloromethane (40 mL) was stirred at –78 °C under nitrogen. Trifluoromethanesulfonic anhydride (3.38 g, 2.0 mL, 12 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. Water was added and the reaction mixture was warmed to 0 °C. Additional water was added and the organic layer was separated, washed with cold 1 M hydrochloric acid, water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated to afford the crude product (14 mmol) as a pale yellow oil, which darkened on

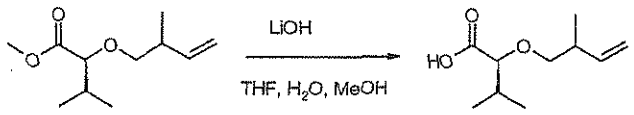
standing. The crude product was used immediately in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J = 6.9 Hz, 3H), 2.66-2.76 (m, 1H), 4.33-4.55 (m, 2H), 5.20 (dd, J = 10.5, 0.9 Hz, 1H), 5.21 (dd, J = 16.3, 0.9 Hz, 1H), 5.66-5.81 (m, 1H).

Compound 27b. (S)-3-Methyl-2-(2-methyl-but-3-enyloxy)-butyric acid methyl ester



A solution of (S)-2-hydroxy-3-methyl-butyric acid methyl ester (1.32 g, 10 mmol) in tetrahydrofuran (30 mL) was stirred at –10 °C under nitrogen. Sodium bis(trimethylsilyl)amide (6 mL, 12 mmol, 2 M in tetrahydrofuran) was added dropwise and the reaction mixture was stirred at –10 °C for 10 min. Trifluoro-methanesulfonic acid 2-methyl-but-3-enyl ester (2.18 g, 10 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 2 h. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic extracts were combined, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/diethyl ether 20:1 to 10:1 to afford the title compound (429 mg, 21% over 2 steps) as an oil, as a 1:1 mixture of two diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96-0.99 (m, 6H), 1.05 (d, J = 6.9 Hz, 1.5H), 1.08 (d, J = 6.6 Hz, 1.5H), 2.01-2.12 (m, 1H), 2.45-2.56 (m, 1H), 3.06-3.21 (m, 1H), 3.44-3.60 (m, 2H), 3.76 (s, 3H), 5.00-5.11 (m, 2H), 5.74-5.88 (m, 1H).

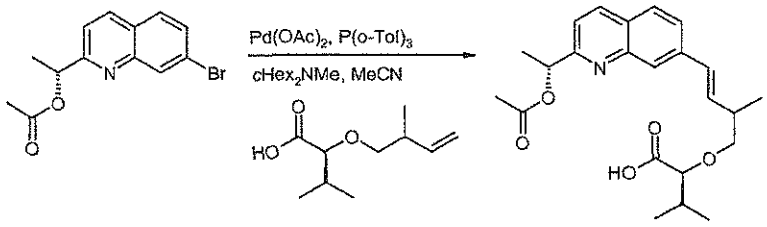
Compound 27c. (S)-3-Methyl-2-(2-methyl-but-3-enyloxy)-butyric acid



A solution of 27b (429 mg, 2.1 mmol) in tetrahydrofuran (10 mL) was stirred at 0 °C under nitrogen. A solution of lithium hydroxide monohydrate (265 mg, 6.3 mmol) in water (5 mL) was added followed by methanol (2 mL) and the reaction mixture was stirred at 0 °C for 30 minutes and then at room temperature for 4 h. Additional lithium hydroxide monohydrate (90 mg, 2.1 mmol) and methanol (3 mL) were added and the reaction mixture was stirred at room temperature for 3 days. The organic solvent was evaporated and the solution was acidified to pH 2 with 2 M hydrochloric acid and the mixture was extracted with ethyl acetate. The organic

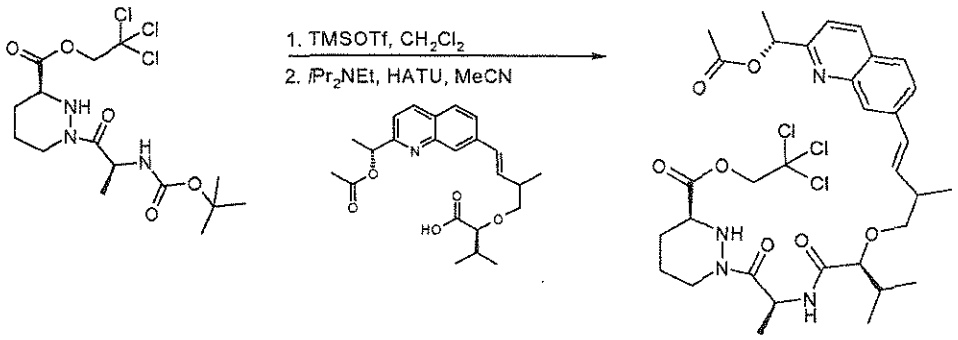
extracts were combined, washed with water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford the title compound (200 mg, 54%) as a colorless oil and as a 1:1 mixture of two diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97-1.11 (m, 9H), 2.14-2.23 (m, 1H), 2.48-2.59 (m, 1H), 3.37-3.50 (m, 2H), 3.70-3.72 (m, 1H), 5.11-5.19 (m, 2H), 5.70-5.88 (m, 1H), 8.50-9.50 (*br* s, 1H). LCMS (m/z) 185.3 [M-H], Tr = 2.33 min.

Compound 27d. (S)-2-{(E)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2-methyl-but-3-enyloxy}-3-methyl-butyric acid



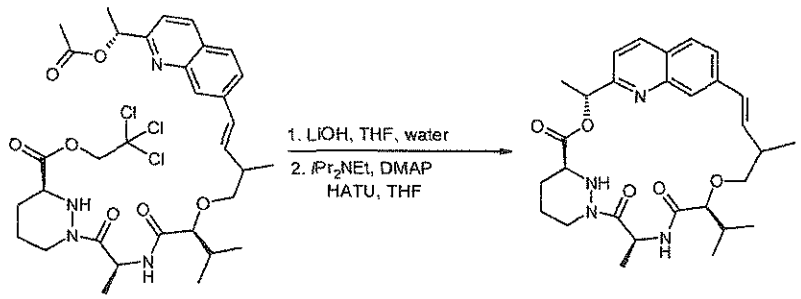
A solution of 27c (200 mg, 1.07 mmol) and 25d (314 mg, 1.07 mmol) in acetonitrile (10 mL) was stirred at room temperature under nitrogen. Palladium(II) acetate (48 mg, 0.2 mmol), tri(*o*-tolyl)phosphine (61 mg, 0.2 mmol) was added followed by *N,N*-dicyclohexylmethylamine (418 mg, 0.46 mL, 2.14 mmol) and the reaction mixture was heated at 120 °C in a microwave reactor for 40 minutes. Additional palladium(II) acetate (48 mg, 0.2 mmol), tri(-tolyl)phosphine (61 mg, 0.2 mmol) was added and the reaction mixture was heated at 130 °C in a microwave reactor for 30 minutes. The solvent was evaporated and the residue was partitioned between ethyl acetate and 1 M hydrochloric acid. The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford the crude product (1.07 mmol) as a 1:1 mixture of two diastereoisomers which was used in the next step without further purification. LCMS (m/z) 400.2 [M+H], Tr = 2.75 min.

Compound 27e. (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2-methyl-but-3-enyloxy}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



A solution of 1d (433 mg, 1.0 mmol) in dichloromethane (30 mL) was stirred at 0 °C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (444 mg, 0.35 mL, 2.0 mmol) was added and the reaction mixture was stirred at 0 °C for 45 minutes. *N,N*-diisopropylethylamine (516 mg, 0.7 mL, 4.0 mmol) was added and the solvent was evaporated and the residue was dried to afford crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (1.0 mmol), which was used in the next step. A solution of crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (1.0 mmol) in acetonitrile (30 mL) was stirred at 0 °C under nitrogen. 27d (1.0 mmol) and *N,N*-diisopropylethylamine (516 mg, 0.7 mL, 4.0 mmol) was added followed by 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (530 mg, 1.4 mmol) and the reaction mixture was stirred at 0 °C for 30 minutes and then at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with cold 1 M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:1 to 1:2 to afford the title compound (420 mg, 58% over 2 steps) as a white solid, as a 1:1 mixture of two diastereoisomers. LCMS (m/z) 713.3/715.3 [M+H], Tr = 3.48 min.

Compound 27 and 28



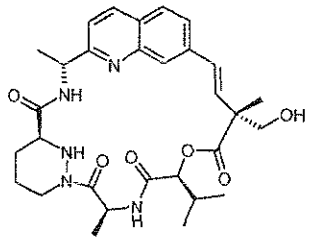
A solution of 27e (143 mg, 0.2 mmol) in tetrahydrofuran (10 mL) was stirred at 0 °C under nitrogen. A solution of lithium hydroxide monohydrate (42 mg, 1.0 mmol) in water (2 mL) was added and the reaction mixture was stirred at 0 °C for 3 h and then at 10 °C for 3 h. 1 M Hydrochloric acid (1 mL, 1.0 mmol) was added and the solvent was evaporated. The residue was co-evaporated with tetrahydrofuran/toluene (1:1, 3 x) and the residue was triturated with diethyl ether (2 x) and dried to afford (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-hydroxy-ethyl)-quinolin-7-yl]-2-methyl-but-3-enyloxy}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (0.2 mmol) as a pale yellow solid, as a mixture of two diastereoisomers which was used crude in the next reaction. LCMS (m/z) 541.2 [M+H], Tr = 1.77 min. A suspension of crude (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-hydroxy-ethyl)-quinolin-7-yl]-2-methyl-but-3-enyloxy}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (0.2 mmol) in tetrahydrofuran (200 mL) was stirred at room temperature under nitrogen. *N,N*-Diisopropylethylamine (129 mg, 0.18 mL, 1.0 mmol) and 4-dimethylaminopyridine (8 mg, 0.06 mmol) was added and the reaction mixture was stirred at room temperature for 5 minutes. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (107 mg, 0.28 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. Additional 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (30 mg, 0.08 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was suspended in ethyl acetate. Cold 1 M hydrochloric acid was added and the organic layer was separated, washed with water, saturated sodium hydrogen carbonate solution, water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:4 to 0:1 to afford a 1:1 mixture of two diastereoisomers. The mixture was purified by reverse phase preparative HPLC eluting with acetonitrile (containing 0.1% formic acid) / water (containing 0.1% formic acid) 45:55. Fractions containing the pure diastereoisomers were combined and evaporated. The residues were partitioned between saturated sodium hydrogen carbonate solution and ethyl acetate. The organic layer was separated, washed with water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford two diastereoisomers.

Example 27 Compound 27 (First eluting) Diastereoisomer 1: (12 mg, 12%) as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.70 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 1.54 (d, J = 6.9 Hz, 3H), 1.55-1.62 (m, 2H), 1.63 (d, J = 6.7 Hz, 3H), 1.73-1.95 (m, 3H), 2.72-2.78 (m, 1H), 3.25-3.30 (m, 1H), 3.45-3.52 (m, 1H), 3.65-3.72 (m, 2H), 4.18-

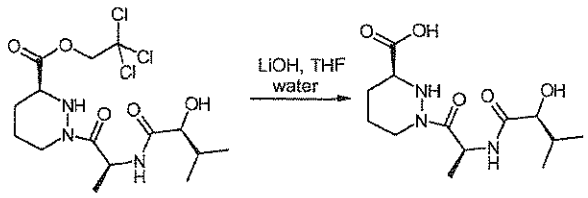
4.22 (m, 1H), 4.87 (d, J = 12.2 Hz, 1H), 5.65-5.73 (m, 1H), 5.96 (q, J = 6.7 Hz, 1H), 6.34 (dd, J = 16.5, 5.5 Hz, 1H), 6.45 (d, J = 16.5 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.80 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 8.28 (d, J = 8.5 Hz, 1H), 8.47 (d, J = 8.3 Hz, 1H). LCMS (m/z) 523.3 [M+H], Tr = 2.30 min.

Example 28, Compound 28 (Second Eluting) Diastereosiomer 2: (12 mg, 12%) as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.73 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.49 (d, J = 7.1 Hz, 3H), 1.55-1.62 (m, 2H), 1.65 (d, J = 6.9 Hz, 3H), 1.75-1.95 (m, 3H), 2.56-2.62 (m, 1H), 2.72-2.82 (m, 1H), 3.64-3.73 (m, 3H), 4.18-4.32 (m, 1H), 4.84 (d, J = 12.1 Hz, 1H), 5.65-5.73 (m, 1H), 5.98 (q, J = 6.7 Hz, 1H), 6.34 (dd, J = 16.5, 5.2 Hz, 1H), 6.48 (d, J = 16.5 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.75 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H). LCMS (m/z) 523.3 [M+H], Tr = 2.34 min.

Example 29: Compound 29

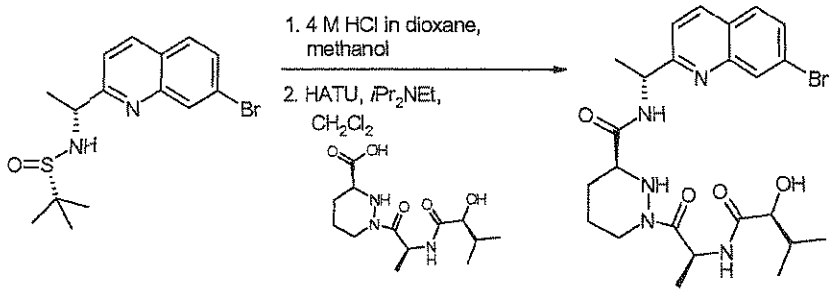


Compound 29a. (S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid



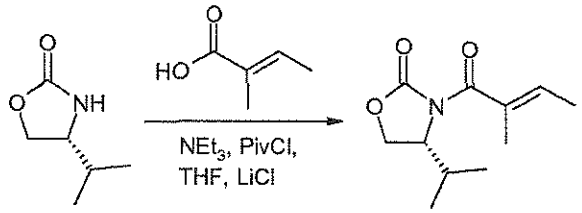
To (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester 1e (502 mg, 1.16 mmol) suspended in tetrahydrofuran (15 mL) and water (3 mL) was added lithium hydroxide monohydrate (69 mg, 1.65 mmol). The reaction mixture was stirred for 45 minutes and then hydrochloric acid (2 M, 0.75 mL) was added. The reaction mixture was stirred for 5 minutes and then evaporated. The crude residue was used directly in the next step without further purification.

Compound 29b. (S)-1-[(S)-2-((S)-2-Amino-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (R)-1-(7-bromo-quinolin-2-yl)-ethyl amide



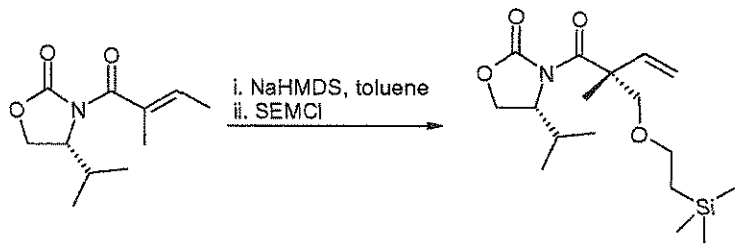
18c (533 mg, 1.50 mmol) was dissolved in hydrochloric acid in 1,4-dioxane (4 M, 7.5 mL) and methanol (7.5 mL). The reaction mixture was stirred for 2 h and then evaporated. The residue was passed through an SCX cartridge eluting with methanol and then 1 M ammonia in methanol. The basic fraction was collected and evaporated. The residue was dissolved in dichloromethane (30 mL) and 23 mL of this solution was added to freshly prepared 29a (350 mg, 1.16 mmol). The reaction vessel was cooled to 0 °C and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (616 mg, 1.62 mmol) and *N,N*-diisopropylethylamine (450 mg, 606 µL, 3.48 mmol) were added. The reaction mixture was allowed to warm to ambient temperature and stirred for 15 h. The mixture was diluted with dichloromethane and washed successively with saturated sodium bicarbonate solution, water and saturated ammonium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified on silica eluting with ethyl acetate/methanol 1:0 to 19:1 to afford the title compound (205 mg, 33 %) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 1.41 (d, J = 6.9 Hz, 3H), 1.58 (d, J = 6.7 Hz, 3H), 1.60-1.81 (m, 2H), 2.04-2.16 (m, 1H), 2.20-2.29 (m, 1H), 3.69-3.79 (m, 1H), 3.26 (*br* s, 1H), 3.43-3.54 (m, 1H), 3.72 (heptet, J = 6.4 Hz, 1H), 3.86 (d, J = 11.8 Hz, 1H), 3.98 (d, J = 3.1 Hz, 1H), 4.47-4.56 (m, 1H), 5.27 (*app* pentet, J = 6.9 Hz, 1H), 5.46 (dq, J = 8.0, 6.9 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.5, 1.8 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 6.7 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.43 (s, 1H). LCMS (m/z) 536.0 [M+H], Tr = 2.21 min.

Compound 29c. (R)-4-Isopropyl-3-((E)-2-methyl-but-2-enoyl)-oxazolidin-2-one



A cooled (–20 °C) solution of tiglic acid (2.005 g, 20.031 mmol) in anhydrous tetrahydrofuran (50 mL) was sequentially treated with triethylamine (6.1 mL, 44.068 mmol) and dropwise pivaloyl chloride (2.7 mL, 22.034 mmol). After stirring at –20 °C for 30 min, lithium chloride (1.019 g, 24.037 mmol) and (R)-(+)-4-isopropyl-2-oxazolidinone (2.587 g, 20.031 mmol) were added. The reaction mixture was allowed to slowly warm to room temperature, stirred for 3 days and was then quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate (2 x). The organics were combined, dried over anhydrous sodium sulfate, filtered and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 4:1 to afford the title compound (3.307 g, 78%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H), 1.83 (d, J = 6.9 Hz, 3H), 1.93 (s, 3H), 2.38 (d of heptet, J = 6.9, 4.2 Hz, 1H), 4.19 (dd, J = 8.9, 4.6 Hz, 1H), 4.33 (*app* t, J = 8.9 Hz, 1H), 4.49-4.58 (m, 1H), 6.23 (q, J = 7.1 Hz, 1H).

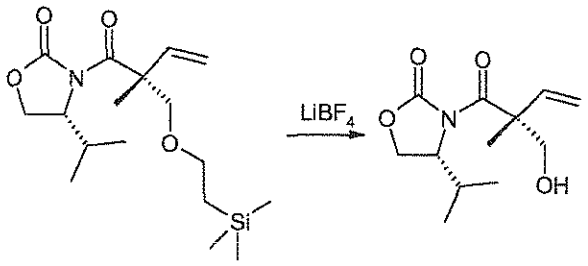
Compound 29d. (R)-4-Isopropyl-3-[(R)-2-methyl-2-(2-trimethylsilanyl-ethoxymethyl)-but-3-enoyl]-oxazolidin-2-one



Residual moisture in 29c (458.9 mg, 2.172 mmol) was removed by azeotroping with anhydrous toluene. A cooled (–78 °C) solution of dried 29c in anhydrous toluene (10 mL) was treated dropwise with a solution of sodium bis(trimethylsily)amide in toluene (0.6 M, 5.4 mL, 3.258 mmol). After stirring the yellow solution at –78 °C for 35 min, 2-(trimethylsilyl)ethoxymethyl chloride (1.1 mL, 6.516 mmol) was added. After stirring at 0 °C for 3.5 h, the reaction was quenched with saturated ammonium chloride. The aqueous layer was

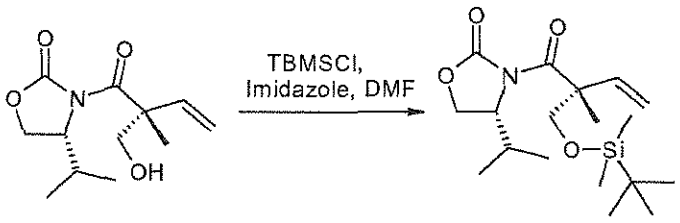
extracted with dichloromethane (2 x). The organics were combined, filtered through a phase separator and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 9:1 to afford the title compound (543.3 mg, 73%) as a colorless oil and as a 5:1 mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.77-0.99 (m, 8H), 1.49 (s, 3H), 2.36 (d of heptet, J = 6.9, 3.8 Hz, 1H), 3.42-3.60 (m, 3H), 4.15-4.31 (m, 3H), 4.49-4.57 (m, 1H), 5.00 (d, J = 17.6 Hz, 1H), 5.10 (d, J = 10.7, 1H), 6.19 (dd, J = 17.8, 10.7 Hz, 1H). LCMS (m/z) 364.1 [M+Na], Tr = 3.32 min.

Compound 29e. (R)-3-((R)-2-Hydroxymethyl-2-methyl-but-3-enoyl)-4-isopropyl-oxazolidin-2-one.



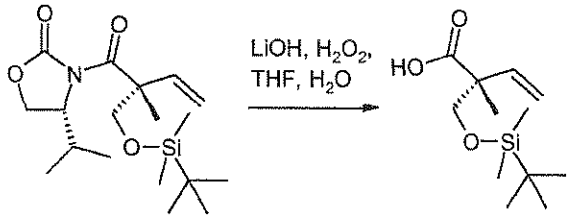
To a stirred solution of 29d (2.93 g, 8.58 mmol) in a mixture of acetonitrile (86 mL) and water (1.72 mL) was added lithium tetrafluoroborate (1 M in acetonitrile, 42.9 mL, 42.9 mmol). The mixture was heated at reflux under nitrogen for 5 h and allowed to cool to ambient temperature. More lithium tetrafluoroborate (1 M in acetonitrile, 8.6 mL, 8.6 mmol) was added and the mixture heated at reflux for a further 75 minutes and allowed to cool to ambient temperature. The mixture was diluted with water/diethyl ether (2:3, 100 mL) and the organic layer was separated and washed with water. The combined aqueous washes were back-extracted with diethyl ether and the combined organic extracts dried over anhydrous sodium sulfate, filtered and evaporated to give the title compound (1.89 g, 91%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.35 (s, 3H), 2.36-2.47 (m, 1H), 2.56-2.70 (*br* s, 1H), 3.47-3.54 (m, 1H), 3.91 (d, J = 11.6 Hz, 1H), 4.22-4.31 (m, 2H), 4.47-4.53 (m, 1H), 4.97 (d, J = 17.8 Hz, 1H), 5.17 (d, J = 10.7 Hz, 1H), 6.09 (dd, J = 17.8, 10.7 Hz, 1H). LCMS (m/z) 242.2 [M+H], Tr = 1.82 min.

Compound 29f. (R)-3-[(R)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-but-3-enoyl]-4-isopropyl-oxazolidin-2-one



To a stirred solution of 29e (660 mg, 2.74 mmol) and *tert*-butyldimethylsilyl chloride (533 mg, 3.56 mmol) in *N,N*-dimethylformamide (10 mL) at 0 °C under nitrogen was added in one portion imidazole (821 mg, 12.1 mmol). The reaction was stirred at 0 °C for 15 minutes and then allowed to warm to ambient temperature and stirred for 5 h. The mixture was concentrated and then partitioned between saturated ammonium chloride solution and ether. The organic layer was separated and washed with water (3 x), dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified on silica gel chromatography eluting with *iso*-hexanes/ethyl acetate 1:0 to 19:1 to afford the title compound (316 mg, 32%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.86-0.94 (m, 6H), 0.89 (s, 9H), 1.45 (s, 3H), 2.27-2.40 (m, 1H), 3.71 (d, J = 9.6 Hz, 1H), 4.10-4.30 (m, 2H), 4.43 (d, J = 9.6 Hz, 1H), 4.49-4.55 (m, 1H), 4.99 (d, J = 17.8 Hz, 1H), 5.10 (d, J = 9.6 Hz, 1H), 6.17 (dd, J = 17.8, 10.9 Hz, 1H). LCMS (m/z) 356.2 [M+H], Tr = 4.02 min

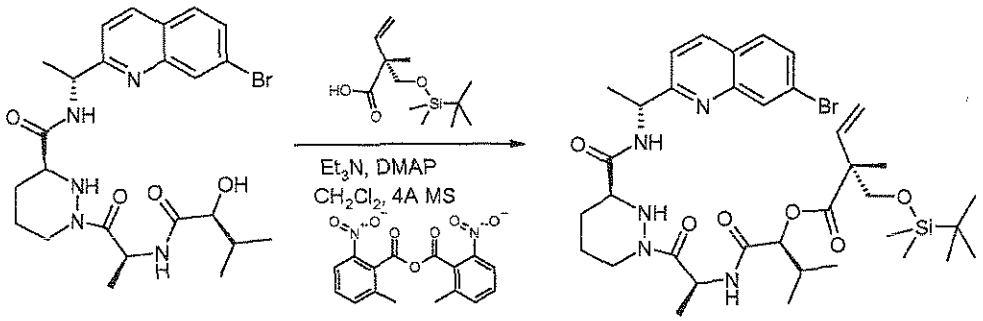
Compound 29g. (R)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-but-3-enoic acid



To a stirred mixture of 29f (310 mg, .872 mmol) in tetrahydrofuran (4.4 mL) and water (2.2 mL) at 0 °C was added hydrogen peroxide solution (30%, 494 mg, 449 µL, 4.36 mmol) followed by lithium hydroxide monohydrate (73 mg, 1.74 mmol). The reaction mixture was stirred at 0 °C for 5 minutes then allowed to warm to ambient temperature and stirred for 16 h. More tetrahydrofuran (1 mL) was added and the mixture cooled to 0 °C and lithium hydroxide monohydrate (37 mg, 0.87 mmol) was added. The reaction mixture was stirred at 0 °C for 40 minutes then allowed to warm to ambient temperature and stirred for 7 h. The reaction was then

quenched with sodium metabisulfite and stirred for 30 minutes. The mixture was acidified to pH<3 with hydrochloric acid (2 M) and extracted with dichloromethane (3 x). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified on silica gel chromatography eluting with *iso*-hexanes/ethyl acetate 9:1 to afford the title compound (144 mg, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 1.31 (s, 3H), 3.65 (d, J = 9.6 Hz,1H), 3.78 (d, J = 9.6 Hz, 1H), 5.24 (d, J = 17.6 Hz,1H), 5.24 (d, J = 10.9 Hz,1H), 5.96 (dd, J = 17.4, 10.9 Hz, 1H).

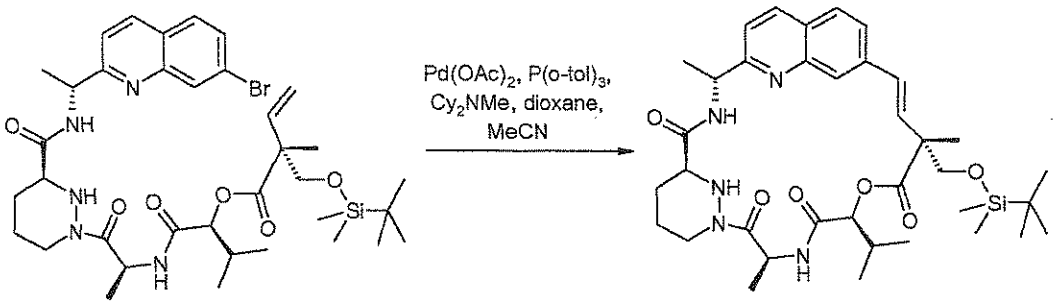
Compound 29h. (S)-1-{(S)-2-[(S)-3-Methyl-2-((R)-2-methyl-2-*tert*-butyl-dimethyl-silanyloxymethyl-but-3-enoylamino)-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid (R)-1-(7-bromo-quinolin-2-yl)-ethyl amide



To a stirred solution 29b (504 mg, 0.944 mmol), 2-methyl-6-nitrobenzoic anhydride (649 mg, 1.89 mmol), 4-(dimethylamino)pyridine (46 mg, 0.378 mmol), triethylamine (238 mg, 328 µL, 2.36 mmol) and powdered 4 Å molecular sieves (~ 1 g) in dichloromethane (10 mL) was added a solution of 29g (346 mg, 1.42 mmol) in dichloromethane (4 mL). The reaction was stirred under nitrogen for 91 h and then more 2-methyl-6-nitrobenzoic anhydride (325 mg, 0.90 mmol), 4-(dimethylamino)pyridine (23 mg, 0.189 mmol) and a solution of 29g (173 mg, 0.71 mmol) in dichloromethane (2 mL) was added and the reaction mixture stirred for a further 23 h. The reaction mixture was filtered through Celite and cooled to 0 °C and ice-cold water was added. The organic layer was separated and washed sequentially with ice-cold saturated ammonium chloride solution, ice-cold saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated and purified on silica gel chromatography eluting with *iso*-hexanes/ethyl acetate 1:1 to 0:1 to afford the title compound (244 mg, 34 %) as a beige oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.93 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 1.37 (d, J = 6.5 Hz, 3H), 1.42 (s, 3H), 1.61 (d, J = 6.7 Hz, 3H), 1.54-1.71 (m, 2H), 1.91-2.01 (m, 1H), 2.23-2.35 (m, 2H), 2.57-2.68 (m, 1H), 3.39-3.50 (m, 1H), 3.65 (d, J = 9.5 Hz, 1H), 3.73 (d, J = 12.1 Hz, 1H), 3.89 (d, J = 9.6 Hz,

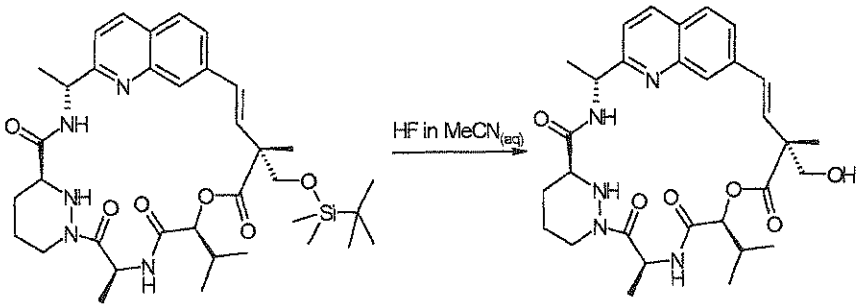
1H), 4.51-4.60 (m, 1H), 5.02 (d, *J* = 3.6 Hz, 1H), 5.21-5.43 (m, 4H), 6.04 (dd, *J* = 17.4, 10.9 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.61-7.71 (m, 2H), 8.02 (d, *J* = 6.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.36 (s, 1H). LCMS (m/z) 760.3, 762.3 [M+H], Tr = 4.16 min.

Compound 29i.



To solid palladium(II) acetate (14 mg, 0.060 mmol) and tri(*o*-tolyl)phosphine (20 mg, 0.060 mmol) was added a solution of 29h (49 mg, 0.060 mmol) in anhydrous 1,4-dioxane (18.4 mL), followed by *N,N*-dicyclohexylmethylamine (25 mg, 27 µL, 0.128 mmol) and anhydrous acetonitrile (0.2 mL). The mixture was heated at 120 °C in a microwave reactor for 25 minutes. Five batches of equivalent amount were reacted and combined and diluted with ethyl acetate, washed with saturated ammonium chloride solution (2 x), brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified on silica gel chromatography eluting with *iso*-hexanes/ethyl acetate 1:1 to 1:3 to afford the title compound (81 mg, 37%) as a yellow gum. LCMS (m/z) 680.3 [M+H], Tr = 3.75 min

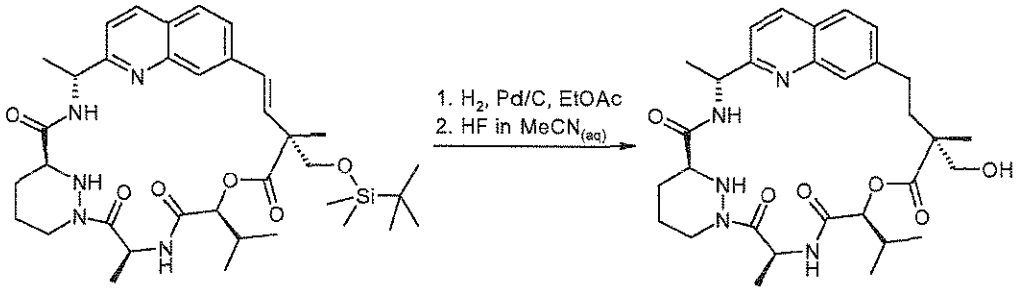
Compound 29.



Compound 29i (40 mg, 0.059 mmol) was dissolved in acetonitrile (20 mL) and hydrofluoric acid (48% in water, 117 mg, 102 µL, 5.88 mmol) was added. The reaction mixture was stirred for 4 h and more hydrofluoric acid (48% in water, 117 mg, 102 µL, 5.88 mmol) was added and stirring continued for a further 3.5 h. Solid sodium bicarbonate was added and the

mixture stirred for 5 minutes, filtered through a hydrophobic frit and the filtrate evaporated. The residue was purified by reverse phase preparative HPLC using a gradient of acetonitrile/water 1:4 to 7:3 to afford the title compound (10.0 mg, 30 %) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.01 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.48-1.78 (m, 2H), 1.56 (s, 3H), 1.60 (d, J = 6.9 Hz, 3H), 1.66 (d, J = 7.4 H, 3H), 1.91-2.00 (m, 1H), 2.10-2.19 (m, 2H), 2.63-2.75 (m, 1H), 3.62 (dd, J = 11.4, 2.7 Hz, 1H), 3.65 (d, J = 10.9 Hz, 1H), 3.95 (d, J = 10.9 Hz, 1H), 4.38-4.47 (m, 1H), 5.08 (q, J = 6.6 Hz, 1H), 5.23 (d, J = 9.2 Hz, 1H), 5.80 (q, J = 7.2 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 6.57 (d, J = 16.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.66 (dd, J = 8.5, 1.3 Hz, 1H), 7.83 (s, 1H), 7.85 (d, J = 8.5 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H). LCMS (m/z) 566.3 [M+H], Tr = 1.79 min.

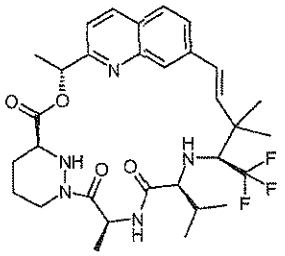
Example 30. Compound 30.



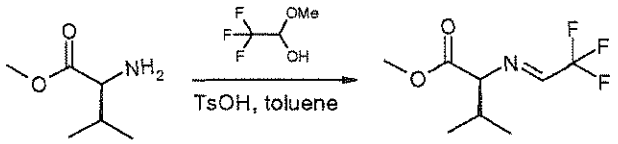
To a stirred solution of compound 29 (40 mg, 0.059 mmol) in ethyl acetate (6 mL) was added 10% palladium on carbon (12.5 mg, 0.012 mmol). The mixture was reacted under an atmosphere of hydrogen for 1 h and then the catalyst was filtered off. Fresh 10% palladium on carbon (12.5 mg, 0.012 mmol) was added to the filtrate and the stirred mixture reacted under an atmosphere of hydrogen for 1 h. The mixture was filtered through Celite and then evaporated. The residue was dissolved in ethyl acetate (6 mL) and fresh 10% palladium on carbon (12.5 mg, 0.012 mmol) was added and the stirred mixture reacted under an atmosphere of hydrogen for 2 h. The mixture was filtered through Celite and evaporated. The residue was dissolved in acetonitrile (20 mL) and hydrogen fluoride (48% in water, 117 mg, 102 µL, 2.82 mmol) was added. The reaction mixture was stirred for 2 h and more hydrogen fluoride (48% in water, 117 mg, 102 µL, 2.82 mmol) was added and stirred for a further 2 h. Solid sodium hydrogen carbonate was added and the mixture stirred for 5 min and then filtered through a hydrophobic frit. The mixture was evaporated and dissolved in ethyl acetate (6 mL) and 10% palladium on carbon (12.5 mg, 0.012 mmol) was added. The stirred mixture was reacted under a hydrogen atmosphere for 7 h and then filtered through Celite and evaporated. The residue was purified by

two consecutive reverse phase preparative HPLCs using a gradient of acetonitrile/water 1:4 to 3:7 and then acetonitrile/water 1:4 to 1:1 modified with 0.1% formic acid to afford the title compound (3.1 mg, 9 %) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.04 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.41 (s, 3H), 1.48-1.75 (m, 2H), 1.58 (d, J = 6.7 Hz, 3H), 1.60 (d, J = 7.1 H, 3H), 1.80-1.99 (m, 3H), 2.12-2.25 (m, 1H), 2.26-2.36 (m, 1H), 2.61-2.73 (m, 1H), 2.74-2.90 (m, 1H), 2.96-3.11 (m, 1H), 3.52 (d, J = 10.9 Hz, 1H), 3.60 (dd, J = 11.2, 2.3 Hz, 1H), 3.80 (d, J = 10.9 Hz, 1H), 4.24-4.42 (m, 1H), 4.81-4.94 (m, 1H), 5.10 (q, J = 6.7 Hz, 1H), 5.94 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.43 (dd, J = 8.3, 1.6 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 8.24 (d, J = 8.5 Hz, 1H). LCMS (m/z) 568.2 [M+H], Tr = 1.94 min.

Example 31, Compound 31.



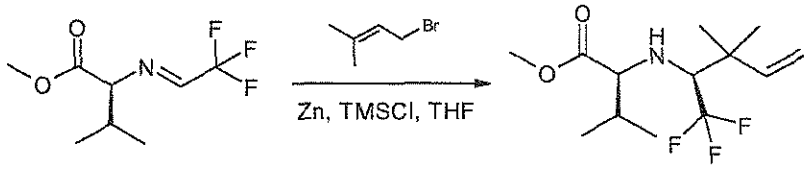
Compound 31a: (S)-3-Methyl-2-[2,2,2-trifluoro-ethylideneamino]-butyric acid methyl ester



A solution of (S)-2-amino-3-methyl-butyric acid methyl ester hydrochloride (6.72 g, 40 mmol) in water (50 mL) was partitioned between saturated sodium hydrogen carbonate solution and dichloromethane. The organic layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated to afford (S)-2-amino-3-methyl-butyric acid methyl ester (40 mmol). A solution of (S)-2-amino-3-methyl-butyric acid methyl ester (40 mmol), 2,2,2-trifluoro-1-methoxy-ethanol (5.2 g, 3.8 mL, 40 mmol) and 4-toluenesulfonic acid hydrate (100 mg) in toluene (125 mL) was heated at reflux using a Dean-Stark apparatus for 3 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 10:1 to 5:1 to afford the title compound (4.79 g, 56%) as a colorless oil. ^{1}H NMR (300

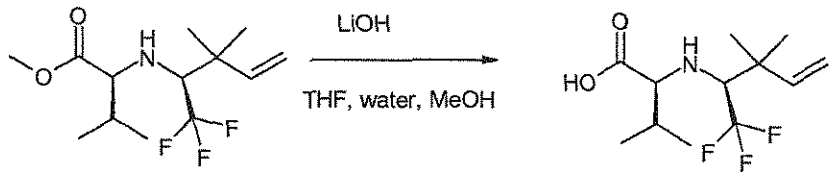
MHz, $CDCl_3$) δ 0.94 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 7.1 Hz, 3H), 2.32-2.44 (m, 1H), 3.73-3.77 (m, 4H), 7.67 (q, J = 3.3 Hz, 1H).

Compound 31b: (S)-2-((S)-2,2-Dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid methyl ester



A solution of 31a (4.2 g, 20 mmol) and 3,3-dimethylallyl bromide (2.98 g, 2.3 mL, 20 mmol) in tetrahydrofuran (30 mL) was stirred at room temperature under nitrogen. Zinc granules (2.6 g, 40 mmol) and chlorotrimethylsilane (10 drops) were added and the reaction mixture was stirred at room temperature for 10 minutes and then heated at reflux for 2 h. The reaction mixture was cooled to room temperature. Saturated ammonium chloride solution was added and the mixture was extracted with diethyl ether. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 50:1 to 40:1 to afford the title compound (1.41 g, 25%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.16 (s, 6H), 1.52-1.55 (m, 1H), 1.81-1.92 (m, 1H), 2.76-2.85 (m, 1H), 3.20 (dd, J = 9.8, 7.1 Hz, 1H), 3.72 (s, 3H), 5.09 (d, J = 17.4 Hz, 1H), 5.11 (d, J = 10.8 Hz, 1H), 5.90 (dd, J = 17.4, 10.8 Hz, 1H). LCMS (m/z) 282.1 [M+H], Tr = 3.51 min.

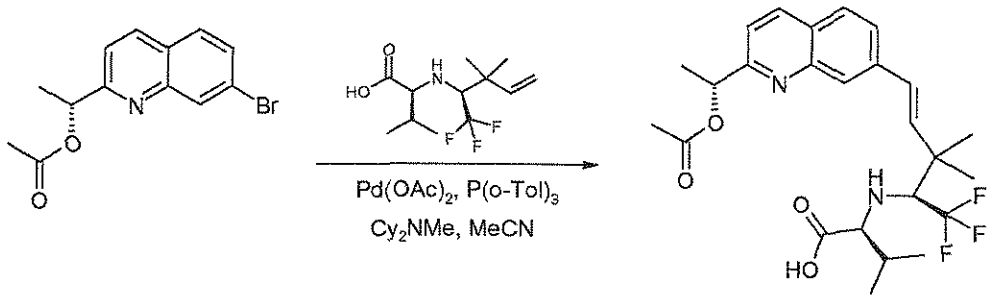
Compound 31c: (S)-2-((S)-2,2-Dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid



A solution of 31b (1.12 g, 4.0 mmol) in tetrahydrofuran (40 mL) was stirred at 0 °C under nitrogen. A solution of lithium hydroxide monohydrate (504 mg, 12.0 mmol) in water (8 mL) was added and the reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. Methanol (5 mL) was added and the reaction mixture was stirred at room temperature for 22 h. Additional lithium hydroxide monohydrate (336 mg, 8.0 mmol) in water (2 mL) was added and the reaction mixture was stirred at room temperature for 24 h. The organic solvent was

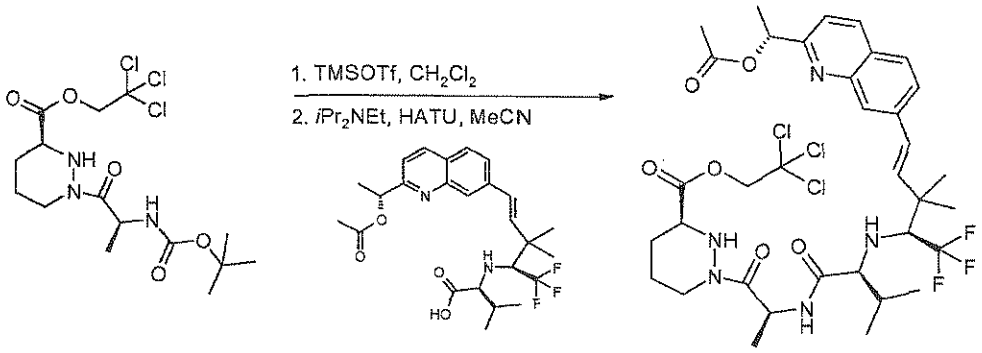
evaporated and the solution was acidified to pH 2 with 2 M hydrochloric acid and the mixture was extracted with ethyl acetate. The organic extracts were combined, washed with water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford the title compound (770 mg, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 1.20 (s, 6H), 1.95-2.04 (m, 1H), 2.87 (q, J = 7.8 Hz, 1H), 3.37 (d, J = 5.8 Hz, 1H), 5.12 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.7 Hz, 1H), 5.90 (dd, J = 17.2, 10.7 Hz, 1H). LCMS (m/z) 268.2 [M+H], Tr = 2.88 min.

Compound 31d: (S)-2-{(E)-(S)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino}-3-methyl-butyric acid



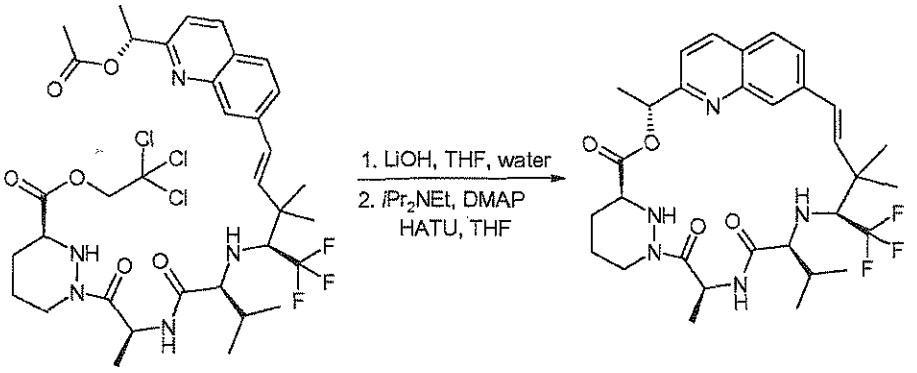
A solution of 31c (267 mg, 1.0 mmol) and 25d (294 mg, 1.0 mmol) in acetonitrile (10 mL) was stirred at room temperature under nitrogen. Palladium(II) acetate (45 mg, 0.2 mmol), tri(*o*-tolyl)phosphine (61 mg, 0.2 mmol) were added followed by *N,N*-dicyclohexylmethylamine (390 mg, 0.43 mL, 2.0 mmol) and the reaction mixture was heated at 120 °C in a microwave reactor for 30 minutes. The solvent was evaporated and the residue was partitioned between ethyl acetate and 1 M hydrochloric acid. The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford the crude product (640 mg, 1.0 mmol) as a yellow waxy solid which was used in the next step without further purification. LCMS (m/z) 481.1 [M+H], Tr = 3.26 min.

Compound 31e: (S)-1-[(S)-2-((S)-2-{(E)-(S)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



A solution of 1d (433 mg, 1.0 mmol) in dichloromethane (30 mL) was stirred at 0 °C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (444 mg, 0.35 mL, 2.0 mmol) was added and the reaction mixture was stirred at 0 °C for 45 minutes. *N,N*-diisopropylethylamine (516 mg, 0.7 mL, 4.0 mmol) was added, the solvent was evaporated and the residue was dried affording crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (1.0 mmol), which was used in the next step. A mixture of crude (S)-1-((S)-2-amino-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (1.0 mmol), *N,N*-diisopropylethylamine (516 mg, 0.7 mL, 4.0 mmol) and crude 31d (1.0 mmol) in acetonitrile (30 mL) was stirred at 0 °C under nitrogen. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (530 mg, 1.4 mmol) was added and the reaction mixture was stirred at 0 °C for 30 minutes and then at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in ethyl acetate and the solution was washed with cold 1 M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 3:1 to 0:1 to afford the title compound (292 mg, 37% over 2 steps) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 7.1 Hz, 3H), 1.30 (d, J = 6.7 Hz, 3H), 1.38 (s, 6H), 1.62-1.68 (m, 3H), 1.69 (d, J = 6.7 Hz, 3H), 1.90-1.96 (m, 2H), 2.18 (s, 3H), 2.18-2.21 (m, 1H), 2.84-3.23 (m, 3H), 3.68-3.72 (m, 1H), 3.79 (d, J = 11.1 Hz, 1H), 4.37-4.42 (m, 1H), 4.72 (d, J = 11.8 Hz, 1H), 4.96 (d, J = 11.8 Hz, 1H), 5.31-5.40 (m, 1H), 6.06 (q, J = 6.7 Hz, 1H), 6.59 (ABq, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 16.2 Hz, 2H), 7.05 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 8.01 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H). LCMS (m/z) 794.2/796.2 [M+H], Tr = 3.48 min.

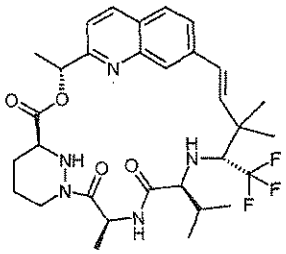
Compound 31.



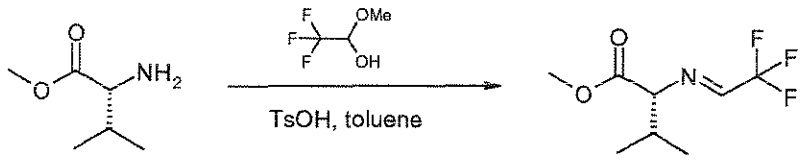
A solution of 31e (200 mg, 0.25 mmol) in tetrahydrofuran (10 mL) was stirred at 0 °C under nitrogen. A solution of lithium hydroxide monohydrate (53 mg, 1.25 mmol) in water (2 mL) was added and the reaction mixture was stirred at 0 °C for 5 h. 1 M Hydrochloric acid (1.25 mL, 1.25 mmol) was added and the solvent was evaporated. The residue was co-evaporated with tetrahydrofuran/toluene (1:1, 3 x) and the residue was triturated with diethyl ether (2 x) and the resulting solid was dried to afford (S)-1-[(S)-2-((S)-2-{(E)-(S)-4-[2-((R)-1-hydroxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (0.25 mmol) as a white solid which was used crude in the next reaction. LCMS (m/z) 622.3 [M+H], Tr = 1.97 min. A suspension of crude (S)-1-[(S)-2-((S)-2-{(E)-(S)-4-[2-((R)-1-hydroxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (0.25 mmol) in tetrahydrofuran (250 mL) was stirred at 0 °C under nitrogen. *N,N*-Diisopropylethylamine (161 mg, 0.22 mL, 1.25 mmol) and 4-dimethylaminopyridine (20 mg) were added and the reaction mixture was stirred at 0 °C for 5 minutes. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (133 mg, 0.35 mmol) was added and the reaction mixture was stirred at 0 °C for 30 minutes and then at room temperature for 3 h. Additional 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (95 mg, 0.25 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated and the residue was suspended in ethyl acetate. Cold 1 M hydrochloric acid was added and the organic layer was separated, washed with water, saturated sodium hydrogen carbonate solution, water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 4:1 to 2:1 to afford the title compound (50 mg, 33% over 2 steps) as a white solid. ^{1}H NMR (300

MHz, CD_3OD) δ 0.74 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.55-1.70 (m, 3H), 1.71 (d, J = 6.7 Hz, 3H), 1.72 (d, J = 6.5 Hz, 3H), 1.87-1.97 (m, 2H), 2.66-2.74 (m, 1H), 2.90 (d, J = 9.4 Hz, 1H), 3.13 (q, J = 7.8 Hz, 1H), 3.70-3.79 (m, 1H), 4.28-4.37 (m, 2H), 5.84 (q, J = 7.1 Hz, 1H), 5.91 (q, J = 6.7 Hz, 1H), 6.33 (d, J = 16.2 Hz, 1H), 6.63 (d, J = 16.2 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.49 (dd, J = 8.3, 1.6 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 8.20-8.23 (m, 2H). LCMS (m/z) 604.3 [M+H], Tr = 3.25 min.

Example 32, Compound 32.

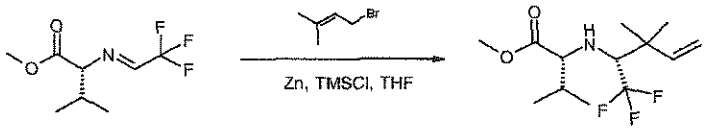


Compound 32a: (R)-3-Methyl-2-[2,2,2-trifluoro-ethylideneamino]-butyric acid methyl ester



Compound 32a was prepared in the same manner as compound 31a using (R)-2-amino-3-methyl-butyric acid methyl ester hydrochloride instead of (S)-2-amino-3-methyl-butyric acid methyl ester hydrochloride in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 7.1 Hz, 3H), 2.32-2.44 (m, 1H), 3.73-3.77 (m, 4H), 7.67 (q, J = 3.3 Hz, 1H).

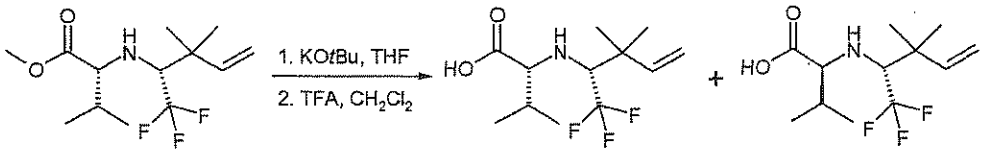
Compound 32b: (R)-2-((R)-2,2-Dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid methyl ester



Compound 32b was prepared in the same manner as compound 31b using 32a instead of 31a in 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.16 (s, 6H), 1.52-1.55 (m, 1H), 1.81-1.92 (m, 1H), 2.76-2.85 (m, 1H), 3.20 (dd, J = 9.8, 7.1

Hz, 1H), 3.72 (s, 3H), 5.09 (d, J = 17.4 Hz, 1H), 5.11 (d, J = 10.8 Hz, 1H), 5.90 (dd, J = 17.4, 10.8 Hz, 1H). LCMS (m/z) 282.1 [M+H], Tr = 3.51 min.

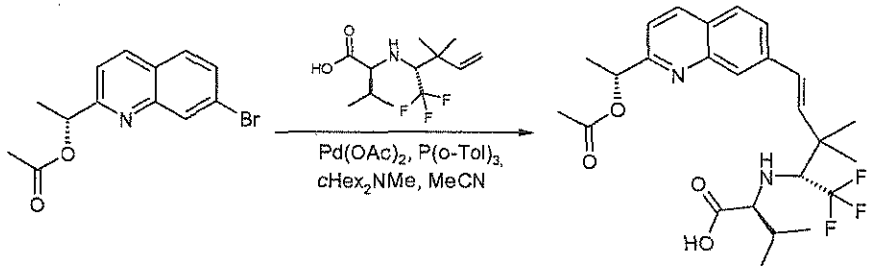
Compound 32c: (S)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid



A solution of 32b (1.30 g, 4.6 mmol) in tetrahydrofuran (30 mL) was stirred at 0 °C under nitrogen. Potassium *tert*-butoxide (1.55 g, 13.8 mmol) was added and the reaction mixture was stirred at 0 °C and warmed to room temperature overnight. The volatiles were evaporated, 2 M hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic extracts were combined, washed with water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford a mixture containing (R)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid *tert*-butyl ester, (S)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid *tert*-butyl ester, (R)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid and (S)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid (4.6 mmol) which was used crude in the next step. A solution of the mixture of (R)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid *tert*-butyl ester, (S)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid *tert*-butyl ester, (R)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid and (S)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid (4.6 mmol) in dichloromethane (10 mL) was stirred at 5 °C under nitrogen. Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred at room temperature for 20 h. Additional trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and the residue was co-evaporated with toluene (3 x). The residue was partitioned between ethyl acetate and water. The organic extracts were combined, washed with water and brine. The organics were filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 10:1 to 5:1 to afford (R)-2-((R)-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino)-3-methyl-butyric acid (152 mg, 12%) as a colorless oil and the title compound (321 mg, 26%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 1.23 (s, 6H), 2.09-2.19 (m, 1H), 2.85

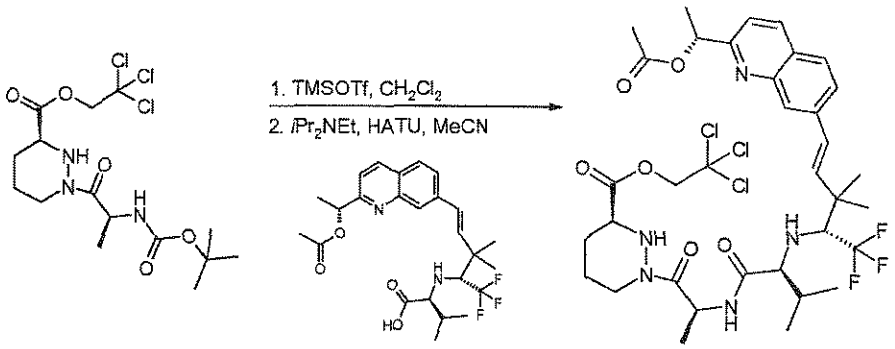
(q, J = 8.0 Hz, 1H), 3.27 (d, J = 4.0 Hz, 1H), 5.16 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.8 Hz, 1H), 5.91 (dd, J = 17.3, 10.8 Hz, 1H). LCMS (m/z) 268.1 [M+H], Tr = 2.95 min.

Compound 32d: (S)-2-{(E)-(R)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino}-3-methyl-butyric acid



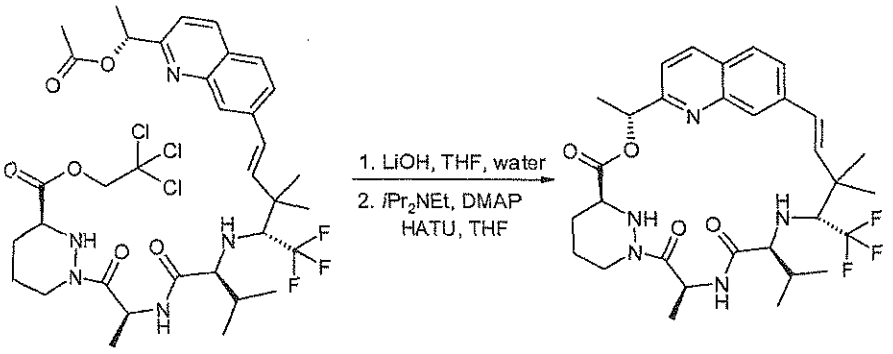
Compound 32d was prepared in the same manner as compound 31d using 32c instead of 31c and used crude in the next step. LCMS (m/z) 481.1 [M+H], Tr = 3.15 min.

Compound 32e: (S)-1-[(S)-2-((S)-2-{(E)-(R)-4-[2-((R)-1-Acetoxy-ethyl)-quinolin-7-yl]-2,2-dimethyl-1-trifluoromethyl-but-3-enylamino}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



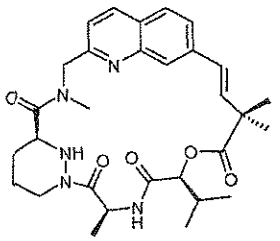
Compound 32e was prepared in the same manner as compound 31e using 32d instead of 32c in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 7.1 Hz, 3H), 0.92 (d, J = 7.1 Hz, 3H), 1.31 (d, J = 6.7 Hz, 3H), 1.38 (s, 6H), 1.69 (d, J = 6.7 Hz, 3H), 1.69-1.79 (m, 3H), 1.89-2.02 (m, 2H), 2.18 (s, 3H), 2.18-2.21 (m, 1H), 2.83-3.12 (m, 3H), 3.66-3.73 (m, 1H), 3.83 (d, J = 11.4 Hz, 1H), 4.42-4.48 (m, 1H), 4.72 (d, J = 11.8 Hz, 1H), 4.95 (d, J = 11.8 Hz, 1H), 5.27-5.34 (m, 1H), 6.06 (q, J = 6.7 Hz, 1H), 6.56 (ABq, $\Delta\delta_{AB}$ = 0.13, J_{AB} = 16.3 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H). LCMS (m/z) 794.2/796.1 [M+H], Tr = 3.65 min.

Compound 32.

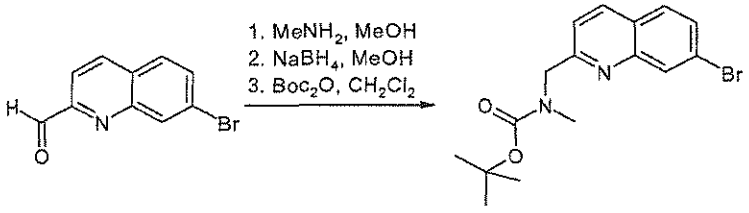


Compound 32 was prepared in the same manner as compound 31 using 32e instead of 31e in 35% as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 0.94 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 1.19 (d, J = 6.7 Hz, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 1.69 (d, J = 6.7 Hz, 3H), 1.70-1.90 (m, 4H), 2.18-2.22 (m, 2H), 3.39-3.60 (m, 3H), 3.81-3.96 (m, 2H), 4.73-4.81 (m, 1H), 6.03-6.16 (m, 2H), 6.78 (ABq, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 16.3 Hz, 2H), 7.39 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.98-8.05 (*br* s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.34 (s, 1H). LCMS (m/z) 604.3 [M+H], Tr = 2.78 min.

Example 33. – Compound 33



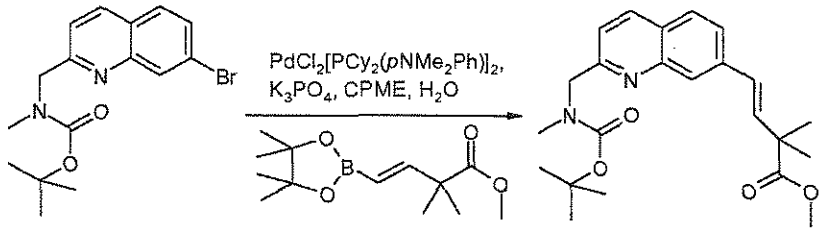
Compound 33a. (7-Bromo-quinolin-2-ylmethyl)-methyl-carbamic acid *tert*-butyl ester



To a stirred slurry of 7-bromo-quinoline-2-carbaldehyde (236 mg, 1.00 mmol, prepared as in EP 239746) in methanol (5 mL) was added methylamine in methanol (2 M, 2.5 mL, 5.00 mmol). The reaction mixture was stirred for 20 h and then evaporated. The residue was

suspended in methanol (5 mL) and sodium borohydride (57 mg, 1.50 mmol) was added portionwise. The reaction mixture was stirred for 1 h and then partitioned between dichloromethane and saturated ammonium chloride solution. The organic layer was separated and washed with saturated ammonium chloride solution and the aqueous extracts were extracted with dichloromethane and the combined organics dried over anhydrous sodium sulfate, filtered and evaporated. The residue was dissolved in dichloromethane (8 mL) and to the resulting stirred solution was added a solution of di-*tert*-butyl dicarbonate (327 mg, 1.50 mmol) in dichloromethane (2 mL). After stirring for 3 h the reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution (2 x) and the aqueous layer was extracted with dichloromethane. The combined organic extracts were passed through a hydrophobic frit and evaporated. The residue was purified by silica gel chromatography eluting with a gradient of *iso*-hexanes/ethyl acetate 1:0 to 4:1 to afford the title compound (206 mg, 59 %) as an orange oil and as a mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.61 (m, 9H), 2.92 (s, 1.5H), 3.00 (s, 1.5H), 4.71 (s, 1H), 4.75 (s, 1H), 7.34-7.46 (m, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 5.8 Hz, 1H), 8.26 (s, 1H). LCMS (m/z) 351.1, 353.1 [M+H], Tr = 3.13 min.

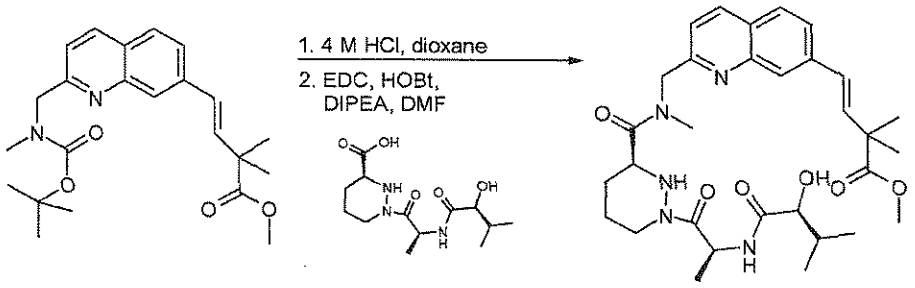
Compound 33b. (E)-4-{2-[(*tert*-Butoxycarbonyl-methyl-amino)-methyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid methyl ester



33a (206 mg, 0.586 mmol), 22d (171 mg, 0.674 mmol), bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine] palladium(II) chloride (24 mg, 0.029 mmol) and potassium phosphate tribasic (373 mg, 1.76 mmol) were suspended in cyclopentyl methyl ether (2 mL) and water (1 mL). The reaction mixture was stirred and heated at 80 °C for 2 h under nitrogen. More bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine] palladium(II) chloride (12 mg, 0.015 mmol) was added and the reaction mixture heated at 90 °C for 90 minutes. The reaction was allowed to cool and diluted with ethyl acetate and washed with water (2 x). The aqueous layers were extracted with ethyl acetate and the combined organic extracts were washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography eluting with a gradient of *iso*-hexanes/ethyl acetate 1:0 to 7:3 to afford

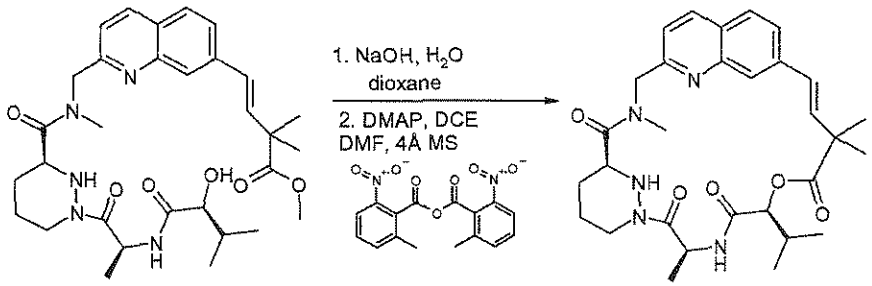
the title compound (178 mg, 76 %) as a yellow gum and as a mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43-1.57 (m, 15H), 2.91 (s, 1.5H), 2.99 (s, 1.5H), 3.74 (s, 3H), 4.71 (s, 1H), 4.74 (s, 1H), 6.64 (*app* s, 2H), 7.27-7.39 (m, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.90 (s, 1H), 8.10 (d, J = 8.5 Hz, 1H). LCMS (m/z) 399.1 [M+H], Tr = 3.02 min.

Compound 33c. (E)-4-{2-[({(S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carbonyl}-methyl-amino)-methyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid methyl ester



33b (134 mg, 0.336 mmol) was suspended in hydrogen chloride in 1,4-dioxane (4 M, 3.4 mL, 13.6 mmol) and the reaction mixture stirred for 2.5 h and then evaporated. To the residue was added a solution of 29a (106 mg, 0.353 mmol) in *N,N*-dimethylformamide (7 mL) followed by *N,N*-diisopropylethylamine (87 mg, 117 µL, 0.672 mmol), 1-hydroxybenzotriazole hydrate (63 mg, 0.470 mmol) and *N*-(3 dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (90 mg, 0.470 mmol) and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with ethyl acetate and washed successively with saturated sodium bicarbonate solution, water, saturated ammonium chloride solution, water and brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography eluting with a gradient of ethyl acetate/methanol 1:0 to 19:1 to afford the title compound (128 mg, 65 %) as a colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80-1.06 (m, 6H), 1.21-1.38 (m, 3H), 1.47 (s, 6H), 1.52-2.18 (m, 5H), 2.63-2.78 (m, 1H), 3.12 (s, 3H), 3.73 (s, 3H), 3.88-3.97 (m, 2H), 4.08-4.26 (m, 2H), 4.41-4.61 (m, 1H), 4.75-4.99 (m, 2H), 5.20-5.40 (m, 1H), 6.63 (*app* d, J = 2.0 Hz, 2H), 7.22-7.34 (m, 1H), 7.59-7.69 (m, 1H), 7.72-7.78 (m, 1H), 7.90-7.97 (d, J = 8.0 Hz, 1H), 8.08-8.20 (m, 1H). LCMS (m/z) 582.3 [M+H], Tr = 2.35 min.

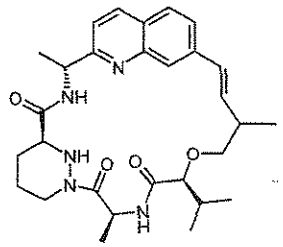
Compound 33.



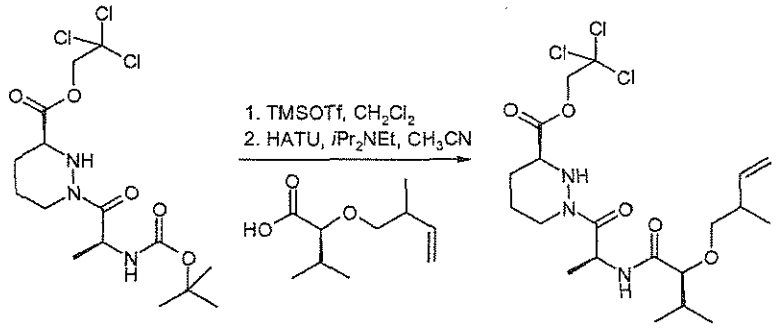
A stirred mixture of 33c (64 mg, 0.110 mmol) and 1M NaOH (0.88 mL, 0.88 mmol) in 1,4-dioxane (5.5 mL) was heated at reflux for 2.5 hours and then allowed to cool. The reaction mixture was neutralized to pH 7 with 2M hydrochloric acid and evaporated. The residue was azeotroped with *tert*-butanol/acetonitrile/toluene and then acetonitrile/toluene to give the crude acid.

To a stirred slurry of 2-methyl-6-nitrobenzoic acid (189 mg, 0.550 mmol), 4-(dimethylamino)pyridine (101 mg, 0.825 mmol) and powdered 4Å molecular sieves (~2g) in 1,2-dichloroethane (37 mL) under nitrogen at 50 °C was added a solution of the crude acid in N,N-dimethylformamide (5 mL) over 3 hours *via* syringe pump. The flask containing the original acid was washed with further N,N-dimethylformamide (1 mL) and this was added to the reaction mixture over 10 minutes. The reaction mixture was stirred at 50 °C for a further 2.5 hours and then allowed to cool. The mixture was filtered through celite and the filtrate washed successively with ice cold saturated ammonium chloride solution, ice cold saturated sodium bicarbonate solution and saturated brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by preparative HPLC using a gradient of acetonitrile/water 1:4 to 7:3 to afford the title compound (3.9 mg, 6.5%) as a white solid. LCMS (m/z) 550.3 [M+H], Tr = 2.35 min.

Examples 34 and 35. Compounds 34 and 35.

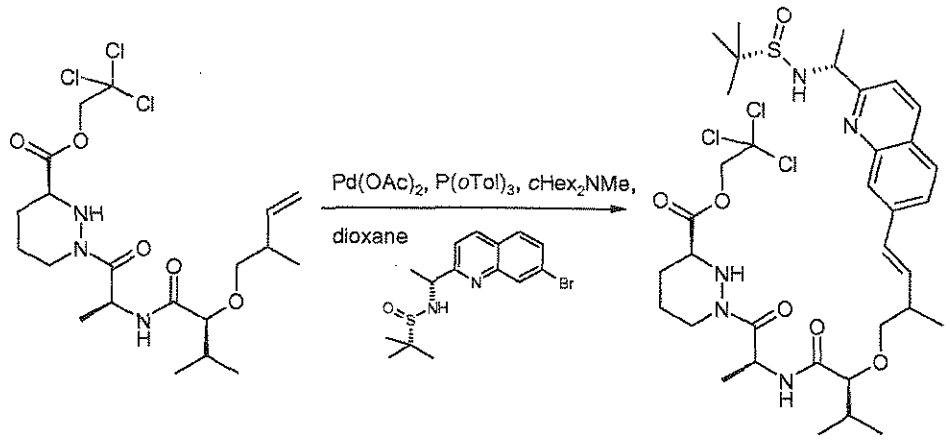


Compound 34a. (S)-1-{(S)-2-[(S)-3-Methyl-2-(2-methyl-but-3-enyloxy)-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



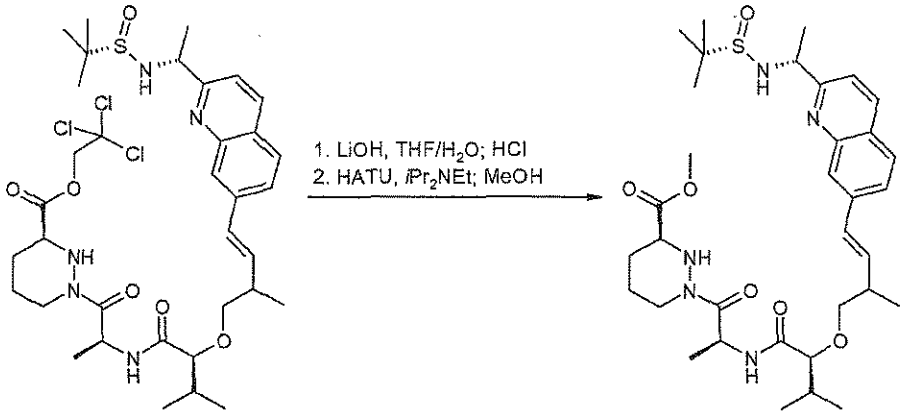
Compound 34a was prepared in the same manner as compound 27e using (S)-3-methyl-2-(2-methyl-but-3-enyloxy)-butyric acid instead of 27d in 72% yield and isolated as a 1:1 mixture of diastereosiomers. LCMS (m/z) 502.1/504.1 [M+H], Tr = 3.32 min.

Compound 34b. (S)-1-{(S)-2-[(S)-3-Methyl-2-((E)-2-methyl-4-{2-[(R)-1-(2(R)-methyl-propane-2-sulfinylamino)-ethyl]-quinolin-7-yl}-but-3-enyloxy)-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



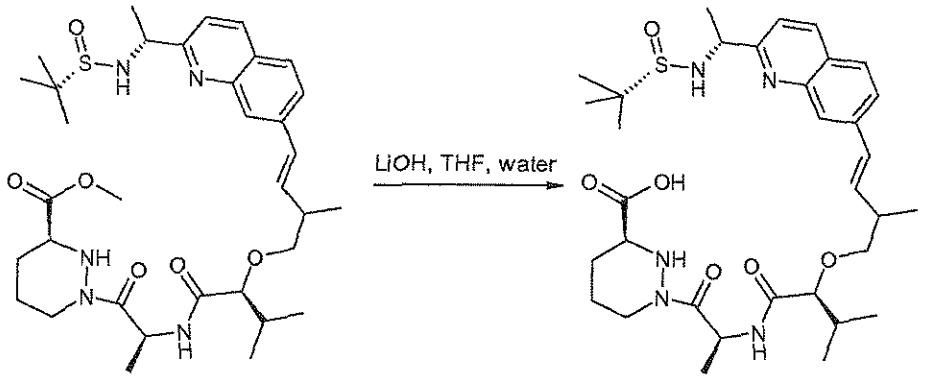
A solution of 34a (642.0 mg, 1.282 mmol), 18c (455.4 mg, 1.282 mmol), *N,N*-dicyclohexylmethylamine (0.83 mL, 3.846 mmol) in 1,4-dioxane (10 mL) was heated to 100 °C for 2 h. After cooling to room temperature, the volatiles were removed *in vacuo* and the residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 0:1 to afford the title compound (500.1 mg, 50%) as an orange gum and as a 1:1 mixture of diastereoisomers. LCMS (m/z) 774.3/776.2 [M+H], Tr = 3.31 min.

Compound 34c. (S)-1-{(S)-2-[(S)-3-methyl-2-((E)-2-methyl-4-{2-[(R)-1-((R)-2-methyl-propane-2-sulfinylamino)-ethyl]-quinolin-7-yl}-but-3-enyloxy)-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid methyl ester



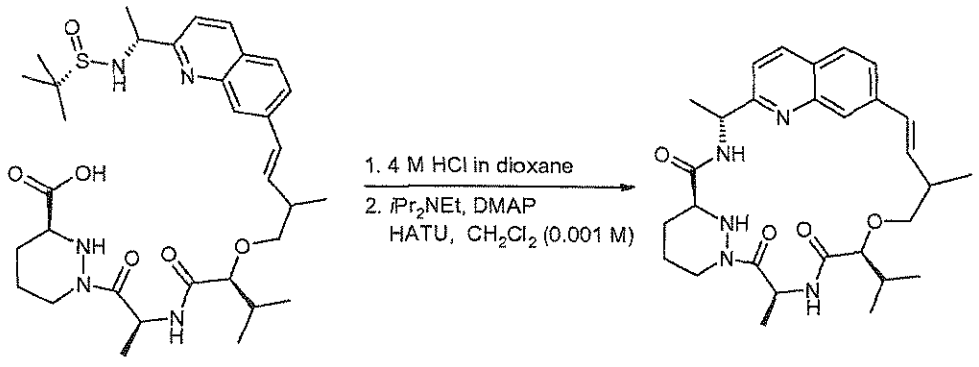
A cooled (0 °C) solution of 34b (500.1 mg, 0.645 mmol) in tetrahydrofuran/water (30 mL, 5:1) was treated with lithium hydroxide monohydrate (100.4 mg, 2.393 mmol). After stirring at 0 °C for 45 minutes, the reaction was quenched with hydrogen chloride solution (2 M, 1.2 mL) and the volatiles were removed *in vacuo*. The residual trichloroethanol was azeotroped off with toluene, toluene/methanol (2 x), toluene then dried *in* high *vacuo*. The white solid was triturated with diethyl ether (2 x) to provide crude (S)-1-{(S)-2-[(S)-3-methyl-2-((E)-2-methyl-4-{2-[(R)-1-((R)-2-methyl-propane-2-sulfinylamino)-ethyl]-quinolin-7-yl}-but-3-enyloxy)-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid (LCMS (m/z) 644.4 [M+H], Tr = 2.44 min) which was used without further purification. A cooled (0 °C) solution of crude (S)-1-{(S)-2-[(S)-3-methyl-2-((E)-2-methyl-4-{2-[(R)-1-((R)-2-methyl-propane-2-sulfinylamino)-ethyl]-quinolin-7-yl}-but-3-enyloxy)-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid (0.645 mmol), *N,N*-diisopropylethylamine (0.56 mL, 3.225 mmol) and 4-dimethylaminopyridine (7.9 mg, 0.064 mmol) in dry tetrahydrofuran (210 mL) was treated with 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (294.3 mg, 0.774 mmol). The reaction was allowed to slowly warm to room temperature. After 16 h, the reaction was quenched with anhydrous methanol (5 mL). The volatiles were removed *in vacuo* and the residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of dichloromethane/methanol 1:0 to 9:1 to afford the title compound (482.0 mg) as an orange gum and as a 1:1 mixture of diastereoisomers. LCMS (m/z) 658.3 [M+H], Tr = 2.68 min.

Compound 34d: (S)-1-{(S)-2-[(S)-3-Methyl-2-((E)-2-methyl-4-{2-[(R)-1-((R)-2-methyl-propane-2-sulfinylamino)-ethyl]-quinolin-7-yl}-but-3-enyloxy)-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid



A solution of crude 34c (480 mg, 0.73 mmol) in tetrahydrofuran (15 mL) was stirred at 0 °C under nitrogen. A solution of lithium hydroxide monohydrate (92 mg, 2.2 mmol) in water (3 mL) was added and the reaction mixture was stirred at 0 °C for 1 h. 1 M Hydrochloric acid (2.2 mL, 2.2 mmol) was added and the volatiles were evaporated. The residue was co-evaporated with tetrahydrofuran/toluene (1:1, 3 x) and then triturated with diethyl ether (2 x) and dried to afford the title compound (0.73 mmol) as a pale yellow gum and as a 1:1 mixture of diastereoisomers. LCMS (m/z) 644.4 [M+H], Tr = 2.44 min.

Compounds 34 and 35.



A solution of crude 34d (500 mg, 0.5 mmol) in 1,4-dioxane (10 mL) was stirred at room temperature under nitrogen. A solution of 4 M hydrogen chloride in 1,4-dioxane (1 mL) was added and the reaction mixture was stirred at room temperature for 30 minutes. The volatiles were evaporated and the residue was co-evaporated with tetrahydrofuran/toluene (1:1, 3 x) and then triturated with diethyl ether (2 x). The residue was dried to afford (S)-1-[(S)-2-((S)-2-{(E)-4-

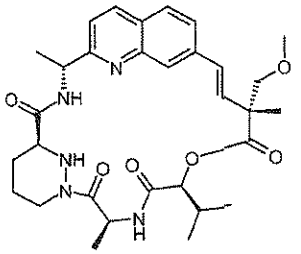
[2-((R)-1-amino-ethyl)-quinolin-7-yl]-2-methyl-but-3-enyloxy}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid hydrochloride as a dark yellow gum (0.5 mmol) and as a 1:1 mixture of diastereoisomers which was used crude in the next reaction. LCMS (m/z) 540.2 [M+H], Tr = 1.57 min. A suspension of (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-amino-ethyl)-quinolin-7-yl]-2-methyl-but-3-enyloxy}-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid hydrochloride (0.5 mmol) in dichloromethane (500 mL) was stirred at 0 °C under nitrogen. *N,N*-Diisopropylethylamine (387 mg, 0.52 mL, 3.0 mmol) and 4-dimethylaminopyridine (20 mg, 0.18 mmol) were added and the reaction mixture was stirred at 0° C for 5 minutes. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (380 mg, 1.0 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 72 h. The volatiles were evaporated. Ethyl acetate was added and the mixture was washed with cold 1 M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:3 to ethyl acetate then ethyl acetate to ethyl acetate/methanol 1:10. The residue was purified by reverse phase preparative HPLC eluting with acetonitrile (containing 0.1% formic acid) / water (containing 0.1% formic acid) 35:65. Fractions containing the pure diastereoisomers were combined and evaporated. The residues were partitioned between saturated sodium hydrogen carbonate solution and ethyl acetate. The organic layers were separated, washed with water and brine. The organic solutions were filtered through a hydrophobic frit and the filtrate was dried to afford two diastereoisomers.

Compound 34 (First Eluting) Diastereomer 1: (3 mg, 1%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.97 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.60-1.65 (m, 2H), 1.66 (d, J = 7.1 Hz, 3H), 1.94-2.07 (m, 2H), 2.28-2.33 (m, 1H), 2.60-2.76 (m, 2H), 3.49 (d, J = 8.5 Hz, 1H), 3.55-3.71 (m, 2H), 3.92 (dd, J = 9.5, 4.4 Hz, 1H), 4.41-4.46 (m, 1H), 5.10 (q, J = 6.5 Hz, 1H), 5.82 (q, J = 7.1 Hz, 1H), 6.51 (dd, J = 16.1, 5.8 Hz, 1H), 6.63 (d, J = 16.1 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 8.24 (d, J = 8.5 Hz, 1H). LCMS (m/z) 522.2 [M+H], Tr = 2.41 min.

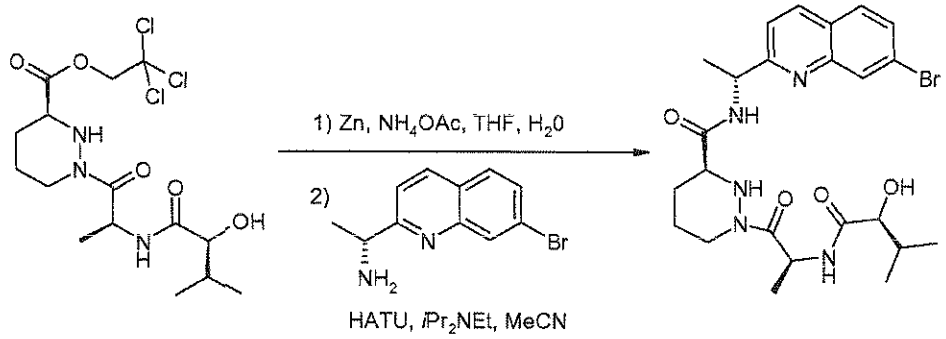
Compound 35 (Second Eluting) Diastereomer 2: (3 mg, 1%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.93 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 1.51-1.55 (m, 1H), 1.59 (d, J = 6.5 Hz, 3H), 1.68 (d, J = 7.1 Hz, 3H), 1.69-1.73 (m, 1H), 1.94-1.99 (m, 2H), 2.29-2.34 (m, 1H), 2.65-2.75 (m, 2H), 3.38-3.43 (m, 2H), 3.57-3.62 (m, 1H), 3.96 (dd, J = 9.0, 3.2 Hz, 1H), 4.40-4.46 (m, 1H), 5.10 (q, J = 6.4 Hz, 1H), 5.84-5.89 (m, 1H), 6.38

(dd, J = 16.1, 6.3 Hz, 1H), 6.65 (d, J = 16.1 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.46 (dd, J = 8.5, 1.6 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 8.05 (*br* s, 1H), 8.24 (d, J = 8.5 Hz, 1H). LCMS (m/z) 522.2 [M+H], Tr = 2.38 min.

Example 36. Compound 36.



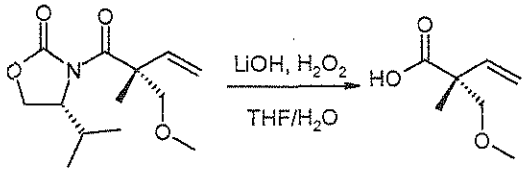
Compound 36a. (S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-amide



Zinc dust (1.3 g, 20.3 mmol) was added to a solution of (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (400 mg, 0.92 mmol) in tetrahydrofuran (20 mL). This suspension was treated with a solution of ammonium acetate (1.1 g, 13.9 mmol) in water (7 mL). After stirring at room temperature for 16 h, the zinc residues were filtered off and the volatiles were removed *in vacuo*. The residue was partitioned between ethyl acetate and saturated potassium hydrogen sulfate solution, the aqueous layer was extracted with ethyl acetate (2 x), the organic layers were combined and the volatiles were removed *in vacuo*. The residual acetic acid was azeotroped off with toluene (3 x 10 mL) to give crude (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid (280 mg, 99%) half of which (140 mg, 0.46mmol) was combined with (R)-1-(7-bromo-quinolin-2-yl)-ethylamine hydrochloride (obtained from ASIBA Pharmatech, Inc.), (194 mg, 0.60 mmol) and *N,N*-diisopropylethylamine (0.400 mL, 2.3 mmol) in anhydrous acetonitrile (10 mL). This solution was then treated with 2-

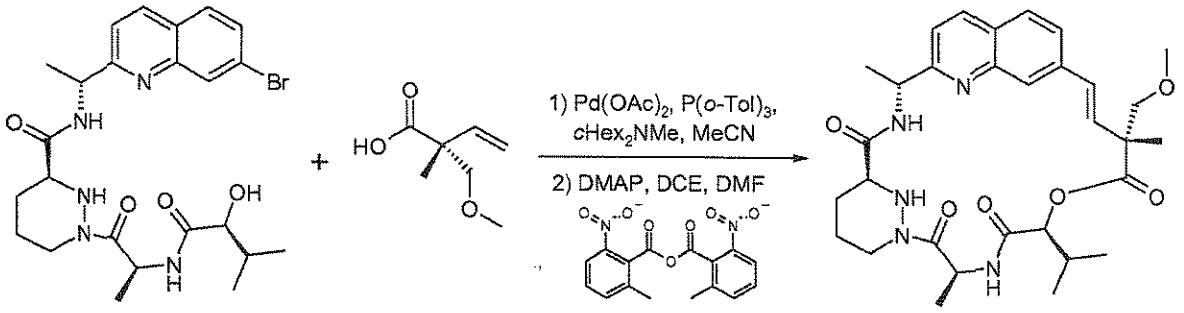
(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (227 mg, 0.60 mmol). After stirring at room temperature for 3 h, the volatiles were removed *in vacuo*. The residue was dissolved in ethyl acetate and subsequently washed with saturated ammonium chloride solution and sodium bicarbonate solution. The organics were combined and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Biotage cartridge eluted with a continuous gradient of *iso*-hexanes/acetone 1:0 to 1:1 to afford the title compound (136 mg, 55%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.83 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 1.38 (d, J = 6.9 Hz, 3H), 1.60 (d, J = 6.9 Hz, 3H), 1.65-1.75 (m, 3H), 1.87-1.96 (m, 1H), 2.02-2.12 (m, 2H), 2.87-3.00 (m, 1H), 3.55-3.62 (m, 1H), 3.81 (d, J = 3.4 Hz, 1H), 4.24-4.34 (m, 1H), 5.18-5.28 (m, 1H), 5.31-5.40 (m, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.69 (dd, J = 8.7, 1.8 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 1.6 Hz, 1H), 8.33 (d, J = 8.7 Hz, 1H). LCMS (m/z) 534.1, 536.1 [M+H], Tr = 2.27 min.

Compound 36b. (R)-2-Methoxymethyl-2-methyl-but-3-enoic acid



Compound 36b was prepared in the same manner as compound 29d using compound (R)-4-isopropyl-3-((R)-2-methoxymethyl-2-methyl-but-3-enoyl)-oxazolidin-2-one (the enantiomer of 58a, prepared as described in *Tet. Lett.* 2000, *41(33)*, 6429-6433) instead of 29c in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 3.41 (s, 3H), 3.43 (d, J = 8.9 Hz, 1H), 3.61 (d, J = 8.9 Hz, 1H), 5.20-5.30 (m, 2H), 6.00 (dd, J = 17.6, 10.7 Hz, 1H).

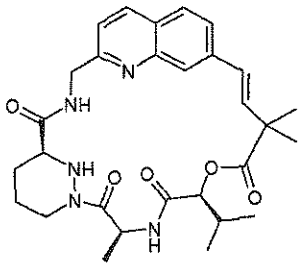
Compound 36.



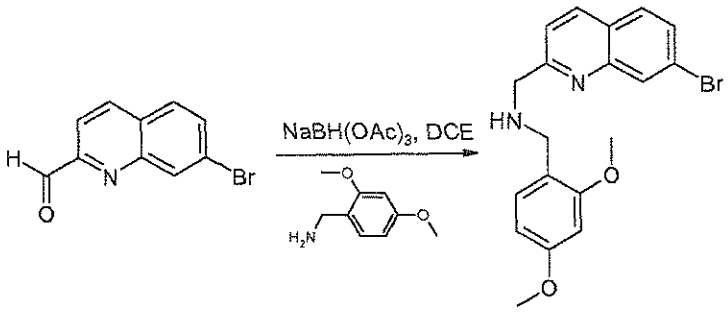
A solution of 36a (123 mg, 0.23 mmol), 36b (40 mg, 0.27 mmol), palladium(II) acetate (11 mg, 0.046 mmol), tris-(*o*-tolyl)phosphine (21 mg, 0.068 mmol) in anhydrous acetonitrile (3

mL) was treated with triethylamine (81 µL, 0.57 mmol). After stirring at 100 °C under microwave irradiation for 20 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The residue was partitioned between dichloromethane and a saturated potassium hydrogen sulfate solution. The organics were combined and the volatiles were removed *in vacuo*. The residue was azeotroped with toluene (3 x 10 mL) to give crude (E)-(R)-4-{2-[(R)-1-({(S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-1-oxo-propyl]-hexahydro-pyridazine-3-carbonyl}-amino)-ethyl]-quinolin-7-yl}-2-methoxymethyl-2-methyl-but-3-enoic acid which was dissolved in *N,N*-dimethylformamide (5 mL) and added *via* syringe pump over 6 h to a stirred slurry of 2-methyl-6-nitrobenzoic anhydride (161 mg, 0.47 mmol) and 4-dimethylaminopyridine (86 mg, 0.70 mmol) in 1,2-dichloroethane (35 mL) at 50 °C under nitrogen. The reaction was cooled down to room temperature and was subsequently washed with 5% citric acid solution and sodium bicarbonate solution. The organics were combined and the volatiles were removed *in vacuo*. The residue was purified by preparative reverse phase HPLC to afford the title compound (8 mg, 15%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.01 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.56 (s, 3H), 1.60 (d, J = 6.9 Hz, 3H), 1.68 (d, J = 6.9 Hz, 3H), 1.69-1.75 (m, 1H), 1.91-1.99 (m, 1H), 2.10-2.30 (m, 2H), 3.36 (s, 2H), 3.41 (s, 3H), 3.49 (d, J = 8.9 Hz, 1H), 3.58-3.68 (m, 1H), 3.80 (d, J = 9.1 Hz, 1H), 4.38-4.48 (m, 1H), 5.03-5.13 (m, 1H), 5.19 (d, J = 9.1 Hz, 1H), 5.74-5.85 (m, 1H), 6.41 (ABq, $\Delta\delta_{AB}$ = 0.34, J_{AB} = 16.4 Hz, 2H), 7.45 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H). LCMS (m/z) 580.2 [M+H], Tr = 2.38 min.

Example 37. Compound 37.

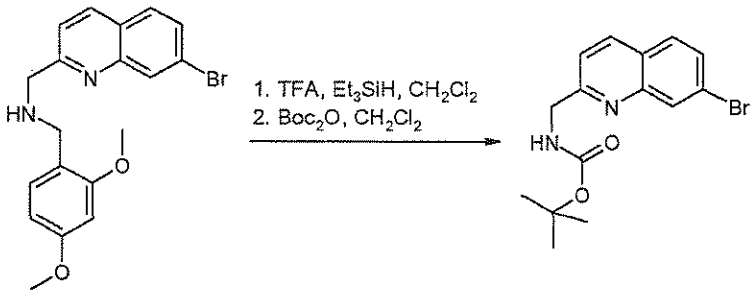


Compound 37a. (7-Bromo-quinolin-2-ylmethyl)-(2,4-dimethoxy-benzyl)-amine



7-Bromo-quinoline-2-carbaldehyde (354 mg, 1.50 mmol, prepared as described in EP 239746) was dissolved in 1,2-dichloroethane (15 mL) and 2,4-dimethoxybenzylamine (251 mg, 225 µL, 1.50 mmol) was added and the reaction mixture stirred for 5 minutes before sodium triacetoxyborohydride (477 mg, 2.25 mmol) was added. After 3.5 h stirring the reaction mixture was quenched with saturated sodium hydrogen carbonate solution and ethyl acetate was added. The organic layer was separated and washed with sodium hydrogen carbonate and the combined aqueous layers were extracted with ethyl acetate. The organic extracts were washed with saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to give the crude, title compound as a yellow gum (571 mg) which was used without further purification. LCMS (m/z) 387.0, 389.0 [M+H], Tr = 1.57 min.

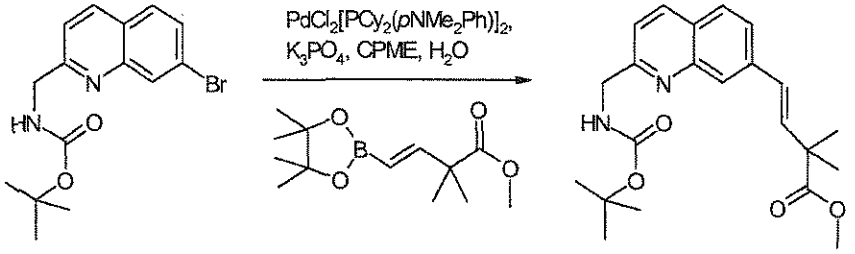
Compound 37b. (7-Bromo-quinolin-2-ylmethyl)-carbamic acid *tert*-butyl ester



37a (290 mg, 0.75 mmol) was dissolved in dichloromethane (8 mL) and triethylsilane (1.6 mL) and trifluoroacetic acid (8 mL) were added. The reaction mixture was heated to reflux and stirred for 20 h and then allowed to cool. The mixture was evaporated and purified by SCX cartridge eluting with methanol and then methanolic ammonia and the basic fraction collected and evaporated. The residue was dissolved in dichloromethane (8 mL) and di-*tert*-butyl dicarbonate (245 mg, 1.13 mmol) added and the reaction mixture stirred for 17 h. Diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution (2 x), the

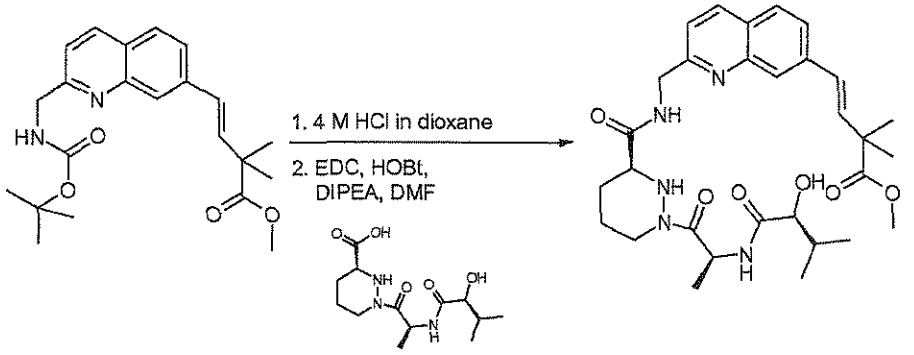
aqueous layer was back-extracted with dichloromethane and the combined organic extracts passed through a hydrophobic frit and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:0 to 4:1 to afford the title compound (150 mg, 59 %) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9H), 4.65 (d, J = 4.9 Hz, 2H), 5.90 (*br* s, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.63 (dd, J = 8.5, 1.9 Hz, 2H), 7.72 (d, J = 8.5 HZ, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H). LCMS (m/z) 337.0, 339.0 [M+H], Tr = 2.79 min.

Compound 37c. (E)-4-[2-(*tert*-Butoxycarbonylamino-methyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enoic acid methyl ester



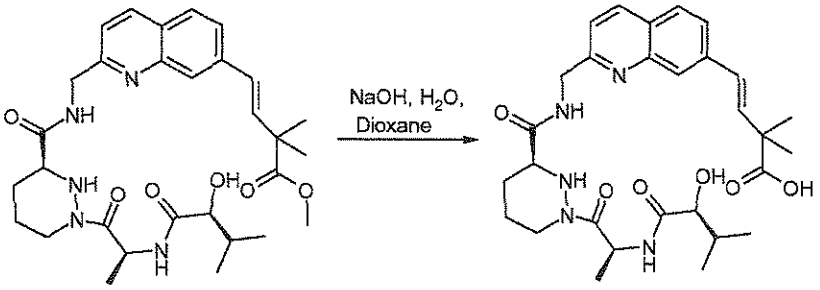
37b (296 mg, 0.878 mmol), 22d (256 mg, 1.01 mmol), bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine] palladium(II) chloride (36 mg, 0.044 mmol) and potassium phosphate tribasic (558 mg, 2.63 mmol) were suspended in cyclopentyl methyl ether (3 mL) and water (1.5 mL). The reaction mixture was stirred and heated at 80 °C for 3 h under nitrogen. The reaction was allowed to cool and diluted with ethyl acetate and washed with water (2 x) and brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:0 to 7:3 to afford the title compound (257 mg, 76 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 6H), 1.52 (s, 9H), 3.75 (s, 3H), 4.63 (d, J = 4.9 Hz, 2H), 5.96 (*br* s, 1H), 6.64 (s, 2H), 7.32 (d, J = 8.5 Hz, 1H), 7.63 (dd, J = 8.5, 1.3 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H). LCMS (m/z) 385.1 [M+H], Tr = 2.64 min.

Compound 37d. (E)-4-{2-[({(S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carbonyl}-amino)-methyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid methyl ester



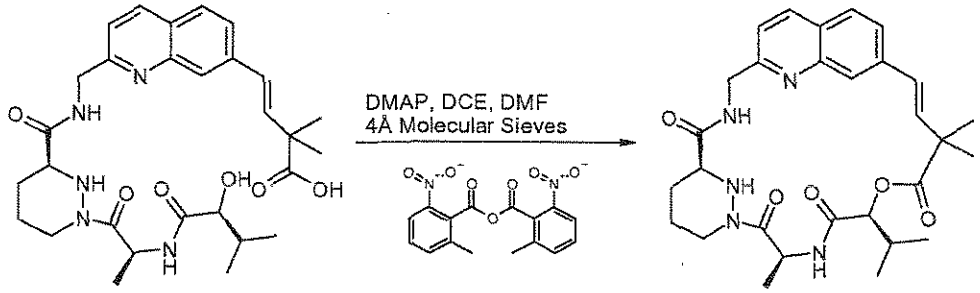
37c (128 mg, 0.333 mmol) was suspended in 4 M hydrogen chloride in 1,4-dioxane (3.3 mL) and the reaction mixture stirred for 2.5 h and then evaporated. To the residue was added a solution of 29a (105 mg, 0.350 mmol) in *N,N*-dimethylformamide (7 mL) followed by *N,N*-diisopropylethylamine (86 mg, 116 µL, 0.666 mmol). To the stirred solution was added 1-hydroxybenzotriazole hydrate (63 mg, 0.466 mmol) and *N*-(3 dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (89 mg, 0.466 mmol) and the reaction mixture stirred for 16 h. The reaction mixture was diluted with ethyl acetate and washed successively with saturated sodium bicarbonate solution, water, saturated ammonium chloride solution, water and then brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/methanol 1:0 to 19:1 to afford the title compound (95 mg, 50 %) as an off-white solid.^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 1.42 (d, J = 6.9 Hz, 3H), 1.48 (s, 6H), 1.65-1.76 (m, 2H), 1.88-1.98 (m, 1H), 2.06-2.14 (m, 1H), 2.19-2.29 (m, 1H), 2.73-2.83 (m, 1H), 3.45-3.56 (m, 1H), 3.73 (s, 3H), 3.95 (d, J = 3.1 Hz, 1H), 3.99 (d, J = 11.6 Hz, 1H), 4.42-4.52 (m, 1H), 4.69-4.76 (m, 2H), 5.41-5.51 (m, 1H), 6.61-6.66 (m, 1H), 6.74 (d, J = 16.3 Hz, 1H), 7.24-7.31 (m, 1H), 7.62-7.69 (m, 1H), 7.71-7.78 (m, 1H), 7.95-8.10 (m, 2H). LCMS (m/z) 568.3 [M+H], Tr = 2.10 min.

Compound 37e. (E)-4-{2-[({(S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carbonyl}-amino)-methyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid



A stirred mixture of 37d (95 mg, 0.167 mmol) and NaOH (1 M, 1.34 mL, 1.34 mmol) in 1,4-dioxane (8 mL) was heated at reflux for 70 minutes and then allowed to cool. The reaction mixture was acidified to pH 4 with hydrochloric acid (2 M) and evaporated. The residue was purified by reverse phase preparative HPLC using a gradient of acetonitrile/water 1:19 to 7:3 to afford the title compound (43 mg, 47 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.8 Hz, 3H), 0.93-1.00 (m, 3H), 1.38 (d, J = 8.2 Hz, 3H), 1.49 (s, 6H), 1.58-1.76 (m, 2H), 1.81-1.94 (m, 1H), 1.99-2.12 (m, 1H), 2.16-2.25 (m, 1H), 2.67-2.79 (m, 1H), 3.41-3.51 (m, 1H), 3.92-4.00 (m, 1H), 4.01-4.08 (d, J = 11.6 Hz, 1H), 4.40-4.54 (m, 1H), 4.74 (d, J = 4.5 Hz, 2H), 5.41-5.52 (m, 1H), 6.63-6.76 (m, 2H), 7.26-7.32 (m, 1H), 7.33-7.39 (m, 1H), 7.55-7.64 (m, 1H), 7.75 (d, J = 8.5 Hz, 1H), 8.04-8.14 (m, 2H). LCMS (m/z) 554.2 [M+H], Tr = 1.77 min.

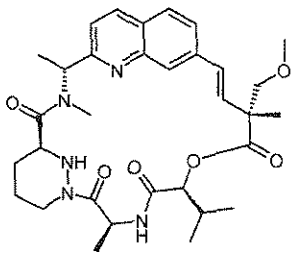
Compound 37.



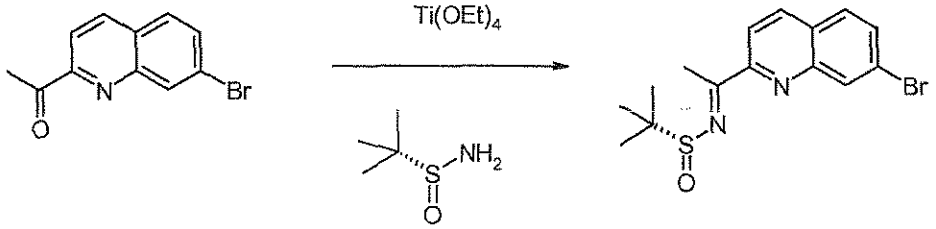
To a stirred slurry of 2-methyl-6-nitrobenzoic acid (134 mg, 0.388 mmol), 4-(dimethylamino)pyridine (71 mg, 0.583 mmol) and powdered 4 Å molecular sieves (~1 g) in 1,2-dichloroethane (26 mL) under nitrogen at 50 °C was added a solution of 37e (43 mg, 0.078 mmol) in *N,N*-dimethylformamide (3 mL) over 4 h *via* syringe pump. The flask containing the original acid was washed with further *N,N*-dimethylformamide (1 mL) and this was added to the reaction mixture over 10 minutes. After the end of addition, the reaction mixture was stirred at 50 °C for 3 h and then allowed to cool. The mixture was filtered through Celite and the filtrate washed successively with ice-cold saturated ammonium chloride solution, ice-cold saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by reverse phase preparative HPLC using a gradient of acetonitrile/water 1:4 to 4:1 modified with 0.1% formic acid and the product triturated with ether to afford the title compound (6.4 mg, 15 %) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.02 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 1.46 (s, 3H), 1.48 (d, J = 7.3 Hz, 3H), 1.54 (s, 3H), 1.55-1.79 (m, 2H), 1.94-2.04 (m, 1H), 2.16-2.30 (m, 1H), 2.30-2.40 (m, 1H), 2.71-2.83 (m, 1H), 3.53-3.60 (m, 1H), 4.42-4.51 (m, 1H), 4.67, 4.75 (ABq, J_{AB} = 18.4 Hz, 2H), 5.20 (d, J = 8.9

Hz, 2H), 5.89 (q, *J* = 7.2, 1H), 6.44 (d, *J* = 16.2 Hz, 1H), 6.69 (d, *J* = 16.2 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.5, 1.3 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H). LCMS (m/z) 536.2 [M+H], Tr = 2.47 min.

Example 38. Compound 38.

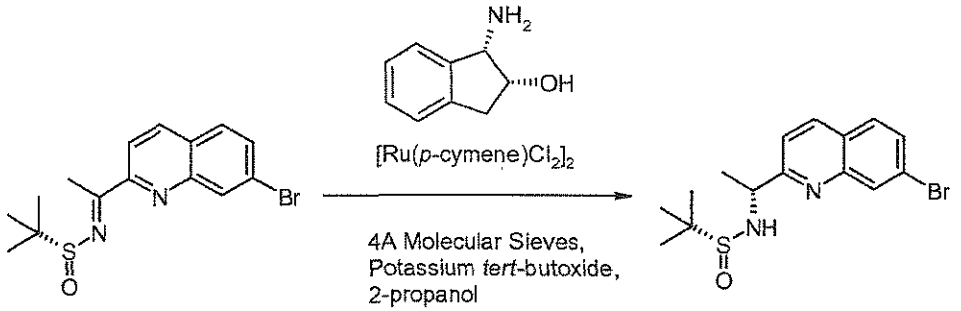


Compound 38a (R)-2-Methyl-propane-2-sulfinic acid [1-(7-bromo-quinolin-2-yl)-eth-(E)-ylidene]-amide



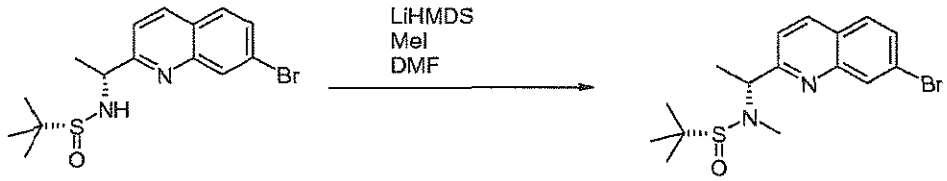
To a solution of 18a (1.42 g, 5.68 mmol) in THF (28 mL) was added titanium (IV) ethoxide (2.6 g, 2.35 mL, 11.4 mmol, tech. grade) followed by (R)-(+)-2-methyl-propanesulfinimide (825 mg, 6.82 mmol). The reaction mixture was stirred at 60°C under nitrogen for 6 hours and allowed to cool. Brine was added followed by ethyl acetate and the suspension filtered through celite and the filter pad was washed with ethyl acetate. The ethyl acetate layer was separated, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of iso-hexane /ethyl acetate 9:1 to 3:1 to give the title compound (448 mg, 22%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.99 (s, 3H), 7.71 (m, 2H), 8.16 (d, *J* = 8.6 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.37 (s, 1H). LCMS (m/z) 352.9/354.9 [M+H], Tr 3.14 minutes.

Compound 38b (R)-2-Methyl-propane-2-sulfinic acid [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-amide.



A mixture of (1S, 2R)-(-)-*cis*-1-amino-2-indanol (19 mg, 0.13 mmol), [Ru (*p*-cymen) $Cl_2]_2$ (39mg, 0.064 mmol) and powdered 4 Å Molecular Sieves (0.7g) was suspended in anhydrous 2-propanol (3 mL) and stirred under nitrogen. The suspension was heated at 90 °C for 30 minutes. The reaction mixture was cooled to 40 °C and a solution 38a (448 mg, 1.27 mmol) in 2-propanol (9 mL) was added followed by a solution of potassium *tert*-butoxide (36 mg, 0.32 mmol) in 2-propanol (3 mL). The reaction mixture was stirred for 2 hours at 40 °C and then allowed to cool. The mixture was poured directly onto a silica gel cartridge and eluted with ethyl acetate. After concentration the residue was further purified by silica gel chromatography using a gradient of iso-hexane /ethyl acetate 1:1 to 0:1 to give the title compound (287 mg, 64%) as a brown gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.60 (d, J = 6.7 Hz, 3H), 4.80 (m, 1H), 5.42 (*br* d, J = 4.2 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.2 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H). LCMS (m/z) 354.9/356.8 [M+H], Tr 2.49 min

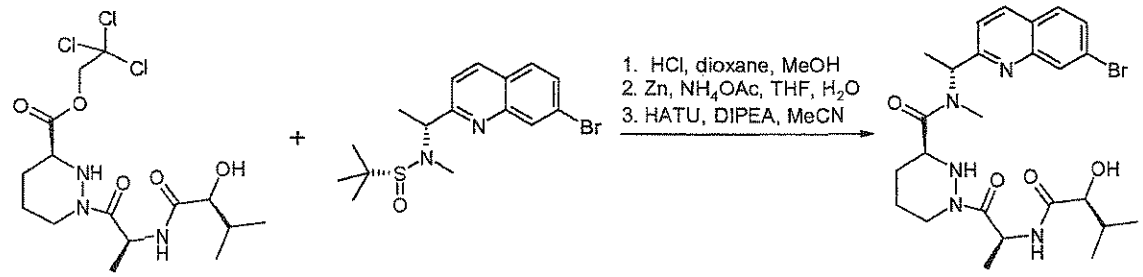
Compound 38c. 2-Methyl-propane-2-sulfinic acid (R)-[(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-methyl-amide



A cooled (–20 °C) solution of 38b (100 mg, 0.28 mmol, same as 18c) in *N,N*-dimethylformamide (5 mL) was treated with lithium bis(trimethylsilyl)amide (0.28 mL, 0.28 mmol, 1 M in hexane). After stirring at this temperature for 1 h, iodomethane (0.035 mL, 0.56 mmol) was added and the temperature raised to room temperature. After stirring at room temperature for 1 h, the reaction was quenched by addition of water (10 mL). The mixture was extracted with diethyl ether (3 x 20mL). The organics were combined and the volatiles were removed *in vacuo*. The residue was

purified by silica gel chromatography using a 10 g Biotage cartridge eluted with a continuous gradient of *iso-hexanes*/ethyl acetate 1:0 to 1:1 to afford the title compound (149 mg, 62%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.74 (d, J = 6.9 Hz, 3H), 2.53 (s, 3H), 4.81 (q, J = 6.9 Hz, 1H), 7.55-7.70 (m, 3H), 8.11 (d, J = 8.5 Hz, 1H), 8.27 (s, 1H). LCMS (m/z) 369.0, 371.0 [M+H], Tr = 2.91 min.

Compound 38d. (S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-methyl-amide

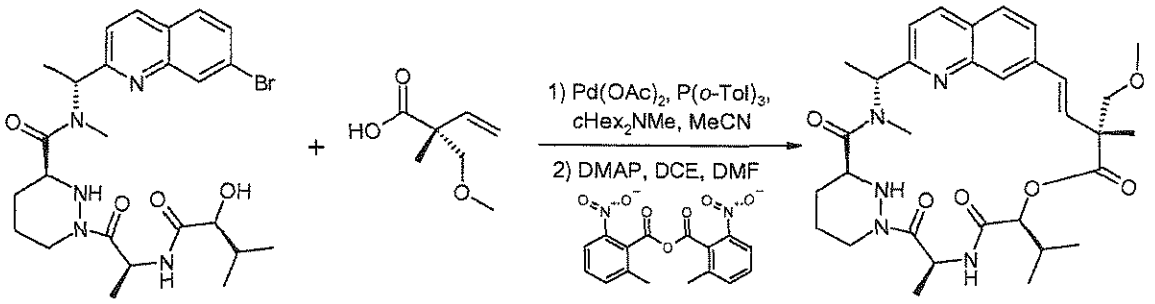


A solution of 38c (450 mg, 1.22 mmol) in methanol (10 mL) was treated with hydrochloric acid in 1,4-dioxane (4 M, 5 mL). After stirring at room temperature for 2 h, the volatiles were removed *in vacuo*. The residual solvent was azeotroped off with toluene (3 x 10 mL) to give crude [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-methyl-amine hydrochloride.

Zinc dust (1.30 g, 20.32 mmol) was added to a solution of (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (400 mg, 0.92 mmol) in tetrahydrofuran (20 mL). This suspension was treated with a solution of ammonium acetate (1.10 g, 13.9 mmol) in water (7 mL). After stirring at room temperature for 16 h, zinc residues were filtered off and the volatiles were removed *in vacuo*. The residue was partitioned between ethyl acetate and saturated potassium hydrogen sulfate solution, the aqueous layer was extracted with ethyl acetate (2 x), the organic layers were combined and the volatiles were removed *in vacuo*. The residual acetic acid was azeotroped off with toluene (3 x 10 mL) to give crude (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid which was combined with crude [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-methyl-amine hydrochloride in anhydrous acetonitrile (15 mL) and *N,N*-diisopropylethylamine (0.801 mL, 4.60 mmol). This solution was then treated with 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (464 mg, 1.22 mmol). After stirring at room temperature for 2 h, the volatiles were removed *in vacuo*. The residue was dissolved in ethyl acetate and subsequently washed with saturated ammonium chloride solution and sodium bicarbonate solution. The organics were combined and the

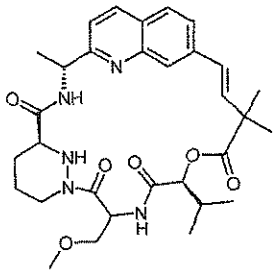
volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Biotage cartridge eluted with a continuous gradient of *iso*-hexanes/acetone 1:0 to 0:1 to afford the title compound (318 mg, 58%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.69 (d, J = 6.9 Hz, 3H), 1.72-2.15 (m, 6H), 2.98 (s, 3H), 2.85-2.95 (m, 1H), 3.80-3.90 (m, 1H), 4.30-4.40 (m, 1H), 5.25-5.35 (m, 1H), 5.95-6.10 (m, 1H), 7.45-7.78 (m, 1H), 7.65-7.72 (m, 1H), 7.80-7.90 (m, 1H), 8.18-8-38 (m, 2H). LCMS (m/z) 548.1, 550.1 [M+H], Tr = 2.60 min.

Compound 38.

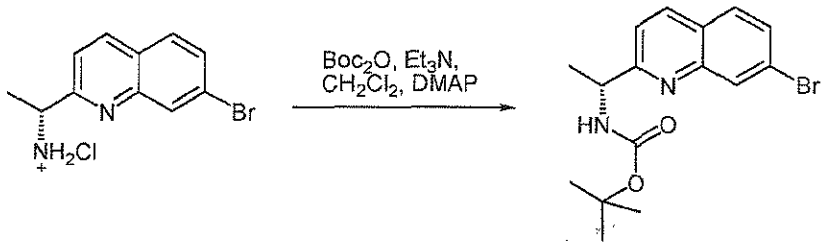


Compound 38 was prepared in the same manner as compound 36 using 38d instead of (36a (123 mg, 0.23 mmol) in 4% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 1.00 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 1.52-1.59 (m, 6H), 1.73 (d, J = 7.4 Hz, 3H), 1.76-1.88 (m, 2H), 1.89-1.99 (m, 2H), 2.09-2.21 (m, 1H), 2.71-2.84 (m, 1H), 3.29 (s, 3H), 3.40 (s, 3H), 3.44 (d, J = 8.7 Hz, 1H), 3.79 (d, J = 8.9 Hz, 1H), 4.13-4.22 (m, 1H), 4.39-4.47 (m, 1H), 5.05 (d, J = 9.1 Hz, 1H), 5.83-5.97 (m, 2H), 6.38 (ABq, $\Delta\delta_{AB}$ = 0.24, J_{AB} = 16.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 1H), 7.64-7.73 (m, 2H), 7.79 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H). LCMS (m/z) 594.2 [M+H], Tr = 2.48 min.

Examples 39 and 40, Compound 39 and 40

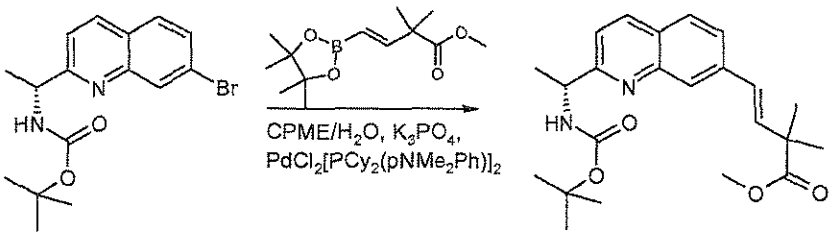


Compound 39a. [(R)-1-(7-Bromo-quinolin-2-yl)-ethyl]-carbamic acid *tert*-butyl ester



To a solution of (R)-1-(7-bromo-quinolin-2-yl)-ethylamine hydrochloride (obtained from ASIBA Pharmatech Inc.), (3.5 g, 12.2 mmol) in anhydrous dichloromethane at 0 °C and under an atmosphere of nitrogen was added triethylamine (5.1 mL, 36.5 mmol), 4-dimethylaminopyridine (297 mg, 2.4 mmol) and di-*tert*-butyl dicarbonate (4.0 g, 18.3 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction was cooled to 0 °C and quenched with hydrochloric acid (1 M). The organic layer was separated, washed with brine, dried through a hydrophobic frit and concentrated *in vacuo*. The product was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 6:1 to afford the title compound (3 g, 70%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.55 (d, J = 6.9 Hz, 3H), 4.93–5.10 (m, 1H), 6.01–6.20 (m, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.7, 1.8 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.29 (s, 1H). LCMS (m/z) 353.0 [M+H], Tr = 3.02 min.

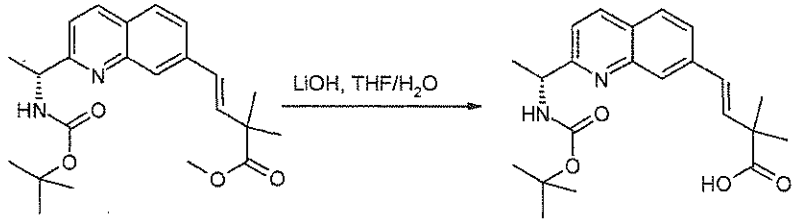
Compound 39b. (E)-4-[2-((R)-1-*tert*-Butoxycarbonylamino-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enoic acid methyl ester



To a solution 39a (1g, 2.86 mmol) in cyclopentylmethyl ether (14 mL) and water (7 mL), at room temperature, was added 22d (840 mg, 3.43 mmol), potassium phosphate tribasic (1.8 g, 8.57 mmol) and bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine] palladium(II) chloride (116 mg, 0.14 mmol). The reaction was heated to 80 °C for 2 h. The reaction was cooled, diluted with ethyl acetate and washed with brine (2 x). The organic layer was dried through a hydrophobic frit and concentrated *in vacuo*. The product was purified by silica gel

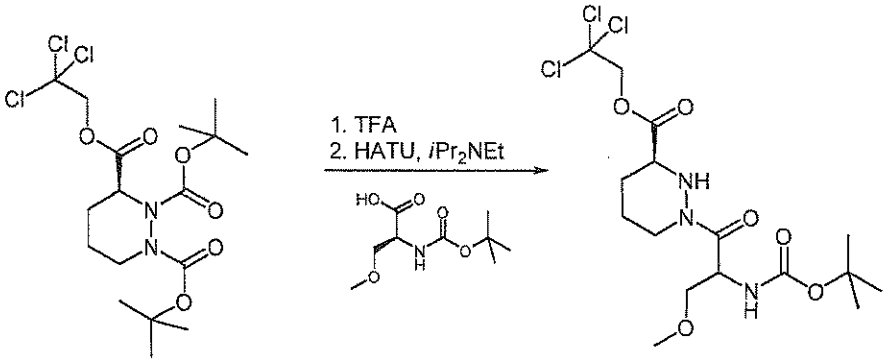
chromatography using *iso*-hexanes/ethyl acetate 2:1 to afford the title compound (1.1 g, 96%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43–1.52 (m, 15H), 1.56 (d, J = 6.7 Hz, 3H), 3.75 (s, 3H), 4.92–5.09 (m, 1H), 6.16–6.32 (m, 1H), 6.64 (s, 2H), 7.30 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.6 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H). LCMS (m/z) 399.3 [M+H], Tr = 2.75 min.

Compound 39c. (E)-4-[2-((R)-1-*tert*-Butoxycarbonylamino-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enoic acid



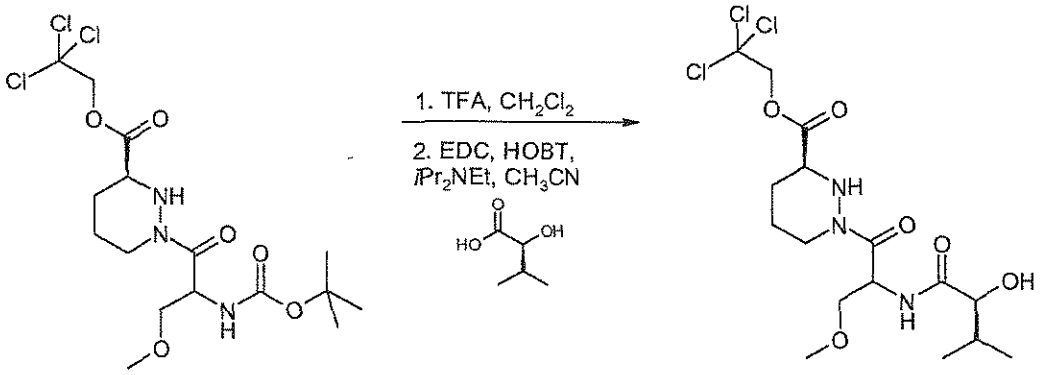
To a solution of 39b (1.1 g, 2.76 mmol) in tetrahydrofuran (24 mL) and water (5 mL) was added lithium hydroxide monohydrate (580 mg, 13.8 mmol). The reaction was heated to 40 °C for 20 h. The reaction was cooled to room temperature and acidified to pH 5 with aqueous hydrochloric acid (2 M). The mixture was evaporated to dryness and dichloromethane and acetonitrile added. This suspension was filtered through a hydrophobic frit and the filtrate concentrated *in vacuo* to afford the title compound (800 mg, 76%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.51 (s, 6H), 1.56 (d, J = 6.7 Hz, 3H), 4.91–5.14 (m, 1H), 6.35–6.52 (m, 1H), 6.66, 6.72 (ABq, J = 16.2 Hz, 2H), 7.31 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.99–8.17 (m, 2H). LCMS (m/z) 385.3 [M+H], Tr = 2.21 min.

Compound 39d: (S)-1-(2-tert-Butoxycarbonylamino-3-methoxy-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



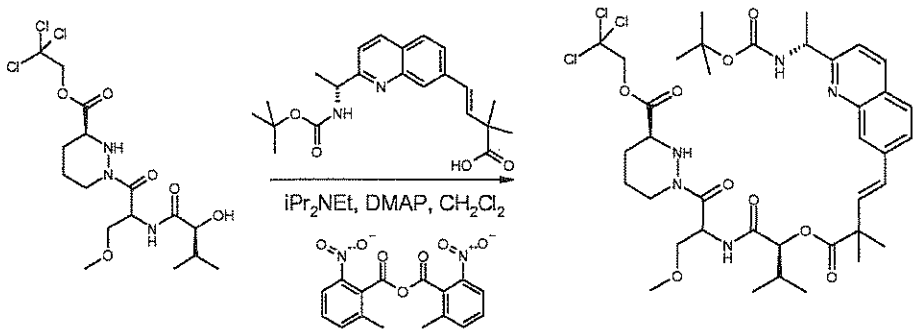
Compound 39d was prepared (starting from bis-*N*-Boc TCE ester prepared as described in *Angew. Chem. Intl. Ed. English*, 1999, *38*, 2443.) in the same manner as intermediate 1d using *N*-α-Boc-O-methyl serine (1 g, 4.56 mmol) instead of L-*N*-Boc-alanine to afford the title compound as a clear viscous oil (1.5 g, 71%) and as a 1:1 mixture of two diastereoisomers. LCMS (m/z) 462.7 [M+H], Tr = 2.71 min.

Compound 39e. (S)-1-[2-((S)-2-Hydroxy-3-methyl-butyrylamino)-3-methoxy-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



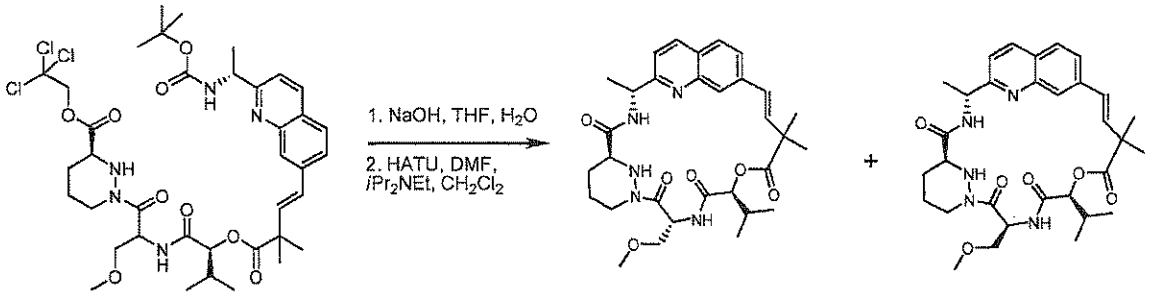
To a solution of 39d (1.0 g, 2.16 mmol) in anhydrous dichloromethane (7 mL) at room temperature and under an atmosphere of nitrogen was added trifluoroacetic acid (1.7 mL). The reaction was stirred at room temperature for 1.5 h and concentrated *in vacuo*. The ensuing residue was co-evaporated from toluene (3 x) to yield a viscous light brown oil. This was dissolved in anhydrous acetonitrile (22 mL) and cooled to 0 °C before adding (S)-2-hydroxy-3-methyl-butyric acid (255 mg, 2.2 mmol), hydroxybenzotriazole monohydrate (497 mg, 3.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (623 mg, 3.3 mmol) and *N,N*-diisopropylethylamine (1.9 mL, 10.8 mmol). The reaction mixture was warmed to ambient temperature and stirred for 72 h. The reaction was diluted with ethyl acetate and washed with hydrochloric acid (1 M), saturated sodium bicarbonate and brine. The organic layer was dried through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexanes/acetone 3:2 to give the title compound (750 mg, 75% over 2 steps) as a clear viscous oil and as a 1:1 mixture of two diastereoisomers. LCMS (m/z) 462.0 [M+H], Tr = 2.24 min.

Compound 39f. (S)-1-[2-((S)-2-{(E)-4-[2-((R)-1-*tert*-Butoxycarbonylamino-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enoyloxy}-3-methyl-butyrylamino)-3-methoxy-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro ethyl ester



To a solution of 39b (300 mg, 0.78 mmol) in anhydrous dichloromethane (5 mL) at room temperature and under an atmosphere of nitrogen was added *N,N*-diisopropylethylamine (0.28 mL, 1.56 mmol), 4-dimethylaminopyridine (200 mg, 1.64 mmol) and 2-methyl-6-nitrobenzoic anhydride (323 mg, 0.94 mmol) followed by a solution of 39e (433 mg, 0.94 mmol) in anhydrous dichloromethane (2.5 mL). The reaction was stirred for 2 h after which it was diluted with ethyl acetate and washed with water and brine. The organic layer was dried through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 1:2 to give the title compound (211 mg, 33%) as a clear viscous oil and as a 1:1 mixture of two diastereoisomers. LCMS (m/z) 828.3 [M+H], Tr = 3.48 min.

Compounds 39 and 40.



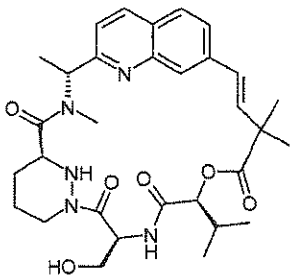
To a solution of 39f (200 mg, 0.24 mmol) in anhydrous tetrahydrofuran (3 mL) at 0 °C was added a 0.4 M aqueous solution of sodium hydroxide (0.7 mL, 0.29 mmol). The reaction was stirred at 0 °C for 1 h before being acidified to pH 5 with hydrochloric acid (2 M) and concentrated *in vacuo*. The resulting residue was partitioned between dichloromethane and water and the organic layer separated, dried through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in anhydrous 1,4-dioxane (1 mL) and at room temperature was added a 4 M solution of hydrochloric acid in dioxane (0.3 mL, 1.2 mmol). The reaction was stirred for 1.5 h, concentrated *in vacuo* and the resulting solid triturated with diethyl ether to afford a light yellow solid. The solid was dissolved in anhydrous *N,N*-dimethylformamide (3 mL)

and *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) and this solution was added to a pre-stirred solution of 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (137 mg, 0.4 mmol) in anhydrous dichloromethane (80 mL) at 0 °C and under an atmosphere of nitrogen. Following the addition, the reaction was stirred at room temperature for 2 h before being concentrated *in vacuo*. The ensuing residue was dissolved in ethyl acetate and washed with hydrochloric acid (0.5 M), saturated sodium bicarbonate and brine. The organic layer was dried through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by reverse phase preparatory HPLC to afford two diastereoisomers as white solids.

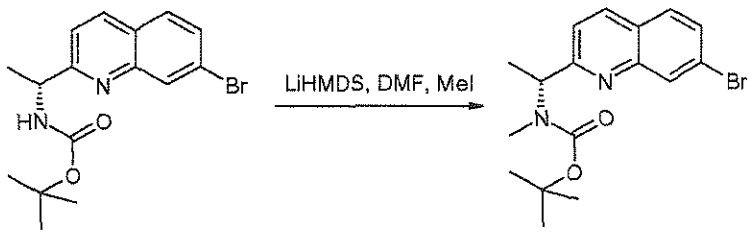
Compound 39. (Second eluting) Diastereoisomer 1 (7 mg, 5%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.48 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.59 (s, 3H), 1.51–1.65 (m, 1H), 1.69–2.11 (m, 4H), 2.19-2.37 (m, 1H), 2.72–2.86 (m, 1H), 2.91 (s, 3H), 3.40–3.58 (m, 3H), 3.80–3.90 (m, 1H), 4.33–4.45 (m, 1H), 5.11–5.22 (m, 3H), 5.57–5.63 (m, 1H), 6.54, 6.71 (ABq, J = 15.9Hz, 2H), 7.44 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.96 (s, 1H), 8.24 (d, J = 8.5 Hz, 1H). LCMS (m/z) 580.2 [M+H], Tr = 2.58 min.

Compound 40 (First eluting) Diastereomer 2. (3 mg, 2%); ^{1}H NMR (300 MHz, CD_3OD) δ 1.00 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.43 (s, 3H), 1.54 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.53–1.75 (m, 1H), 1.91–2.02 (m, 1H), 2.12–2.24 (m, 1H), 2.25–2.36 (m, 1H), 2.64–2.76 (m, 1H), 3.46 (s, 3H), 3.59–3.70 (m, 1H), 3.87 (d, J = 6.0 Hz, 2H), 4.41–4.50 (m, 1H), 5.12 (q, J = 6.7 Hz, 1H), 5.18 (d, J = 11.6 Hz, 1H), 5.27 (d, J = 8.5 Hz, 1H), 6.09 (t, J = 6.3 Hz, 1H), 6.41, 6.61 (ABq, J = 16.3 Hz, 2H), 7.43 (d, J = 8.5 Hz, 1H), 7.58 (dd, J = 8.5, 1.5 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 8.03 (s, 1H), 8.24 (d, J = 8.5 Hz, 1H). LCMS (m/z) 580.2 [M+H], Tr = 2.62 min.

Example 41: Compound 41

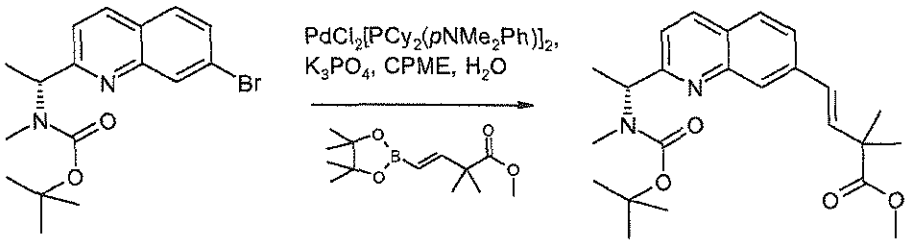


Compound 41a. [(R)-1-(7-Bromo-quinolin-2-yl)-ethyl]-methyl-carbamic acid *tert*-butyl ester



To a solution 39a (500 mg, 1.4 mmmol) in anhydrous *N, N*-dimethylformamide (5 mL), at –20 °C and under an atmosphere of nitrogen, was added dropwise lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.7 mL, 1.71 mmol) over 10 minutes. Following the addition the reaction was stirred at –20 °C for 45 minutes and then iodomethane (0.18 mL, 2.85 mmol) was added. The reaction was warmed to room temperature and stirred for 1 h before quenching with saturated aqueous ammonium chloride and extracting with diethyl ether (2 x). The combined organics were washed with 5% aqueous lithium chloride solution, dried through a hydrophobic frit and concentrated *in vacuo*. The product was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 6:1 to afford the title compound (500 mg, 96%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.68 (d, J = 6.9 Hz, 3H), 2.72 (*br* s, 3H), 5.34–5.92 (m, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.8 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 8.29 (d, J = 1.6 Hz, 1H). LCMS (m/z) 367.0 [M+H], Tr = 3.61 min.

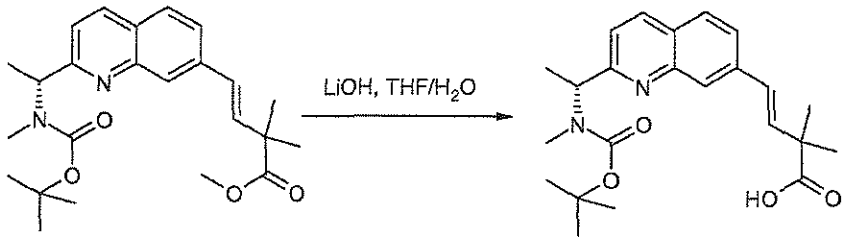
Compound 41b. (E)-4-{2-[(R)-1-(*tert*-Butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid methyl ester



Compound 41b was prepared in the same manner as compound 39b using 41a instead of 39a in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.56 (s, 6H), 1.69 (d, J = 7.1 Hz, 3H), 2.72 (*br* s, 3H), 3.74 (s, 3H), 5.28–6.01 (m, 1H), 6.64 (s, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.61

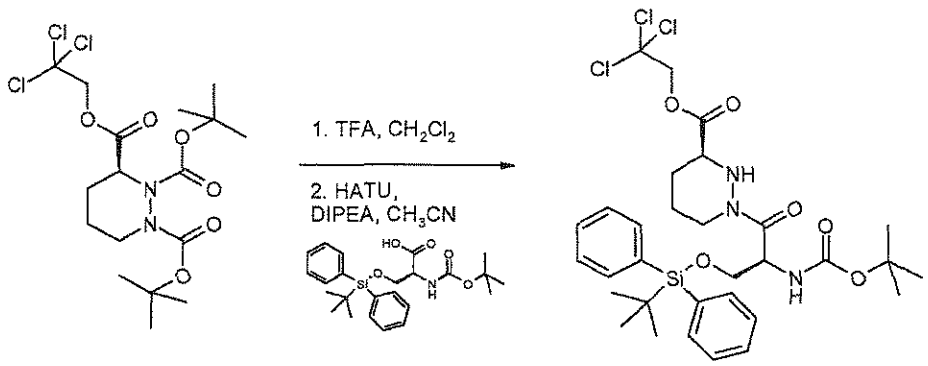
(dd, J = 8.7, 1.6 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 8.01–8.08 (m, 2H). LCMS (m/z) 413.2 [M+H], Tr = 3.42 min.

Compound 41c. (E)-4-{2-[(R)-1-(*tert*-Butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid



Compound 41c was prepared in the same manner as compound 39c using 41b instead of (E)-4-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enoic acid methyl ester in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.52 (s, 6H), 1.69 (d, J = 7.1 Hz, 3H), 2.73 (*br* s, 3H), 5.29–5.84 (m, 1H), 6.66, 6.70 (ABq, J = 16.3 Hz, 2H), 7.34 (d, J = 8.9 Hz, 1H), 7.59–7.66 (m, 1H), 7.74 (d, J = 8.5 Hz, 1H), 8.00–8.09 (m, 2H). LCMS (m/z) 399.1 [M+H], Tr = 2.75 min.

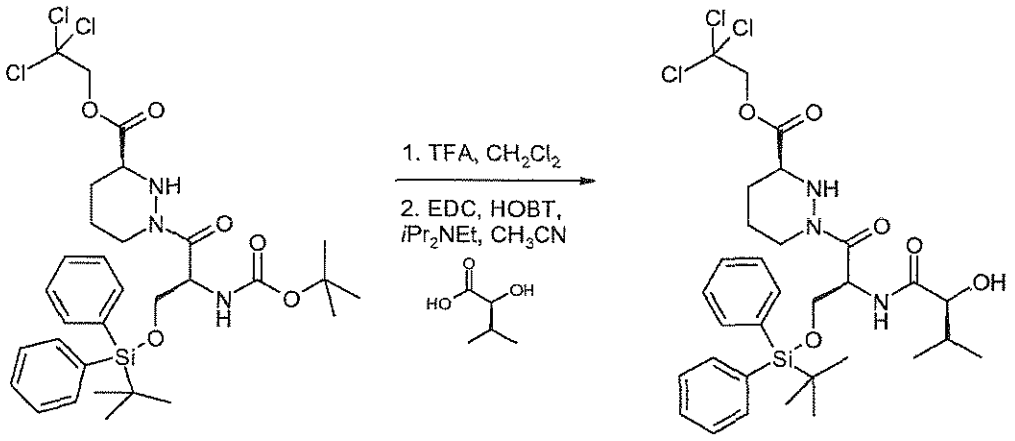
Compound 41d. (S)-1-[(S)-2-*tert*-Butoxycarbonylamino-3-(*tert*-butyl-diphenyl-silanyloxy)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



To (S)-tetrahydro-pyridazine-1,2,3-tricarboxylic acid 1,2-di-*tert*-butyl ester 3-(2,2,2-trichloro-ethyl) ester (prepared according to the procedure desribed in *Angew. Chem. Int. Ed. English* 1999, *38*, 2443.), (5.0 g, 10.8 mmol) in anhydrous dichloromethane (33 mL) at 0 °C and under an atmosphere of nitrogen was added trifluoroacetic acid (33 mL, 432 mmol). The solution was warmed to room temperature and stirred for 16 h. The reaction was concentrated *in vacuo* and the residue co-evaporated from toluene (3 x). The resulting brown viscous oil was dissolved in anhydrous acetonitrile (5 mL) and added to a solution of (S)-2-*tert*-

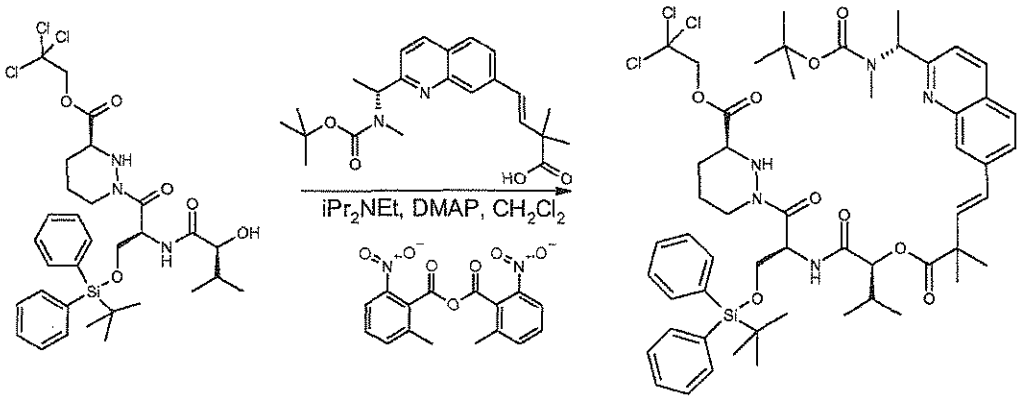
butoxycarbonylamino-3-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (2.39 g, 5.4 mmol, prepared as in *PCT Int. Appl.* 2006, WO 2006004880 A2), *N,N*-diisopropylethylamine (3.76 mL, 21.6 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (2.05 g, 5.4 mmol) in anhydrous acetonitrile (25 mL) that had been previously stirred at 0 °C for 20 minutes. The reaction was warmed to room temperature and stirred for 16 h before being concentrated *in vacuo*. The residue was purified by silica gel chromatography using *iso*-hexanes/ethyl acetate 4:1 to give the title compound (1.8 g, 49%) as a clear viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.46 (s, 9H), 1.53–1.67 (m, 1H), 1.80–2.01 (m, 2H), 2.82–2.96 (m, 1H), 3.19–3.32 (m, 1H), 3.62 (d, J = 10.9 Hz, 1H), 3.80–3.97 (m, 3H), 4.23–4.34 (m, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.90 (d, J = 12.0 Hz, 1H), 5.18–5.27 (m, 1H), 5.51–5.63 (m, 1H), 7.35–7.49 (m, 6H), 7.58–7.70 (m, 4H). LCMS (m/z) 686.2 [M+H], Tr = 4.32 min.

Compound 41e. (S)-1-[(S)-3-(*tert*-Butyl-diphenyl-silanyloxy)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



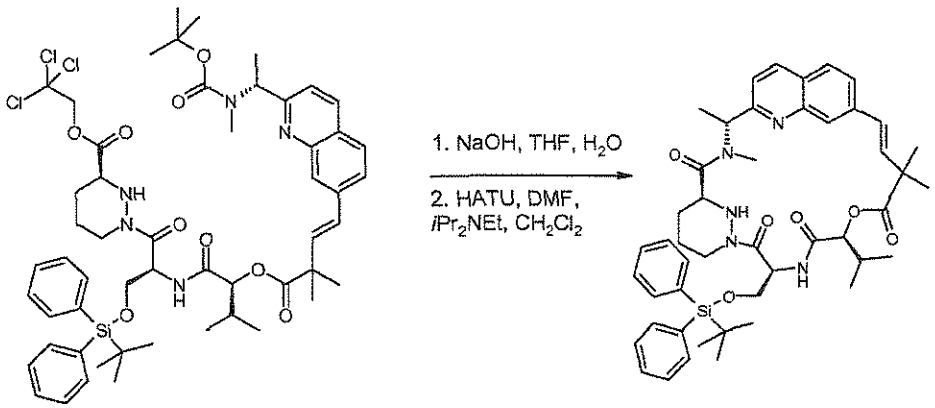
Compound 41e was prepared in the same manner as compound 39e using (S)-1-[(S)-2-*tert*-butoxycarbonylamino-3-(*tert*-butyl-diphenyl-silanyloxy)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester instead of (S)-1-((S)-2-*tert*-butoxycarbonylamino-3-methoxy-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester in 50% yield.^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.7 Hz, 3H), 1.07–1.09 (m, 12H), 1.42–1.71 (m, 2H), 1.80–1.91 (m, 1H), 1.93–2.02 (m, 1H), 2.07–2.15 (m, 1H), 2.72 (d, J = 5.9 Hz, 1H), 2.86–3.02 (m, 1H), 3.17–3.28 (m, 1H), 3.60 (d, J = 10.5 Hz, 1H), 3.90–3.99 (m, 3H), 4.18–4.29 (m, 1H), 4.62, 4.91 (ABq, J = 11.9 Hz, 2H), 5.42–5.50 (m, 1H), 7.35–7.51 (m, 7H) 7.58–7.71 (m, 4H). LCMS (m/z) 686.2 [M+H], Tr = 3.93 min.

Compound 41f.



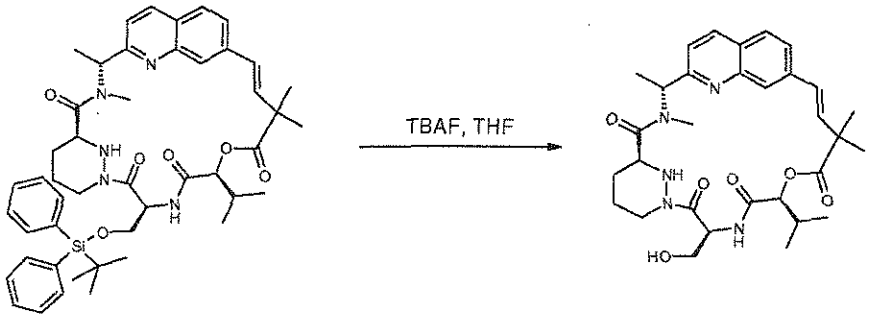
Compound 41f was prepared in the same manner as compound 39f using (E)-4-{2-[(R)-1-(*tert*-butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid and (S)-1-[(S)-3-(*tert*-butyl-diphenyl-silanyloxy)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester instead of (E)-4-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enoic acid and (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-3-methoxy-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester in 32% yield.^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98-1.05 (m, 6H), 1.07 (s, 9H), 1.50 (s, 9H), 1.52–1.60 (m, 2H), 1.57 (s, 3H), 1.61 (s, 3H), 1.68 (d, J = 6.9 Hz, 3H), 1.72–1.93 (m, 2H), 2.31–2.46 (m, 1H), 2.63–3.01 (m, 5H), 3.47 (d, J = 11.2 Hz, 1H), 3.87 (dd, J = 10.3, 2.7 Hz, 1H), 4.04 (dd, J = 10.3, 3.4 Hz, 1H), 4.11–4.23 (m, 1H), 4.60, 4.88 (ABq, J = 12.0 Hz, 2H), 5.21 (d, J = 3.6 Hz, 1H), 5.38–5.44 (m, 1H), 6.72, 6.76 (ABq, J = 16.3 Hz, 2H), 7.31–7.49 (m, 8H), 7.56–7.62 (m, 2H), 7.64–7.71 (m, 4H), 7.99–8.06 (m, 2H). LCMS (m/z) 1066.5 [M+H], Tr = 4.94 min.

Compound 41g.



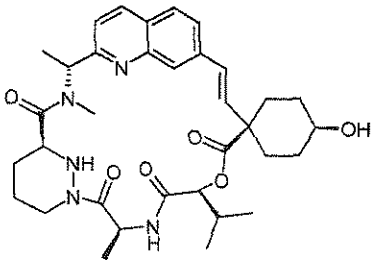
Compound 41g was prepared in the same manner as compound 39 using 41f instead of (S)-1-[(S)-2-((S)-2-{(E)-4-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-2,2-dimethyl-but-3-enoyloxy}-3-methyl-butyrylamino)-3-methoxy-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro ethyl ester in 77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95–1.04 (m, 6H), 1.46 (s, 3H), 1.53 (s, 3H), 1.54–1.61 (m, 12H), 1.65–2.01 (m, 4H), 2.19–2.37 (m, 1H), 2.61 (s, 3H), 2.65–2.78 (m, 1H), 3.57–3.76 (m, 2H), 3.79 (d, J = 12.0 Hz, 1H), 4.03–4.10 (m, 1H), 4.52–4.63 (m, 1H), 4.89 (d, J = 8.5 Hz, 1H), 5.93 (q, J = 7.1 Hz, 1H), 5.98–6.07 (m, 1H), 6.28, 6.47 (ABq, J = 16.4 Hz, 2H), 6.56–6.63 (m, 1H), 7.21–7.54 (m, 7H), 7.61–7.75 (m, 7H), 8.02 (d, J = 8.3 Hz, 1H). LCMS (m/z) 818.4 [M+H], Tr = 4.22 min.

Compound 41.

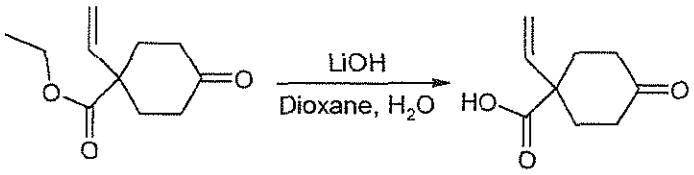


To a solution of compound 41g (190 mg, 0.23 mmol) in anhydrous tetrahydrofuran (1 mL), at room temperature and under an atmosphere of nitrogen, was added tetrabutylammonium fluoride (1 M in THF, 1.2 mL, 1.2 mmol). The reaction was stirred for 45 minutes before being diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried through a hydrophobic frit and concentrated *in vacuo*. The product was purified by silica gel chromatography using *iso*-hexanes/acetone 1:1 to give the title compound (35 mg, 27%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.98 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 1.72 (d, J = 7.4 Hz, 3H), 1.72–1.97 (m, 4H), 2.09–2.25 (m, 1H), 2.71–2.86 (m, 1H), 3.30 (s, 3H), 3.96 (d, J = 6.3 Hz, 2H), 4.18–4.30 (m, 1H), 4.42–4.53 (m, 2H), 5.08 (d, J = 8.7 Hz, 1H), 5.88 (q, J = 7.4 Hz, 1H), 6.06 (t, J = 6.0 Hz, 1H), 6.40, 6.49 (ABq, J = 16.5 Hz, 2H), 7.44 (d, J = 8.7 Hz, 1H), 7.64 (dd, J = 8.5, 1.3 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.89 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H). LCMS (m/z) 580.2 [M+H], Tr = 2.14 min.

Example 42. Compound 42.

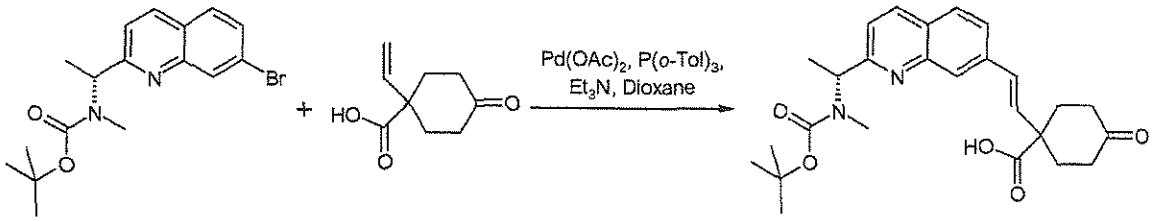


Compound 42a. 4-Oxo-1-vinyl-cyclohexanecarboxylic acid



A solution of the commercially available 4-oxo-1-vinyl-cyclohexanecarboxylic acid ethyl ester (provided by Small Molecules Inc.), (1.20 g, 6.11 mmol) in 1,4-dioxane (20 mL) was treated with a solution of lithium hydroxide monohydrate (734 mg, 30.6 mmol) in water (10 mL). After stirring at 50 °C for 2 h, the volatiles were removed *in vacuo*. The residue was partitioned between water and diethyl ether. The aqueous layer was acidified to pH 1 by addition of saturated potassium hydrogen sulfate solution and was extracted with ethyl acetate (3 x). The organic layer was dried over anhydrous magnesium sulfate, filtered and the volatiles were removed *in vacuo* to afford the title compound (1.00 g, 97%) as a clear gum. 1H NMR (300 MHz, CDCl3) δ 1.92-2.08 (m, 2H), 2.36-2.59 (m, 6H), 5.34 (d, J = 17.5 Hz, 1H), 5.35 (d, J = 10.5 Hz, 1H), 5.97 (dd, J = 17.5, 10.5 Hz, 1H), 11.30 (br s, 1H).

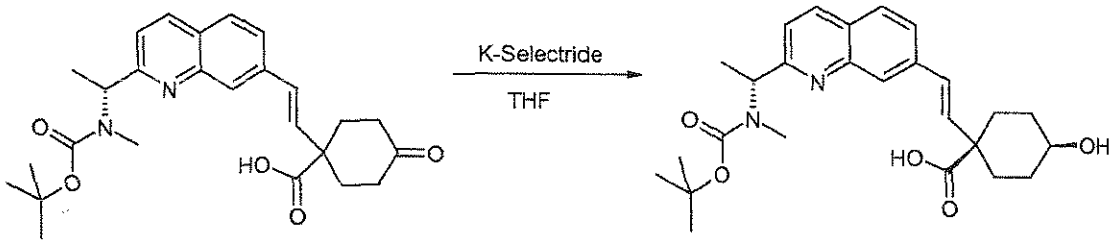
Compound 42b. 1-((E)-2-{2-[(R)-1-(*tert*-Butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-vinyl)-4-oxo-cyclohexanecarboxylic acid



A solution of [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-methyl-carbamic acid *tert*-butyl ester (200 mg, 0.55 mmol), 4-oxo-1-vinyl-cyclohexanecarboxylic acid (138 mg, 0.82 mmol), palladium(II) acetate (25 mg, 0.11 mmol), tri-(*o*-tolyl)phosphine (50 mg, 0.16 mmol) in

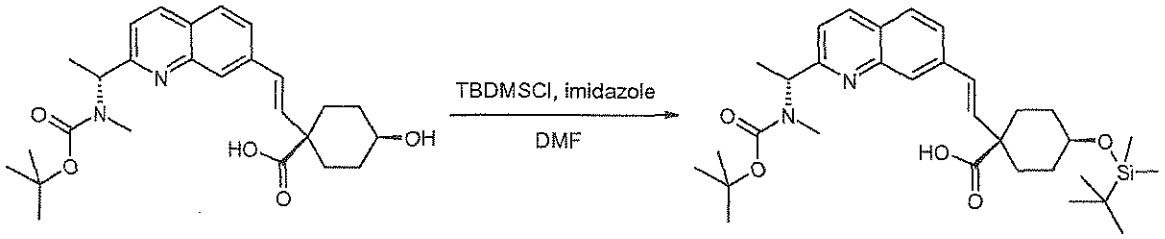
anhydrous 1,4-dioxane (2 mL) was treated with triethylamine (267 µL, 1.91 mmol). After stirring at 100 °C under microwave irradiation for 30 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The residue was partitioned between ethyl acetate and a 5% citric acid solution, the aqueous layer was extracted with ethyl acetate (2 x), the organics were combined and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Biotage cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 1:1 to afford the title compound (235 mg, 94%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.68 (d, J = 7.1 Hz, 3H), 2.07-2.22 (m, 2H), 2.44-2.70 (m, 6H), 2.75 (*br* s, 3H), 5.61 (*br* s, 1H), 6.68 (ABq, $\Delta\delta_{AB}$ = 0.31, J_{AB} = 16.3 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 8.05-8.12 (m, 2H). LCMS (m/z) 453.1 [M+H], Tr = 2.48 min.

Compound 42c. 1-((E)-2-{2-[(R)-1-(*tert*-Butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-vinyl)-4-*cis*-hydroxy-cyclohexanecarboxylic acid



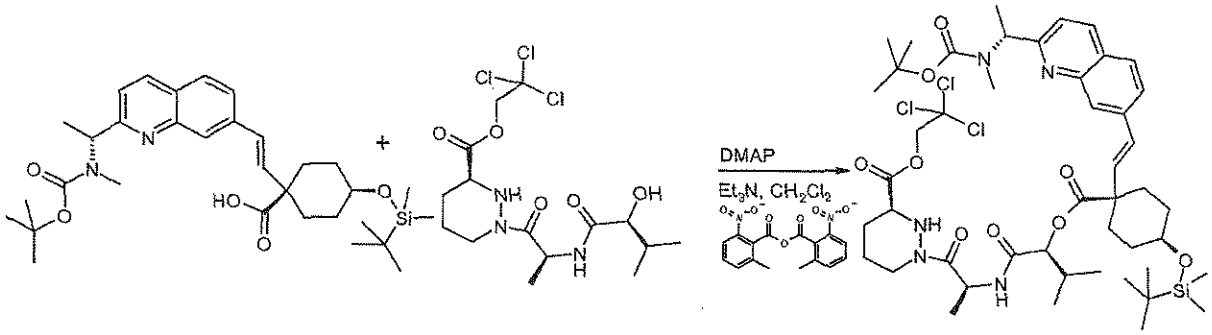
A cooled (–50 °C) solution of 1-((E)-2-{2-[(R)-1-(*tert*-butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-vinyl)-4-oxo-cyclohexanecarboxylic acid (235 mg, 0.52 mmol) in anhydrous tetrahydrofuran (15 mL) was treated with potassium tri-*sec*-butylborohydride (1.56 mL, 1.56 mmol, 1 M in tetrahydrofuran). The temperature was raised to –30 °C. After stirring for 20 minutes, the reaction was quenched by addition of a saturated ammonium chloride solution (10 mL). The temperature was raised to room temperature, the pH adjusted to pH 2 by addition of citric acid then extracted with ethyl acetate (3 x). The organics were combined and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Biotage cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 0:1 to afford the title compound (185 mg, 78%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.52-1.62 (m, 4H), 1.67 (d, J = 6.9 Hz, 3H), 1.95-2.05 (m, 2H), 2.42-2.55 (m, 2H), 2.73 (*br* s, 3H), 3.73 (*br* s, 1H), 5.57 (*br* s, 1H), 6.58 (ABq, $\Delta\delta_{AB}$ = 0.29, J_{AB} = 16.3 Hz, 2H), 7.34 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 8.01-8.10 (m, 2H). LCMS (m/z) 455.1 [M+H], Tr = 2.31 min.

Compound 42d. 1-((E)-2-{2-[(R)-1-(*tert*-Butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-vinyl)-4-*cis*-(*tert*-butyl-dimethyl-silanyloxy)-cyclohexanecarboxylic acid



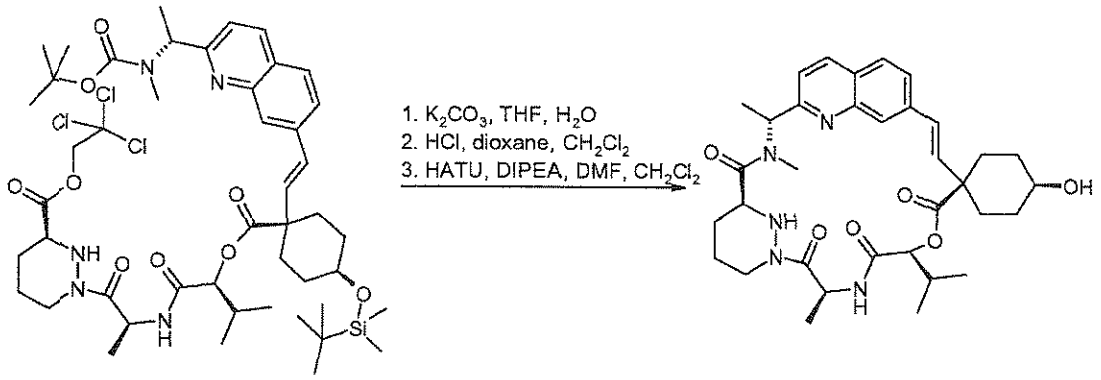
A solution of 1-((E)-2-{2-[(R)-1-(*tert*-butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-vinyl)-4-*cis*-hydroxy-cyclohexanecarboxylic acid (185 mg, 0.41 mmol) and imidazole (138 mg, 2.03 mmol) in anhydrous in *N,N*-dimethylformamide (5 mL) was treated with *tert*-butyldimethylsilyl chloride (153 mg, 1.02 mmol). After stirring for 16 h, the reaction was quenched by addition of a potassium carbonate solution (10 mL). After stirring for 3 h, the pH was adjusted to pH 3 by addition of potassium hydrogen sulfate solution then extracted with ethyl acetate (3 x). The organics were combined and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Biotage cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 7:3 to afford the title compound (142 mg, 61%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.49 (s, 9H), 1.53-1.64 (m, 4H), 1.67 (d, J = 6.9 Hz, 3H), 1.80-1.92 (m, 2H), 2.38-2.51 (m, 2H), 2.72 (*br* s, 3H), 3.70 (br s, 1H), 5.59 (*br* s, 1H), 6.58 (ABq, $\Delta\delta_{AB}$ = 0.30, J_{AB} = 16.3 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 7.58 (dd, J = 8.5, 1.3 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 8.00-8.06 (m, 2H). LCMS (m/z) 569.2 [M+H], Tr = 4.37 min.

Compound 42e. (S)-1-((S)-2-{(S)-2-[1-((E)-2-{7-[(R)-1-(*tert*-Butoxycarbonyl-methyl-amino)-ethyl]-quinolin-2-yl}-vinyl)-4-*cis*-(*tert*-butyl-dimethyl-silanyloxy)-cyclohexanecarbonyloxy]-3-methyl-butyrylamino}-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



A solution of 1-((E)-2-{2-[(R)-1-(*tert*-butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-vinyl)-4-*cis*-(*tert*-butyl-dimethyl-silanyloxy)-cyclohexanecarboxylic acid (142 mg, 0.25 mmol), (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (108 mg, 0.25 mmol), triethylamine (0.087 mL, 0.62 mmol) and 4-dimethylaminopyridine (15 mg, 0.12 mmol) in anhydrous dichloromethane (10 mL) was treated with 2-methyl-6-nitrobenzoic anhydride (146 mg, 0.42 mmol). After stirring for 60 h, the reaction was quenched by addition of a sodium bicarbonate solution (10 mL), the aqueous layer was extracted with dichloromethane (2 x), the organics were combined and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Biotage cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 1:1 to afford the title compound (105 mg, 43%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.10 (s, 6H), 0.93 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.40-1.50 (m, 9H), 1.68 (d, J = 6.9 Hz, 3H), 1.72-1.81 (m, 4H), 1.82-1.94 (m, 4H), 1.95-2.10 (m, 2H), 2.25-2.32 (m, 2H), 2.37-2.44 (m, 1H), 2.46-2.57 (m, 2H), 2.80 (*br* s, 3H), 3.52-3.70 (m, 1H), 3.74-3.85 (m, 2H), 4.73-4.80 (m, 1H), 5.01 (d, J = 4.7 Hz, 1H), 5.30-5.45 (m, 2H), 6.70 (ABq, $\Delta\delta_{AB}$ = 0.28, J_{AB} = 16.3 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.73-7.85 (m, 2H), 7.97 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H).

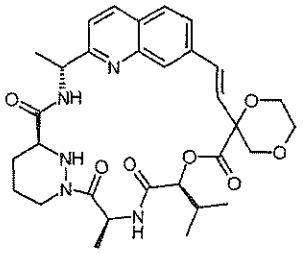
Compound 42.



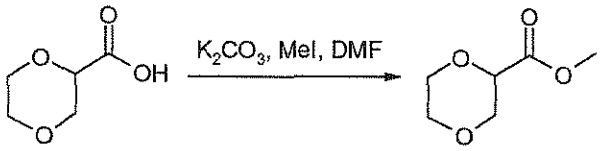
A solution of (S)-1-((S)-2-{(S)-2-[1-((E)-2-{7-[(R)-1-(*tert*-butoxycarbonyl-methyl-amino)-ethyl]-quinolin-2-yl}-vinyl)-4-*cis*-(*tert*-butyl-dimethyl-silanyloxy)-cyclohexanecarbonyloxy]-3-methyl-butyrylamino}-propionyl)-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (105 mg, 0.11 mmol) in tetrahydrofuran (10 mL) was treated with a solution of potassium carbonate (221 mg, 1.60 mmol) in water (5 mL). After stirring at room temperature for 3 h, the pH was adjusted to pH 3 by addition of dilute hydrochloric acid then extracted with ethyl acetate (3 x). The organics were combined and the volatiles were removed *in vacuo*. The residue was dissolved in dichloromethane (10 mL) and treated with hydrochloric acid in 1,4-dioxane (4 M, 5 mL). After stirring at room temperature for 1 h, the volatiles were removed *in vacuo*. The residual solvent was azeotroped off with toluene (3 x 15 mL) to give crude (S)-1-{(S)-2-[(S)-2-(4-*cis*-hydroxy-1-{(E)-2-[7-((R)-1-methylamino-ethyl)-quinolin-2-yl]-vinyl}-cyclohexanecarbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid. This residue was dissolved in *N,N*-dimethylformamide (4 mL) and *N,N*-diisopropylethylamine (0.093 mL, 0.53 mmol) and added via syringe pump over 1 h to a stirred solution of 2-(1H-7-azabenzotriazol-1-yl) -1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (61 mg, 0.16 mmol) in dichloromethane (50 mL) at room temperature under nitrogen. The reaction was quenched by addition of a sodium bicarbonate solution (10 mL), the aqueous layer was extracted with dichloromethane (2 x), The organics were combined and the volatiles were removed *in vacuo*. The residue was purified by preparative reverse phase HPLC to afford the title compound (13 mg, 19%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.02 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.27-1.48 (m, 3H), 1.54 (d, J = 7.1 Hz, 3H), 1.72 (d, J = 7.6 Hz, 3H), 1.78-2.05 (m, 5H), 2.11-2.25 (m, 1H), 2.28-2.40 (m, 1H), 2.50-2.62 (m, 1H), 2.71-2.84 (m, 1H), 3.27 (s, 3H), 3.52-3.80 (m, 3H), 4.11-4.24 (m, 1H), 4.38-4.51 (m, 1H), 5.16 (d, J = 9.1 Hz, 1H), 5.86-5.98 (m,

2H), 6.36 (ABq, $\Delta\delta_{AB}$ = 0.17, J_{AB} = 16.5 Hz, 2H), 7.44 (d, J = 8.7 Hz, 1H), 7.64-7.72 (m, 2H), 7.78 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H). LCMS (m/z) 620.5 [M+H], Tr = 2.09 min.

Examples 43 and 44, Compounds 43 and 44

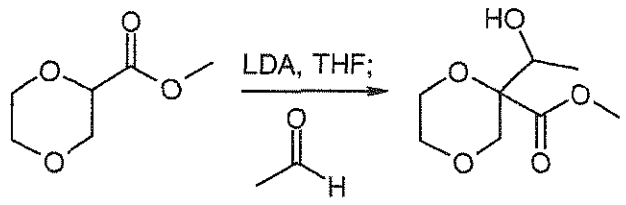


Compound 43a. [1,4]Dioxane-2-carboxylic acid methyl ester



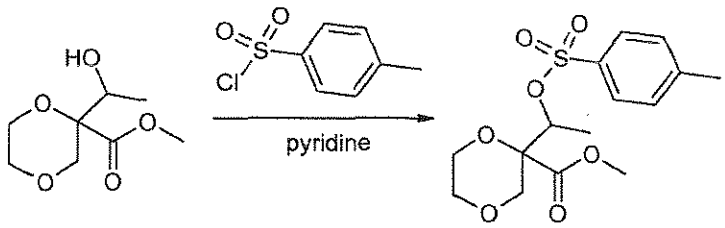
A solution of [1,4]dioxane-2-carboxylic acid (supplied by Enamine Ltd.), (2.90 g, 22.0 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at room temperature. Potassium carbonate (6.07 g, 44.0 mmol) was added and the suspension was stirred at 5 °C. Iodomethane (6.25 g, 2.75 mL, 44.0 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. Water and brine were added and the mixture was extracted with diethyl ether. The aqueous layer was saturated with sodium chloride and the mixture was extracted with ethyl acetate (3 x). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography using a gradient of pentane/diethyl ether 4:1 to 1:1 to afford the title compound (3.06 g, 95%) as a volatile, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68-3.78 (m, 4H), 3.81 (s, 3H), 3.97-4.05 (m, 2H), 4.29 (dd, J = 8.5, 3.1 Hz, 1H). LCMS (m/z) 169.2 [M+Na], Tr = 0.69 min.

Compound 43b. 2-(1-Hydroxy-ethyl)-[1,4]dioxane-2-carboxylic acid methyl ester



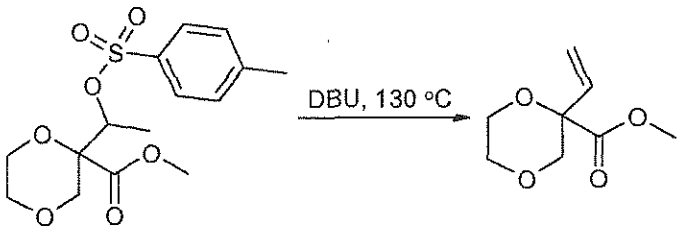
A solution of *N,N*-diisopropylamine (1.67 g, 2.3 mL, 16.5 mmol) in anhydrous tetrahydrofuran (10 mL) was stirred at –78 °C under nitrogen. *n*-Butyllithium (6.6 mL, 16.5 mmol, 2.5 M solution in hexane) was added dropwise and the reaction mixture was stirred at –78 °C for 30 minutes. A solution of [1,4]dioxane-2-carboxylic acid methyl ester (1.61 g, 11 mmol) in tetrahydrofuran (10 mL) was added and the reaction mixture was stirred at –78 °C for 30 minutes. Acetaldehyde (1.45 g, 1.8 mL, 33 mmol) was added in one portion. The cooling bath was removed and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was cooled to 5 °C and ice-cold 1 M hydrochloric acid was added to acidify the reaction mixture to pH 2. Sodium chloride was added to saturate the solution and the mixture was extracted with diethyl ether (4 x). The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of pentane/diethyl ether 1:1 to 0:1 to afford the title compound (1.49 g, 71%), as an oil, and as a 3:1 mixture of diastereoisomers. LCMS (m/z) 213.2 [M+H], Tr = 0.62 min.

Compound 43c. 2-[1-(Toluene-4-sulfonyloxy)-ethyl]-[1,4]dioxane-2-carboxylic acid methyl ester



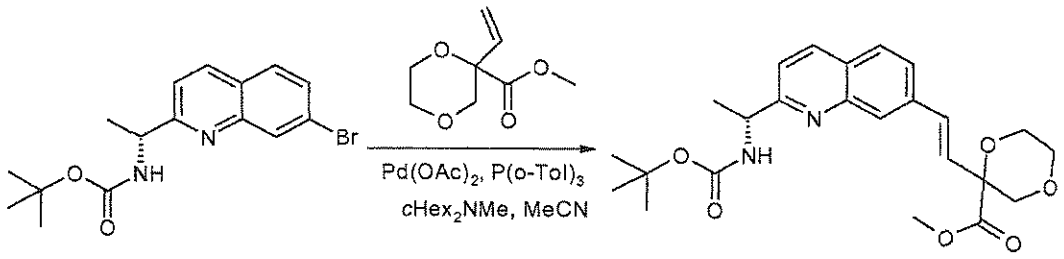
A solution of 2-(1-hydroxy-ethyl)-[1,4]dioxane-2-carboxylic acid methyl ester (1.49 g, 7.8 mmol) in pyridine (8 mL) was stirred at room temperature. 4-Toluenesulfonyl chloride (1.50 g, 7.8 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The majority of the pyridine was evaporated, 1 M hydrochloric acid was added to acidify the mixture to pH 2 and the mixture was extracted with ethyl acetate. The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of pentane/diethyl ether 3:1 to 0:1 to afford the title compound (1.70 g, 63%) as a yellow gum and as a 3:1 mixture of diastereoisomers. LCMS (m/z) 367.0 [M+Na], Tr = 2.44 min.

Compound 43d. 2-Vinyl-[1,4]dioxane-2-carboxylic acid methyl ester



A solution of 2-[1-(toluene-4-sulfonyloxy)-ethyl]-[1,4]dioxane-2-carboxylic acid methyl ester (1.68 g, 4.9 mmol) in 1,8-diazabicycloundec-7-ene (3 mL) was heated in a sealed tube at 130 °C for 2 h. The reaction mixture was cooled to room temperature and 2 M hydrochloric acid and diethyl ether were added. The mixture was extracted with diethyl ether and the organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of pentane/diethyl ether 3:1 to 1:1 to afford the title compound (308 mg, 36%) as a volatile, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (d, J = 11.6 Hz, 1H), 3.62-3.78 (m, 2H), 3.81-3.86 (m, 1H), 3.84 (s, 3H), 3.99-4.07 (m, 1H), 4.33 (d, J = 11.6 Hz, 1H), 5.34 (dd, J = 10.7, 1.1 Hz, 1H), 5.52 (dd, J = 17.4, 1.1 Hz, 1H), 5.79 (dd, J = 17.4, 10.7 Hz, 1H). LCMS (m/z) 195.1 [M+Na], Tr = 1.23 min.

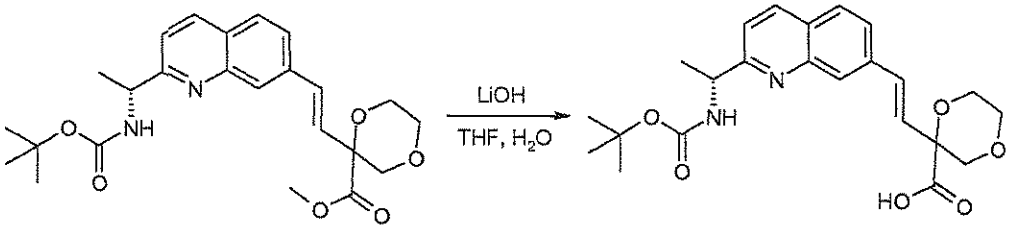
Compound 43e. 2-{(E)-2-[2-((R)-1-*tert*-Butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carboxylic acid methyl ester



A solution of [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-carbamic acid *tert*-butyl ester (316 mg, 0.9 mmol), 2-vinyl-[1,4]dioxane-2-carboxylic acid methyl ester (154 mg, 0.9 mmol), palladium(II) acetate (41 mg, 0.18 mmol), tri(*o*-tolyl)phosphine (54 mg, 0.18 mmol) and *N,N*-dicyclohexylmethylamine (351 mg, 0.38 mL, 1.8 mmol) in acetonitrile (8 mL) was heated at 120 °C in a microwave reactor for 30 minutes. The reaction mixture was filtered and the solvent was evaporated. The residue was dissolved in dichloromethane; brine and ice-cold 1 M hydrochloric acid were added to acidify the mixture to pH 2. The organic layer was separated and washed

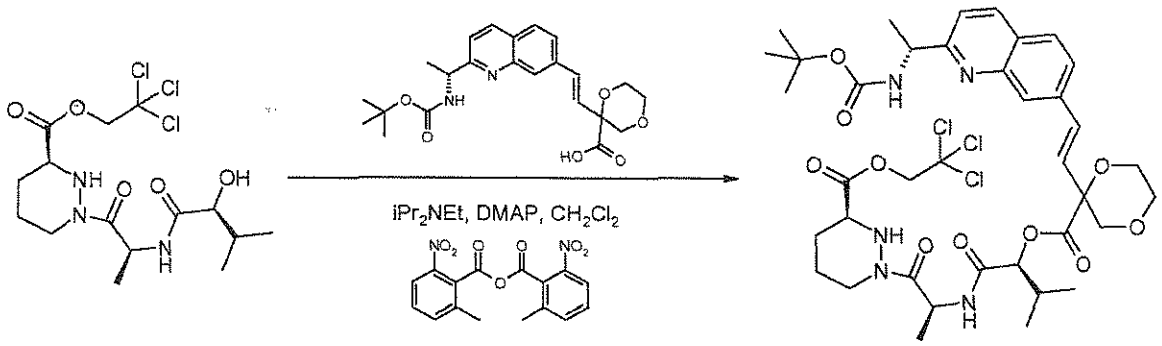
with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 7:3 to 6:4 to afford the title compound (157 mg, 40%) as a yellow gum and as a 1:1 mixture of diastereoisomers. LCMS (m/z) 443.1 [M+H], Tr = 2.34 min.

Compound 43f. 2-{(E)-2-[2-((R)-1-*tert*-Butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carboxylic acid



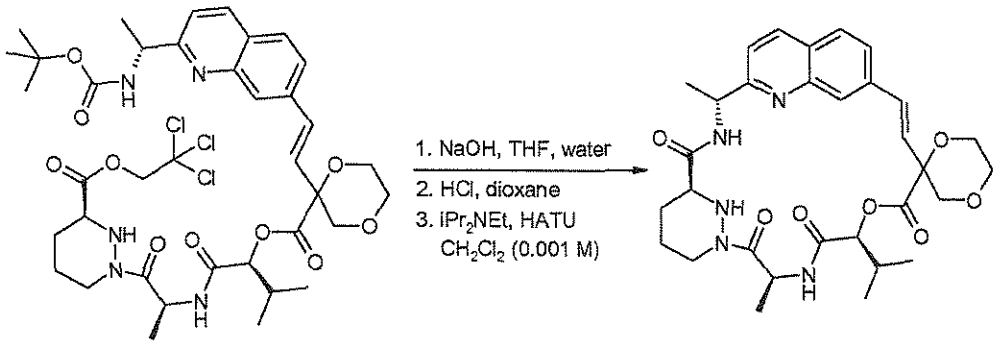
A solution of 2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carboxylic acid methyl ester (157 mg, 0.35 mmol) in tetrahydrofuran (6 mL) was stirred at 5 °C under nitrogen. A solution of lithium hydroxide monohydrate (30 mg, 0.71 mmol) in water (1.5 mL) was added and the reaction mixture was stirred at room temperature for 18 h. The majority of the organic solvent was evaporated. The solution was acidified to pH 2 with 2 M hydrochloric acid and the mixture was extracted with dichloromethane. The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford the title compound (149 mg, 100%) as a pale yellow foam and as a 1:1 mixture of diastereoisomers. LCMS (m/z) 429.1 [M+H], Tr = 1.87 min.

Compound 43g. (S)-1-{(S)-2-[(S)-2-(2-{(E)-2-[2-((R)-1-*tert*-Butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



A solution of 2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carboxylic acid (50 mg, 0.1 mmol), [(S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (44 mg, 0.1 mmol), *N,N*-diisopropylethylamine (32 mg, 0.043 mL, 0.25 mmol), 4-dimethylaminopyridine (6 mg, 0.05 mmol) and 2-methyl-6-nitrobenzoic anhydride (58 mg, 0.17 mmol) in dichloromethane (5 mL) was stirred at room temperature under nitrogen for 18 h. The reaction mixture was diluted with dichloromethane and the solution was washed with ice-cold saturated ammonium chloride solution, ice-cold saturated sodium hydrogen carbonate solution and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:1 to 1:3 to afford the title compound (47 mg, 55%) as a white solid and as a 1:1 mixture of diastereoisomers. LCMS (m/z) 842.2/844.0 [M+H], Tr = 3.25 and 3.31 min.

Compounds 43 and 44



A solution of (S)-1-{(S)-2-[(S)-2-(2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (69 mg, 0.081 mmol) in tetrahydrofuran (4 mL) was stirred at 0 °C under nitrogen. An ice-cold aqueous solution of sodium hydroxide (0.1

M, 0.82 mL, 0.082 mmol) was added and the reaction mixture was stirred at 0 °C for 20 minutes. Cold 1 M hydrochloric acid was added to acidify the mixture to pH 2 and the solvent was evaporated. The residue was co-evaporated with tetrahydrofuran/toluene (1:1, 3 x) and the residue was triturated with diethyl ether (2 x) and the resulting solid was dried to afford (S)-1-{(S)-2-[(S)-2-(2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid (0.081 mmol) as a yellow solid and as a 1:1 mixture of diastereoisomers which was used crude in the next reaction. LCMS (m/z) 712.3 [M+H], Tr = 2.46 min.

A mixture of crude (S)-1-{(S)-2-[(S)-2-(2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid (0.081 mmol) in 4 M hydrogen chloride in 1,4-dioxane (2 mL) was stirred at room temperature for 1 h. The solvent was evaporated and the residue was co-evaporated with diethyl ether (2 x) and the resulting solid was dried to afford (S)-1-{(S)-2-[(S)-2-(2-{(E)-2-[2-((R)-1-amino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid hydrochloride (0.081 mmol) as an off-white solid and as a 1:1 mixture of diastereoisomers which was used crude in the next reaction. LCMS (m/z) 612.1 [M+H], Tr = 1.38 min.

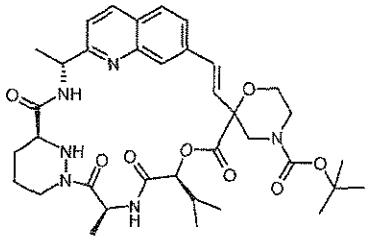
A suspension of crude (S)-1-{(S)-2-[(S)-2-(2-{(E)-2-[2-((R)-1-amino-ethyl)-quinolin-7-yl]-vinyl}-[1,4]dioxane-2-carbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid hydrochloride (0.081 mmol) in dichloromethane (75 mL) was stirred at 0 °C under nitrogen. A solution of *N,N*-diisopropylethylamine (42 mg, 0.324 mmol) in dichloromethane (6 mL) was added and the resulting solution was stirred at 0 °C. 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (62 mg, 0.162 mmol) was added and the reaction mixture was stirred at 0 °C for 30 minutes and then at room temperature for 1 h. The majority of the solvent was evaporated and the solution (~20 mL) was washed with ice-cold 1 M hydrochloric acid and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 1:4 to 0:1 to afford a 1:1 mixture of diastereoisomers. The mixture was purified by reverse phase preparative HPLC eluting with acetonitrile/water 3:7 to afford the two separate diastereoisomers.

Compound 43 (First eluting) Diastereoisomer 1: (4.0 mg, 8%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H), 1.56-1.60 (m, 7H), 1.68-1.73 (m, 1H), 1.95-2.00 (m, 1H), 2.20-2.35 (m, 2H), 2.69-2.78 (m, 1H), 3.55-3.85 (m, 5H), 4.03-

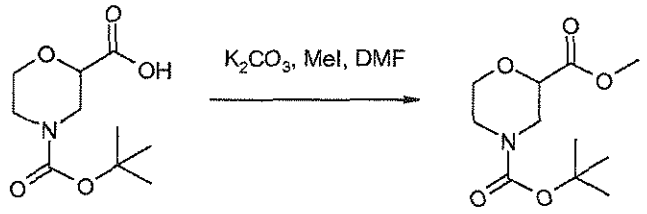
4.12 (m, 1H), 4.43-4.48 (m, 1H), 4.57 (d, J = 11.6 Hz, 1H), 5.12 (q, J = 6.7 Hz, 1H), 5.24 (d, J = 10.4 Hz, 1H), 5.39 (d, J = 8.5 Hz, 1H), 5.83 (q, J = 7.2 Hz, 1H), 6.29 (d, J = 16.3 Hz, 1H), 6.97 (d, J = 16.3 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.61 (dd, J = 8.5, 1.3 Hz, 1H), 7.86-7.90 (m, 2H), 8.28 (d, J = 8.5 Hz, 1H). LCMS (m/z) 594.2 [M+H], Tr = 2.14 min.

Compound 44 (Second eluting) Diastereoisomer 2: (4.6 mg, 10%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.08 (d, J = 6.5 Hz, 3H), 1.10 (d, J = 6.5 Hz, 3H), 1.49-1.54 (m, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.64 (d, J = 7.1 Hz, 3H), 1.66-1.71 (m, 1H), 1.90-1.96 (m, 1H), 2.20-2.28 (m, 2H), 2.63-2.71 (m, 1H), 3.55-3.93 (m, 6H), 4.40-4.47 (m, 2H), 4.98 (d, J = 12.0 Hz, 1H), 5.09 (q, J = 6.7 Hz, 1H), 5.20 (d, J = 8.9 Hz, 1H), 5.79 (q, J = 7.1 Hz, 1H), 6.10 (d, J = 16.3 Hz, 1H), 6.88 (d, J = 16.3 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.6 Hz, 1H), 7.85-7.88 (m, 2H), 8.26 (d, J = 8.5 Hz, 1H). LCMS (m/z) 594.2 [M+H], Tr = 2.17 min.

Examples 45 and 46, Compounds 45 and 46.



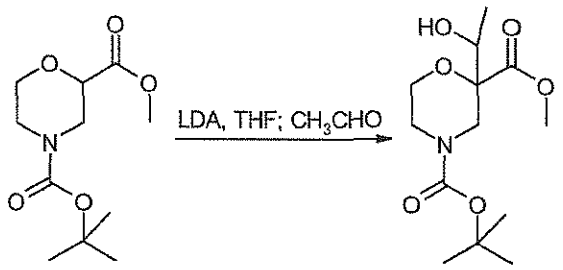
Compound 45a. Morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester.



A solution of morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester (supplied by NeoMPS, Inc.), (5.78 g, 25.0 mmol) in *N,N*-dimethylformamide (30 mL) was subsequently treated with potassium carbonate (4.14 g, 30.0 mmol) and iodomethane (7.10 g, 3.1 mL, 50.0 mmol). After stirring at room temperature for 18 h, the reaction mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The organic extracts were combined, washed with water (4 x) and brine then filtered through a hydrophobic frit and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 3:1 to 1:3 to afford the title compound (4.83 g, 79%) as a white solid. ^{1}H

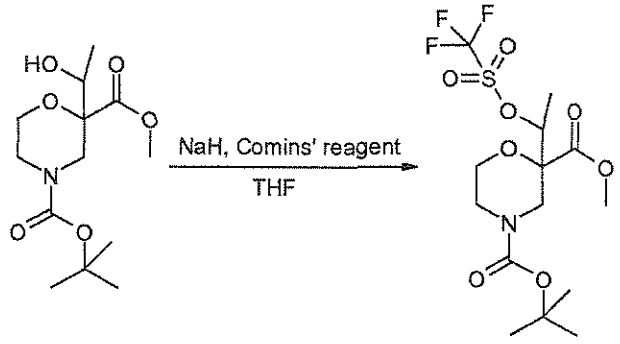
NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 3.06-3.15 (m, 2H), 3.56-3.64 (m, 1H), 3.75-3.79 (m, 1H), 3.81 (s, 3H), 4.00-4.14 (m, 3H). LCMS (m/z) 268.1 [M+Na], Tr = 1.94 min.

Compound 45b. 2-(1-Hydroxy-ethyl)-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester.



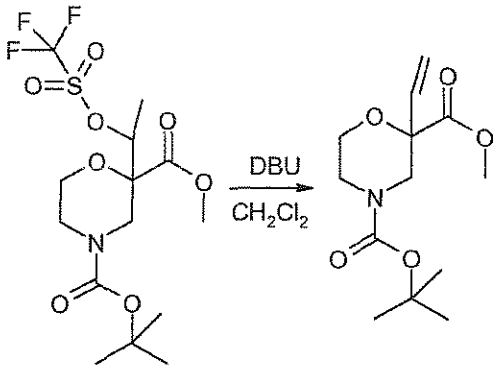
A cooled (–78 °C) solution of *N,N*-diisopropylamine (1.3 mL, 9.092 mmol, dried over calcium hydride) in anhydrous tetrahydrofuran (10 mL) was treated with a solution of *n*-butyllithium in hexanes (3.4 mL, 8.524 mmol, 2.5 M). After stirring at –78 °C for 30 minutes, the mixture was treated with a solution of morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (1.394 g, 5.683 mmol) in anhydrous tetrahydrofuran (10 mL). After stirring at –78 °C for 20 minutes, the mixture was treated with acetaldehyde (0.96 mL, 17.05 mmol). After stirring at room temperature for 1 h, the reaction was quenched at 0 °C with hydrochloric acid (1 M, 40 mL). The aqueous layer was extracted with dichloromethane (2 x). The organics were combined, filtered through a phase separator and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 3:2 to afford the title compound (1.476 g, 90%) as a yellow oil and as a 2:1 mixture of diastereoisomers.

Compound 45c. 2-(1-Trifluoromethanesulfonyloxy-ethyl)-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester



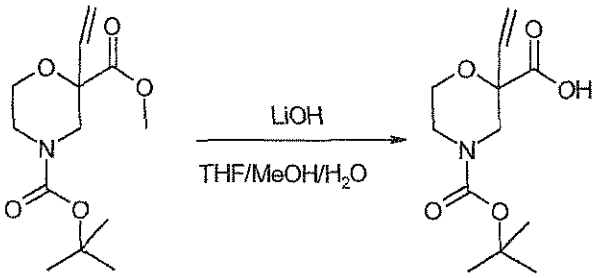
A cooled (–78 °C) suspension of sodium hydride (262 mg, 6.542 mmol, 60% in mineral oil) in anhydrous tetrahydrofuran (10 mL) was treated with a solution of 2-(1-hydroxy-ethyl)-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (1.262 g, 4.361 mmol) in anhydrous tetrahydrofuran (10 mL). The light yellow suspension was stirred at –78 °C for 15 minutes and then treated with a solution of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (3.425 g, 8.722 mmol) in anhydrous tetrahydrofuran (10 mL). After stirring at room temperature for 1.5 h, the reaction was quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with dichloromethane (2 x). The organics were combined, filtered through a phase separator and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 50 g Isolute cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 4:1 to afford the title compound (1.384 g, 75%) as a light yellow oil and as a 2:1 mixture of diastereoisomers.

Compound 45d. 2-Vinyl-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester



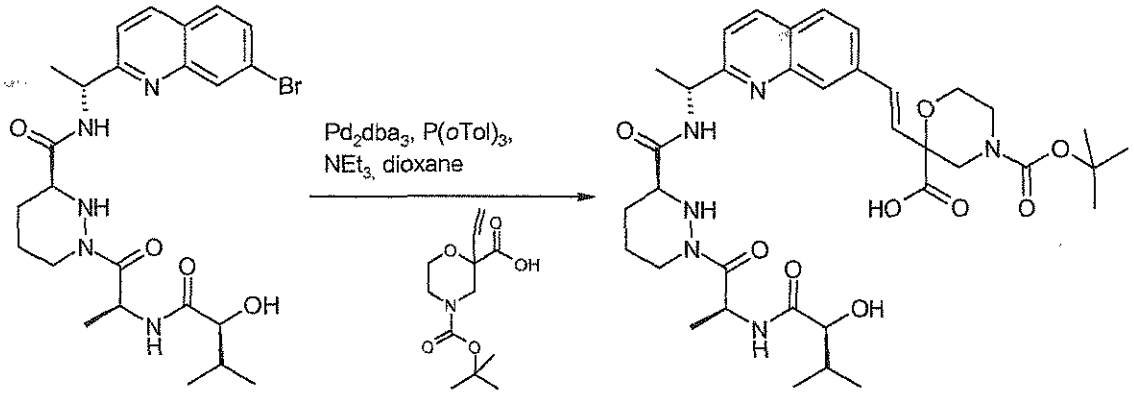
A warm (35 °C) solution of 2-(1-trifluoromethanesulfonyloxy-ethyl)-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (1.384 g, 3.284 mmol) in dichloromethane (40 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (2.5 mL, 16.422 mmol). After stirring at 35 °C for 2 h, the reaction was cooled to 0 °C and quenched with hydrochloric acid (1 M, 50 mL). The aqueous layer was extracted with dichloromethane. The organics were combined, filtered through a phase separator and the volatiles were removed *in vacuo* to provide the title compound as an orange oil which was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 3.13-3.29 (m, 2H), 3.60-3.73 (m, 1H), 3.79 (s, 3H), 3.83-3.92 (m, 2H), 4.24 (d, J = 13.1 Hz, 1H), 5.37 (d, J = 10.9 Hz, 1H), 5.55 (d, J = 17.4 Hz, 1H), 5.84 (dd, J = 17.4, 10.9 Hz, 1H).

Compound 45e. 2-Vinyl-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester



A solution of crude 2-vinyl-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (3.284 mmol) in tetrahydrofuran/methanol/water (50 mL, 2:2:1) was treated with lithium hydroxide monohydrate (413.3 mg, 9.852 mmol). After stirring at room temperature for 2 h, the volatiles were removed *in vacuo* and the residue was cooled to 0 °C and quenched with hydrochloric acid (1 M). The aqueous layer was extracted with dichloromethane (2 x). The combined organics were filtered through a phase separator and the volatiles were removed *in vacuo* to provide the title compound (761.4 mg, 90% over 2 steps) as colorless needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 3.31-3.42 (m, 1H), 3.45-3.61 (m, 2H), 3.87-3.94 (m, 2H), 4.02 (d, J = 13.6 Hz, 1H), 5.44 (d, J = 10.7 Hz, 1H), 5.60 (d, J = 17.4 Hz, 1H), 5.85 (dd, J = 17.4, 10.7 Hz, 1H).

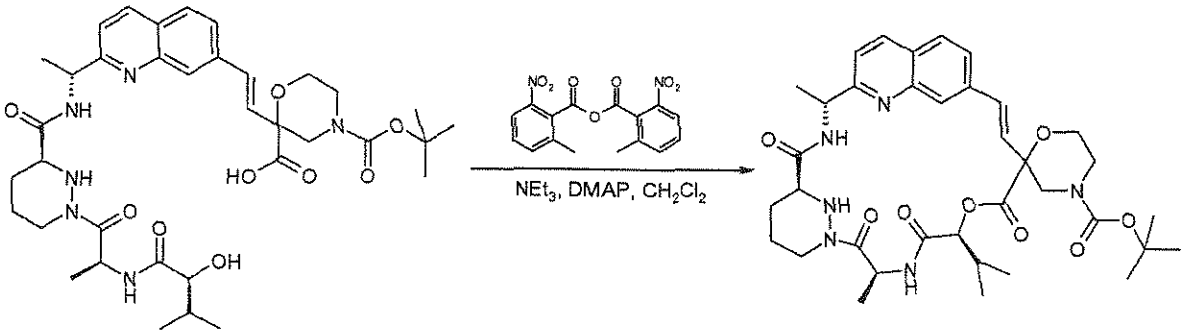
Compound 45f. 2-((E)-2-{2-[(R)-1-({(S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carbonyl}-amino)-ethyl]-quinolin-7-yl}-vinyl)-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester



A solution of (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-amide (95 mg, 0.178 mmol), 2-vinyl-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester (45.7 mg, 0.178 mmol), tri(*o*-

tolyl)phosphine (11 mg, 0.036 mmol) and triethylamine (0.08 mL, 0.534 mmol) in 1,4-dioxane (5 mL) was degassed by bubbling nitrogen through for 5 minutes then warmed to 50 °C and treated with tris(dibenzylideneacetone)dipalladium(0) (16.3 mg, 0.018 mmol). After stirring at 100 °C for 50 minutes the reaction was cooled to room temperature, filtered through a pad of Celite, which was rinsed with ethyl acetate. The volatiles were removed *in vacuo* to provide crude title compound as an orange foam that was used without further purification. LCMS (m/z) 711.3 [M+H], Tr = 2.14 min.

Compound 45 and 46.



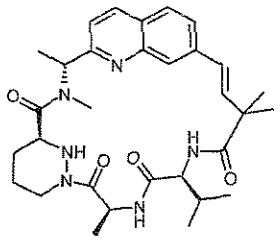
A solution of crude 2-((E)-2-{2-[(R)-1-({(S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carbonyl}-amino)-ethyl]-quinolin-7-yl}-vinyl)-morpholine-2,4-dicarboxylic acid 4-*tert*-butyl ester (0.178 mmol), 4-dimethylaminopyridine (21.7 mg, 0.178 mmol) and triethylamine (0.08 mL, 0.534 mmol) in dry dichloromethane (150 mL) was treated with 2-methyl-6-nitrobenzoic anhydride (122.6 mg, 0.356 mmol). After stirring at room temperature for 1.5 h, more 2-methyl-6-nitrobenzoic anhydride (122.6 mg, 0.356 mmol) was added. After stirring at room temperature for 16 h, more triethylamine (0.2 mL) and 4-dimethylaminopyridine (217 mg, 1.780 mmol) were added. After stirring at room temperature for 4 h, the volatiles were removed *in vacuo*. The residue was partitioned between dichloromethane and a saturated solution of sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The organics were combined, filtered through a phase separator and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Isolute cartridge eluted with a continuous gradient of *iso*-hexanes/ethyl acetate 1:0 to 0:1 then by reverse phase preparative HPLC eluting with a continuous gradient of water/acetonitrile 95:5 to 0:1 to afford the title compound as two separate isomers.

Compound 45 (Second eluting) Diastereomer 1 (1.9 mg, 1.5%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (d, J = 6.7 Hz, 6H), 1.47-1.54 (m, 10H), 1.55-1.77 (m, 8H), 1.90-2.00

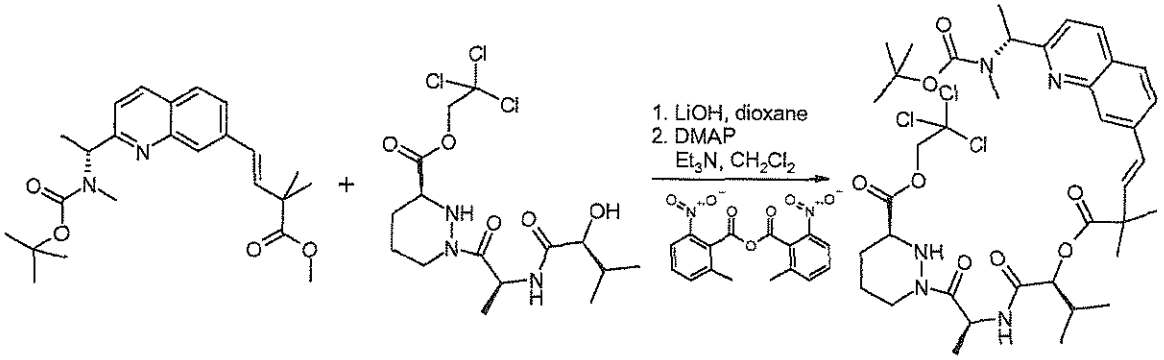
(m, 1H), 2.16-2.31 (m, 2H), 2.62-2.74 (m, 1H), 3.04-3.18 (m, 2H), 3.54-3.62 (m, 1H), 3.68-3.80 (m, 1H), 3.83-3.93 (m, 1H), 3.94-4.03 (m, 1H), 4.38-4.47 (m, 1H), 4.57-4.67 (m, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 5.10 (q, *J* = 6.7 Hz, 1H), 5.19 (d, *J* = 8.7 Hz, 1H), 5.80 (q, *J* = 7.3 Hz, 1H), 6.18 (d, *J* = 16.3 Hz, 1H), 6.93 (d, *J* = 16.3 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.62 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.90 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H). LCMS (m/z) 693.3 [M+H], Tr = 2.68 min.

Compound 46 (First eluting) Diastereomer 2 (0.8 mg, 1%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.97-1.06 (m, 6H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.43-1.58 (m, 13H), 1.65-1.74 (m, 1H), 1.97-2.07 (m, 1H), 2.18-2.37 (m, 2H), 3.42-3.49 (m, 1H), 3.74-4.03 (m, 4H), 5.16 (q, *J* = 7.1 Hz, 1H), 5.27-5.33 (m, 1H), 5.35 (q, *J* = 6.7 Hz, 1H), 6.58 (d, *J* = 16.3 Hz, 1H), 6.78 (d, *J* = 7.1 Hz, 1H), 7.20 (d, *J* = 16.0 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.74-7.81 (m, 1H), 7.99 (s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H). LCMS (m/z) 693.5 [M+H], Tr = 3.39 min.

Example 47. Compound 47.

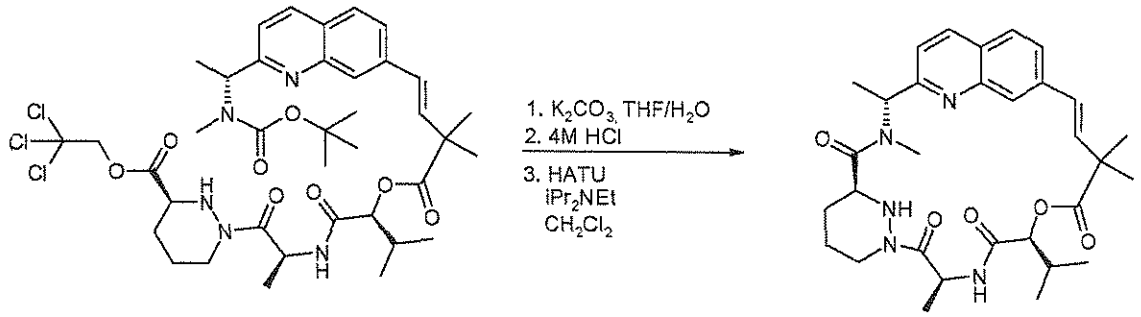


Compound 47a. (S)-1-{(S)-2-[(S)-2-((E)-4-{2-[(R)-1-(*tert*-Butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester



A solution of (E)-4-{2-[(R)-1-(tert-butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoic acid methyl ester (193 mg, 0.47 mmol) in 1,4-dioxane (10 mL) was treated with a solution of lithium hydroxide monohydrate (112mg, 4.7 mmol) in water (5 mL). After stirring at 50 °C for 1 h, the volatiles were removed *in vacuo*. The residue was partitioned between water and diethyl ether. The aqueous layer was acidified to pH 2 by addition of hydrochloric acid then extracted with ethyl acetate (3 x). The organics were combined and the volatiles were removed *in vacuo*. The residue was dissolved in dichloromethane (10 mL) and was treated with 4-dimethylaminopyridine (57 mg, 0.47 mmol), 2-methyl-6-nitrobenzoic anhydride (275 mg, 0.80 mmol), and triethylamine (0.197 mL, 1.41 mmol). After stirring for 30 min (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (203 mg, 0.47 mmol) was added. After stirring for 16 h, the reaction was quenched by addition of a sodium bicarbonate solution (10 mL), the aqueous layer was extracted with dichloromethane (2 x), the organics were combined and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using a 25 g Biotage cartridge eluted with a continuous gradient of *iso*-hexanes/acetone 1:0 to 3:1 to afford the title compound (260 mg, 68%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.97-1.05 (m, 6H), 1.29 (d, J = 6.9 Hz, 3H), 1.44 (*br* s, 9H), 1.55 (s, 3H), 1.57 (s, 3H), 1.68 (d, J = 6.9 Hz, 3H), 1.71-2.00 (m, 4H), 2.02-2.30 (m, 3H), 2.80 (*br* s, 3H), 3.56 (*br* s, 1H), 3.78-3.83 (m, 1H), 4.75-4.82 (m, 1H), 4.93-5.01 (m, 2H), 5.35-5.45 (m, 1H), 6.65-6.82 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.72-7.83 (m, 2H), 7.98 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H). LCMS (m/z) 814.1 [M+H], Tr = 3.97 min.

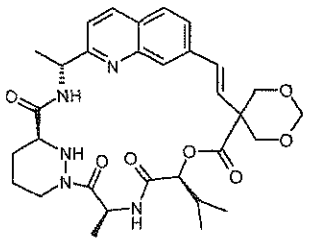
Compound 47.



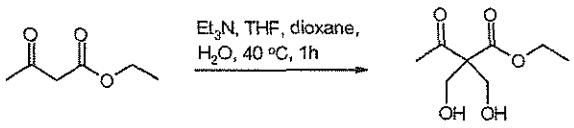
A solution of (S)-1-{(S)-2-[(S)-2-((E)-4-{2-[(R)-1-(*tert*-butoxycarbonyl-methyl-amino)-ethyl]-quinolin-7-yl}-2,2-dimethyl-but-3-enoyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (260 mg, 0.32 mmol) in tetrahydrofuran (30 mL) was prepared and a solution of potassium carbonate (663 mg, 4.80 mmol) in water (15

mL) was added. The reaction was stirred at room temperature for 1.5 h. The reaction mixture was acidified to pH 3 with hydrochloric acid (1 M) then extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue was dried under vacuum for 1 h before dissolving in dichloromethane (30 mL) and treating with hydrogen chloride in 1,4-dioxane (4 M, 15 mL). It was stirred for 1 h at room temperature then evaporated. Residual water was azeotroped off with toluene (2 x 20 mL) to yield a white solid (251 mg). The white solid was dissolved in anhydrous *N,N*-dimethylformamide (10 mL) and *N,N*-diisopropylethylamine (279 µL, 1.6 mmol) was added. This solution was then added *via* a syringe pump to a stirred solution of 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (183 mg, 0.48 mmol) in anhydrous dichloromethane (150 mL) over 1 h. The reaction mixture was washed with saturated sodium bicarbonate solution (30 mL), filtered through a phase separator and evaporated. The residue was purified by reverse phase preparative HPLC to yield the title product (54 mg, 30%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 0.99 (s, 3H), 1.44 (s, 3H), 1.50-1.55 (m, 6H), 1.56-2.03 (m, 4H), 1.68 (d, J = 7.4 Hz, 3H), 2.20-2.34 (m, 1H), 2.64-2.79 (m, 1H), 3.14 (s, 3H), 3.90-4.01 (m, 1H), 4.50-4.61 (m, 1H), 4.85 (d, J = 8.5 Hz, 3H), 5.88-6.15 (m, 1H), 6.30 (d, J = 16.5 Hz, 1H), 6.38 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 16.3 Hz, 1H), 6.61-6.87 (m, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H). LCMS (m/z) 564.2 [M+H], Tr = 2.54 min.

Example 48, Compound 48.



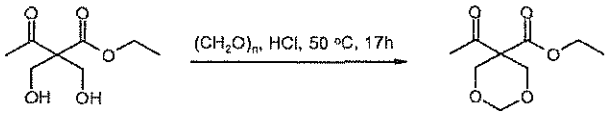
Compound 48a. Ethyl 2,2-bis(hydroxymethyl)-3-oxobutanoate.



To a stirred solution of ethyl acetoacetate (150 g, 1.2 mol) in formaldehyde (210 mL, 2.8 mol, 40% aq.) and dioxane (550 mL) was added dropwise triethylamine (1.0 M in tetrahydrofuran, 57 mL, 0.06 mol) at 0 °C. The temperature was raised up to 35- 40 °C and the

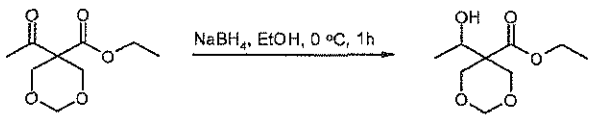
mixture was stirred for 1h. The reaction mixture was diluted with water (400 mL), and the side products were extracted with toluene (3 x 600 mL). The aqueous phase was evaporated at 35 °C to one fourth of the initial volume and extracted with ethyl acetate (3 x 900 mL). The extracts were dried over sodium sulfate and evaporated to get the crude product (75 g) as yellow oil, which was used directly to the next step without purification.

Compound 48b. Ethyl 5-acetyl-1,3-dioxane-5-carboxylate.



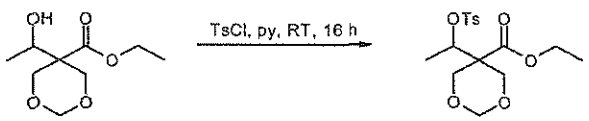
A solution of ethyl 2,2-bis(hydroxymethyl)-3-oxobutanoate (75 g, 0.39 mol) and 40% formaldehyde (360 mL) in concentrated hydrochloric acid (360 mL) was heated at 50 °C for 17 h. The two-phase solution was cooled to room temperature and extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed with water, dried over magnesium sulfate, and evaporated to give a residue, which was purified by flash column chromatography eluting with a continuous gradient of petroleum ether/ethyl acetate 15:1 to 9:1 to afford the title compound (33 g, 14%, 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (m, 3H), 2.31 (s, 3H), 4.25- 4.19 (m, 4H), 4.35 (d, J = 12.0 Hz, 2H), 4.77 (d, J = 6.0 Hz, 1H), 4.82 (d, J = 6.0 Hz, 1H).

Compound 48c. Ethyl 5-(1-hydroxyethyl)-1,3-dioxane-5-carboxylate.



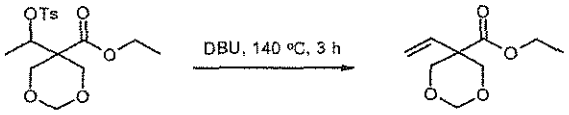
Ethyl 5-acetyl-1,3-dioxane-5-carboxylate (2) (22.3 g, 0.11 mol) was dissolved in ethanol (100 mL) and sodium borohydride (2.08 g, 0.055 mol) was added at 0 °C in portions. The mixture was stirred at the same temperature for 1h. The excess of sodium borohydride was destroyed with acetone and the solution was extracted with ethyl acetate (3 x 600 mL). The combined organic extracts were concentrated in vacuo to give the title compound (18.9 g, 84%) as colorless oil.

Compound 48d. Ethyl 5-(1-(tosyloxy)ethyl)-1,3-dioxane-5-carboxylate.



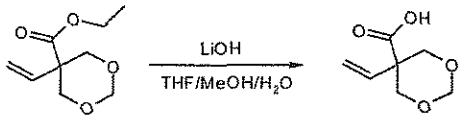
To a mixture of ethyl 5-(1-hydroxyethyl)-1,3-dioxane-5-carboxylate (16.8 g, 83 mmol) in dry pyridine (40 mL) at 0 °C was added 4- toluenesulfonyl chloride (19.1 g, 99 mmol). The mixture was stirred at rt for 16 h. Water (40 mL) was added, and the mixture was extracted with ethyl acetate (2 x 400 mL). The organic layer was washed with brine (3x). After concentrated in vacuo, the crude product was purified by silica gel chromatography eluting with petroleum ether/ethyl acetate 25:1 to 5:1 to provide the title compound (22.7 g, 76%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (m, 3H), 1.34 (d, J = 6.8 Hz, 3H), 2.45 (s, 3H), 3.80 (d, J = 11.6 Hz , 1H), 3.87 (d, J = 11.6 Hz , 1H), 4.02 (d, J = 11.6 Hz, 1H), 4.08 (d, J = 12.0 Hz, 1H), 4.20-4.17 (m, 2H), 5.03-4.98 (m, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H).

Compound 48e. 5-Vinyl-[1,3]dioxane-5-carboxylic acid ethyl ester.



A mixture of ethyl 5-(1-(tosyloxy)ethyl)-1,3-dioxane-5-carboxylate (20.7 g, 58 mmol) and DBU (25 mL) was heated at 140°C for 3h. After being cooled to rt, the reaction mixture was poured into ether (300 mL), and the organic layer was washed with brine (3x). The ether layer was dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with petroleum ether/ether 30:1 to 20:1 to give a crude product, which was distilled under reduced pressure (45-49 °C/0.3 mbar) to afford the title compound (3.6 g, 33%) as colorless oil. ^{1}H NMR (400 MHz, CDCl3) δ 1.29 (t, J = 11.0 Hz, 3H), 3.70 (d, J = 11.6 Hz, 2H), 4.25 (t, J = 7.2 Hz, 2H), 4.44 (t, J = 11.2 Hz, 2H), 4.71 (d, J = 8.0 Hz, 1H), 4.95 (d, J = 6.0 Hz, 1H), 5.24 (m, 1H), 5.27 (m, 1H), 5.65 (m, 1H). This ^{1}H spectral data is in good agreement with that reported for the synthesis of the title compound, the which is described in Borremans, F. et al. *Bull. Soc. Chim. Belg.* **1976**, *85*, 681-696.

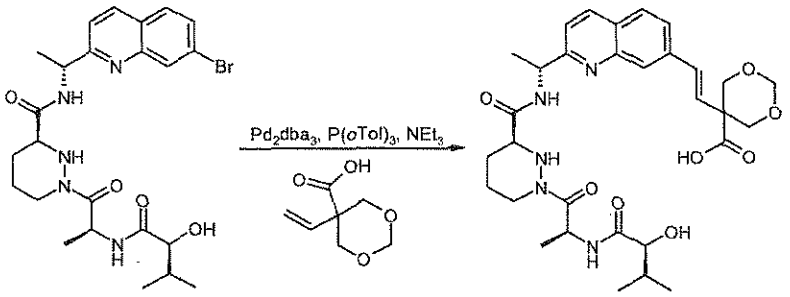
Compound 48f. 5-Vinyl-[1,3]dioxane-5-carboxylic acid.



A solution of 5-vinyl-[1,3]dioxane-5-carboxylic acid ethyl ester (397.7 mg, 2.136 mmol) in tetrahydrofuran/methanol/water (15 mL, 2:2:1) was treated with lithium hydroxide monohydrate (269 mg, 6.408 mmol). After stirring at room temperature for 1.5 h, the volatiles were removed *in vacuo* and the residue was cooled to 0 °C and quenched with hydrochloric acid (1 M). The

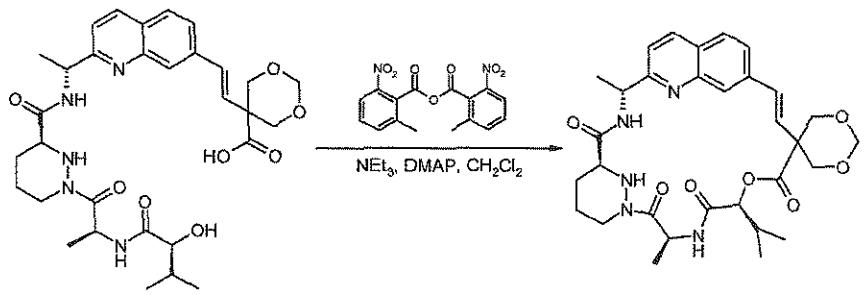
aqueous layer was saturated with sodium chloride, extracted with dichloromethane (3 x). The combined organics were filtered through a phase separator and the volatiles were removed *in vacuo* to provide the title compound (320.3 mg, 95%) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (d, J = 11.6 Hz, 2H), 4.50 (d, J = 11.4 Hz, 2H), 4.73 (d, J = 6.2 Hz, 1H), 5.02 (d, J = 6.0 Hz, 1H), 5.27-5.39 (m, 2H), 5.69 (dd, J = 17.6, 10.9 Hz, 1H).

Compound 48g. 5-((E)-2-{2-[(R)-1-({(S)-1-[(S)-2-((S)-2-Hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carbonyl}-amino)-ethyl]-quinolin-7-yl}-vinyl)-[1,3]dioxane-5-carboxylic acid.



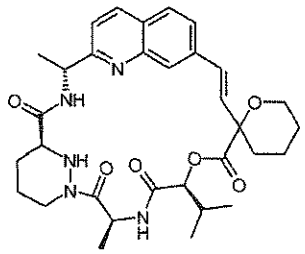
A solution of (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-amide (398.4 mg, 0.745 mmol), 5-vinyl-[1,3]dioxane-5-carboxylic acid (117.9 mg, 0.745 mmol), tri(*o*-tolyl)phosphine (45.3 mg, 0.149 mmol) and triethylamine (0.32 mL, 2.235 mmol) in 1,4-dioxane (15 mL) was degassed by bubbling nitrogen through for 5 minutes then warmed to 50 °C and treated with tris(dibenzylideneacetone)dipalladium(0) (68.2 mg, 0.074 mmol). After stirring at 100 °C for 40 minutes the reaction was cooled to room temperature, filtered through a pad of Celite, which was rinsed with ethyl acetate. The volatiles were removed *in vacuo* to provide crude title compound as an orange foam that was used without further purification. LCMS (m/z) 612.2 [M+H], Tr = 1.70 min.

Compound 48.

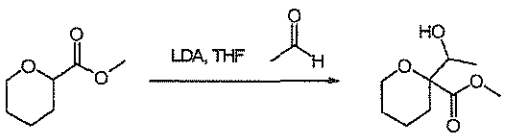


A solution of crude 5-((E)-2-{2-[(R)-1-({(S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carbonyl}-amino)-ethyl]-quinolin-7-yl}-vinyl)-[1,3]dioxane-5-carboxylic acid (0.745 mmol) in dry dichloromethane (18 mL) was added *via* syringe pump to a solution of 2-methyl-6-nitrobenzoic anhydride (385.0 mg, 1.117 mmol), 4-dimethylaminopyridine (273.0 mg, 2.235 mmol) in dry dichloromethane (230 mL) containing 4 Å molecular sieves over 3 h. After the end of the addition, the reaction was stirred at room temperature for 40 minutes then filtered and the volatiles were partially removed *in vacuo*. The organics were washed with pH 4 citrate buffer, a saturated solution of sodium bicarbonate and filtered on a phase separator. The volatiles were removed *in vacuo* and the residue was purified by silica gel chromatography using a 25 g Isolute cartridge eluted with a continuous gradient of *iso*-hexanes/acetone 1:0 to 1:1 to provide the title compound at 90% purity (133.8 mg, 30% yield). A third of this material was purified by reverse phase preparative HPLC eluting with a continuous gradient of water/acetonitrile 95:5 to 0:1 to afford the title compound (8.1 mg) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (d, J = 6.7 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.47-1.80 (m, 8H), 2.12-2.31 (m, 2H), 2.65-2.77 (m, 1H), 3.59-3.66 (m, 1H), 3.85 (d, J = 11.4 Hz, 1H), 3.92 (d, J = 11.4 Hz, 1H), 4.39-4.53 (m, 2H), 4.63-4.71 (m, 1H), 4.98 (d, J = 6.2 Hz, 1H), 5.08 (q, J = 6.9 Hz, 1H), 5.35 (d, J = 9.1 Hz, 1H), 5.82 (q, J = 7.3 Hz, 1H), 6.15 (d, J = 16.5 Hz, 1H), 6.63 (d, J = 16.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.69 (dd, J = 8.5, 1.8 Hz, 1H), 7.75 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H). LCMS (m/z) 594.1 [M+H], Tr = 2.60 min.

Example 49. Compound 49.

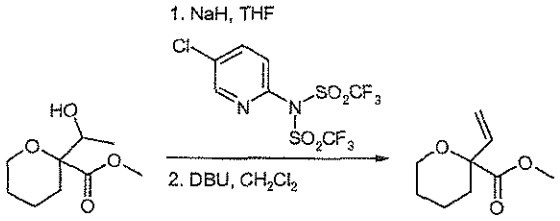


Compound 49a. 2-(1-Hydroxy-ethyl)-tetrahydro-pyran-2-carboxylic acid methyl ester



A solution of *N,N*-diisopropylamine (909 mg, 1.25 mL, 9 mmol) in tetrahydrofuran (4 mL) was stirred at –78 °C under nitrogen. *n*-Butyllithium (3.6 mL, 9 mmol, 2.5 M solution in hexane) was added dropwise and the reaction mixture was stirred at –78 °C for 30 minutes. A solution of tetrahydro-pyran-2-carboxylic acid methyl ester (864 mg, 6 mmol) in tetrahydrofuran (8 mL) was added and the reaction mixture was stirred at –78 °C for 20 minutes. Acetaldehyde (792 mg, 1.0 mL, 18 mmol) was added in one portion. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and ice-cold hydrochloric acid (2 M) was added to acidify the reaction mixture to pH 2. Sodium chloride was added to saturate the aqueous phase and the mixture was extracted with diethyl ether. The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of pentane/diethyl ether 1:1 to 0:1 to afford the title compound (1.28 g) as an oil and as a 2:1 mixture of diastereoisomers. LCMS (m/z) 189.3 [M+H], Tr = 1.23 min.

Compound 49b. 2-Vinyl-tetrahydro-pyran-2-carboxylic acid methyl ester

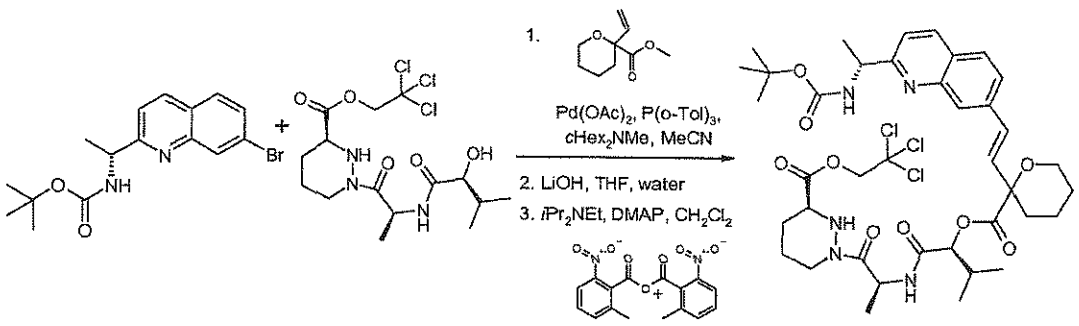


A suspension of sodium hydride (200 mg, 5 mmol, 60% dispersion in oil) in tetrahydrofuran (6 mL) was stirred at –78 °C under nitrogen. A solution of 2-(1-hydroxy-ethyl)-tetrahydro-pyran-2-carboxylic acid methyl ester (620 mg, 3.3 mmol) in tetrahydrofuran 3 mL) was added and the reaction mixture was stirred at –78 °C for 15 minutes. A solution of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (2.60 g, 6.6 mmol) in tetrahydrofuran (10 mL) was added and the reaction mixture was stirred at –78 °C for 30 minutes. The reaction mixture was warmed to room temperature and then stirred at room temperature for 1 h. The reaction mixture was cooled to 5°C and saturated ammonium chloride solution was cautiously added. The reaction mixture was extracted with diethyl ether. The organics were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of pentane/diethyl ether 10:1 to 5:1 to afford 2-(1-trifluoromethanesulfonyloxy-ethyl)-tetrahydro-pyran-2-carboxylic acid methyl ester (2.12 g, 3.3 mmol) as an oil and as a 2:1 mixture of

diastereoisomers which was used immediately in the next step. LCMS (m/z) 321.0 [M+H], Tr = 2.88 min.

A solution of 2-(1-trifluoromethanesulfonyloxy-ethyl)-tetrahydro-pyran-2-carboxylic acid methyl ester (2.12 g, 3.3 mmol) in dichloromethane (5 mL) was stirred at room temperature under nitrogen. 1,8-Diazabicycloundec-7-ene (2.0 g, 2 mL, 13.2 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C and acidified to pH 2 with ice cold hydrochloric acid (2 M). The mixture was extracted with dichloromethane. The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of pentane/diethyl ether 10:1 to 5:1 to afford the title compound (466 mg, 75% over two steps) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-1.80 (m, 5H), 2.21-2.29 (m, 1H), 2.68-2.77 (m, 1H), 3.79 (s, 3H), 3.91-3.98 (m, 1H), 5.26 (dd, J = 10.7, 0.9 Hz, 1H), 5.41 (dd, J = 17.4, 1.1 Hz, 1H), 5.87 (dd, J = 17.4, 10.7 Hz, 1H). LCMS (m/z) 193.2 [M+H], Tr = 2.01 min.

Compound 49c. (S)-1-{(S)-2-[(S)-2-(2-{(E)-2-[2-((R)-1-*tert*-Butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-tetrahydro-pyran-2-carbonyloxy)-3-methyl-butyrylamino]-propionyl}-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloroethyl ester



A solution of [(R)-1-(7-bromo-quinolin-2-yl)-ethyl]-carbamic acid *tert*-butyl ester (320 mg, 0.9 mmol), 2-vinyl-tetrahydro-pyran-2-carboxylic acid methyl ester (330 mg, 0.9 mmol), tris(dibenzylideneacetone)dipalladium(0) (82 mg, 0.09 mmol), tri(*o*-tolyl)phosphine (54 mg, 0.18 mmol) and *N,N*-dicyclohexylmethylamine (526 mg, 0.58 mL, 2.7 mmol) in acetonitrile (4 mL) was heated at 120 °C in a microwave reactor for 30 minutes. The reaction mixture was filtered and the solvent was evaporated. The residue was dissolved in ethyl acetate and the solution was washed with ice-cold hydrochloric acid (1 M). The aqueous layer was extracted with ethyl acetate and the organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford 2-{(E)-2-[2-((R)-

1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-tetrahydro-pyran-2-carboxylic acid methyl ester (130 mg, 21%) as an oil LCMS (m/z) 441.1 [M+H], Tr = 2.75 min.

A solution of 2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-tetrahydro-pyran-2-carboxylic acid methyl ester (130 mg, 0.3 mmol) in tetrahydrofuran (6 mL) was stirred at 5 °C under nitrogen. A solution of lithium hydroxide monohydrate (25 mg, 0.6 mmol) in water (1.5 mL) was added and the reaction mixture was stirred at room temperature for 18 h. The majority of the organic solvent was evaporated. The solution was acidified to pH 2 with ice-cold hydrochloric acid (2 M) and the mixture was extracted with dichloromethane. The organic extracts were combined and washed with brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated to afford 2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-tetrahydro-pyran-2-carboxylic acid (135 mg, 0.3 mmol) as a yellow gum which was used crude in the next step. LCMS (m/z) 427.1 [M+H], Tr = 2.17 min.

A solution of 2-{(E)-2-[2-((R)-1-*tert*-butoxycarbonylamino-ethyl)-quinolin-7-yl]-vinyl}-tetrahydro-pyran-2-carboxylic acid (135 mg, 0.3 mmol), *N,N*-diisopropylethylamine (96 mg, 0.133 mL, 0.75 mmol), 4-dimethylaminopyridine (80 mg, 0.66 mmol) and 2-methyl-6-nitrobenzoic anhydride (193 mg, 0.56 mmol) in dichloromethane (5 mL) was stirred at 0 °C under nitrogen. A solution of (S)-1-[(S)-2-((S)-2-hydroxy-3-methyl-butyrylamino)-propionyl]-hexahydro-pyridazine-3-carboxylic acid 2,2,2-trichloro-ethyl ester (142 mg, 0.33 mmol) in dichloromethane (2 mL) was added and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with dichloromethane and the solution was washed with ice-cold saturated sodium hydrogen carbonate solution, water, ice-cold hydrochloric acid (1 M), water and brine. The organic solution was filtered through a hydrophobic frit and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of *iso*-hexanes/ethyl acetate 3:1 to 1:3 to afford the title compound (44 mg, 17%) as a white solid and as a 1:1 mixture of two diastereoisomers. LCMS (m/z) 840.2, 842.0 [M+H], Tr = 3.75 min.