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(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VENKATRAMAN, Srikanth** [IN/US]; 35 Roanoke Street, Woodbridge, New Jersey 07095 (US). **NJOROGE, F., George** [US/US]; 11 Softwood Way, Warren, New Jersey 07059 (US). **WU, Wanli** [US/US]; 802 Orange Street, 3rd Floor, New Haven, Connecticut 06511 (US). **GIRIJAVALLABHAN, Viyyoor** [US/US]; 10 Maplewood Drive, Parsippany, NJ 07054 (US). **MCKITTRICK, Brian** [US/US]; 14 Millbrook Road, New Vernon, New Jersey 07976 (US). **SU, Jing** [US/US]; 1398 Graymill Drive, Scotch Plains, New Jersey 07076 (US). **VELAZQUEZ, Francisco** [MX/US]; 4 Alexandra Way, Clinton, New Jersey 08809 (US). **PINTO, Patrick, A.** [US/US]; 34 Battle Ridge Road, Morris Plains, New Jersey 07950 (US).

(74) Agent: **FARQUHARSON-TORRES, Serena**; Schering Corporation, 2000 Galloping Hill Road, Patent Dept K-6-1 1990, Kenilworth, New Jersey 07033 (US).

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(54) **Title:** MACROCYCLIC INHIBITORS OF HEPATITIS C VIRUS NS3 SERINE PROTEASE

(57) **Abstract:** The present invention discloses novel compounds which have HCV protease inhibitory activity as well as methods for preparing such compounds. In another embodiment, the invention discloses pharmaceutical compositions comprising such compounds as well as methods of using them to treat disorders associated with the HCV protease.

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MACROCYCLIC INHIBITORS OF HEPATITIS C VIRUS NS3 SERINE PROTEASE

Field of Invention

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention additionally discloses novel macrocyclic compounds as inhibitors of the HCV NS3/NS4a serine protease.

Background of the Invention

Hepatitis C virus (HCV) is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH) (*see*, International Patent Application Publication No. WO 89/04669, equal to US 2003162167). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed; (*see*, e.g., U.S. Patent No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. Other chymotrypsin-like enzymes are elastase, factor Xa, thrombin, trypsin, plasmin, urokinase, tPA and PSA. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at

the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy. The inventive compounds can inhibit such protease. They also can modulate the processing of hepatitis C virus (HCV) polypeptide.

It has been determined that the NS4a protein, an approximately 6 kda polypeptide, is a co-factor for the serine protease activity of NS3. Autocleavage of the NS3/NS4a junction by the NS3/NS4a serine protease occurs intramolecularly (i.e., *cis*) while the other cleavage sites are processed intermolecularly (i.e., *trans*).

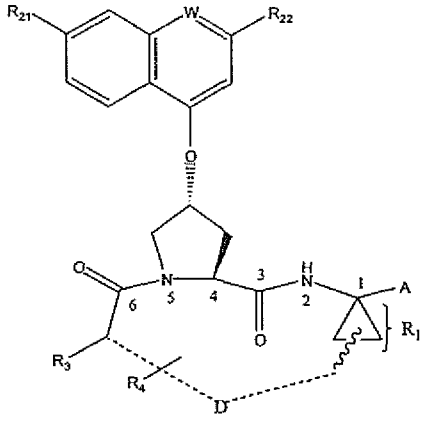
Analysis of the natural cleavage sites for HCV protease revealed the presence of cysteine at P1 and serine at P1' and that these residues are strictly conserved in the NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions. The NS3/NS4a junction contains a threonine at P1 and a serine at P1'. The Cys→Thr substitution at NS3/NS4a is postulated to account for the requirement of *cis* rather than *trans* processing at this junction. *See*, e.g., Pizzi et al. (1994) Proc. Natl. Acad. Sci (USA) 91:888-892, Failla et al. (1996) Folding & Design 1:35-42. The NS3/NS4a cleavage site is also more tolerant of mutagenesis than the other sites. *See*, e.g., Kollykhalov et al. (1994) J. Virol. 68:7525-7533. It has also been found that acidic residues in the region upstream of the cleavage site are required for efficient cleavage. *See*, e.g., Komoda et al. (1994) J. Virol. 68:7351-7357.

Inhibitors of HCV protease that have been reported include antioxidants (*see*, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (*see*, International Patent Application Publication No. WO 98/17679 (equal to US2002032175), Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella et al. (1998) Biochem. 37:8906-8914, Llinàs-Brunet et al. (1998) Bioorg. Med. Chem. Lett. 8:1713-1718), inhibitors based on the 70-amino acid polypeptide eglin c (Martin et al. (1998) Biochem. 37:11459-11468, inhibitors affinity selected from human pancreatic secretory trypsin inhibitor (hPSTI-C3) and minibody repertoires (MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cV_HE2 (a "camelized" variable domain antibody fragment) (Martin et al.(1997) Protein Eng. 10:607-614), and α1-antichymotrypsin (ACT) (Elzouki et al.) (1997) J. Hepat. 27:42-28). A ribozyme designed to selectively destroy hepatitis C virus RNA has recently been disclosed (*see*, *BioWorld Today* 9(217): 4 (November 10, 1998)).

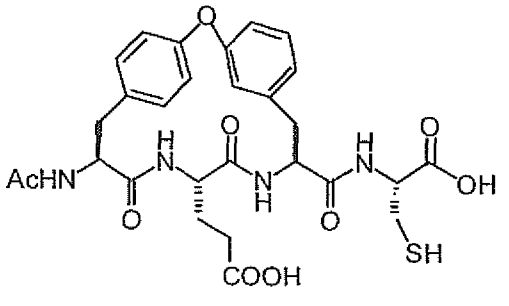
Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (equal to U.S. 6,018,020 and U.S. 5,866,684; F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (equal to U.S. 6,143,715; Boehringer Ingelheim Canada Ltd.).

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular carcinoma have a five-year survival rate of 10-30%, whereas those with localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.

Reference is made to WO 00/59929 (equal to US2004002448 and U.S. 6,608,027; Assignee: Boehringer Ingelheim (Canada) Ltd.; Published October 12, 2000) which discloses peptide derivatives of the formula:

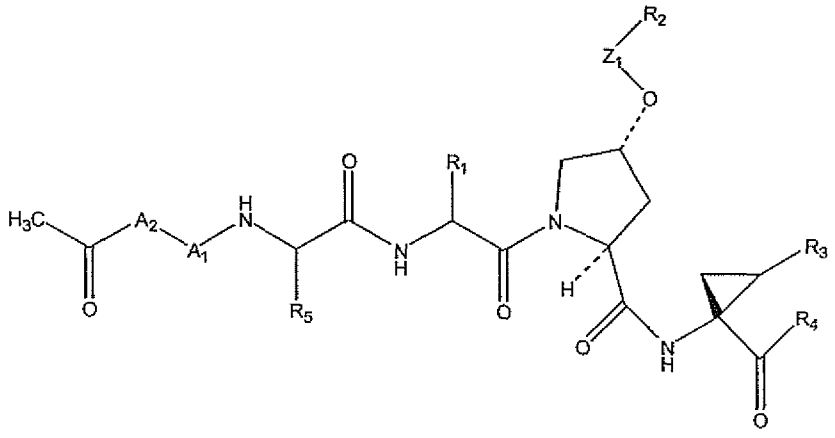


Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

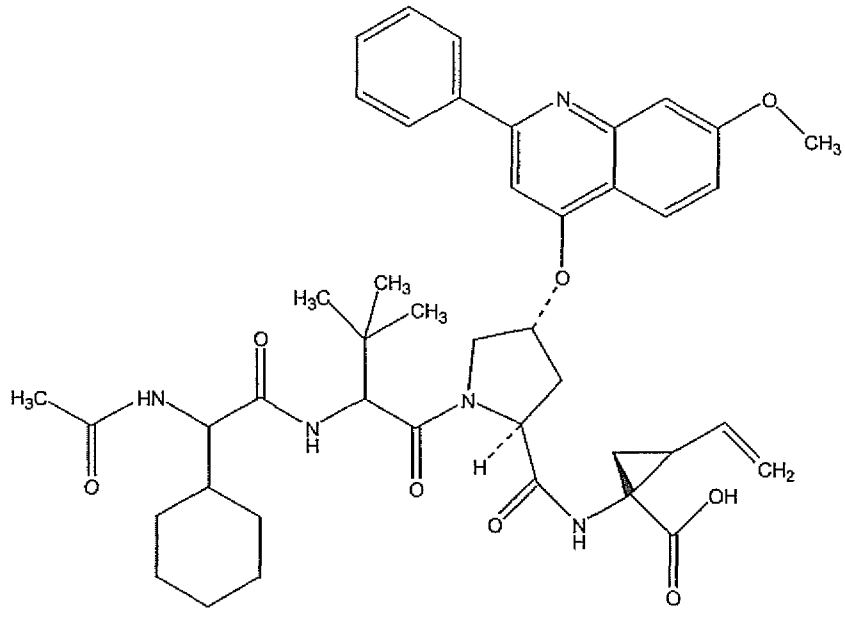


Reference is also made to W. Han *et al, Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

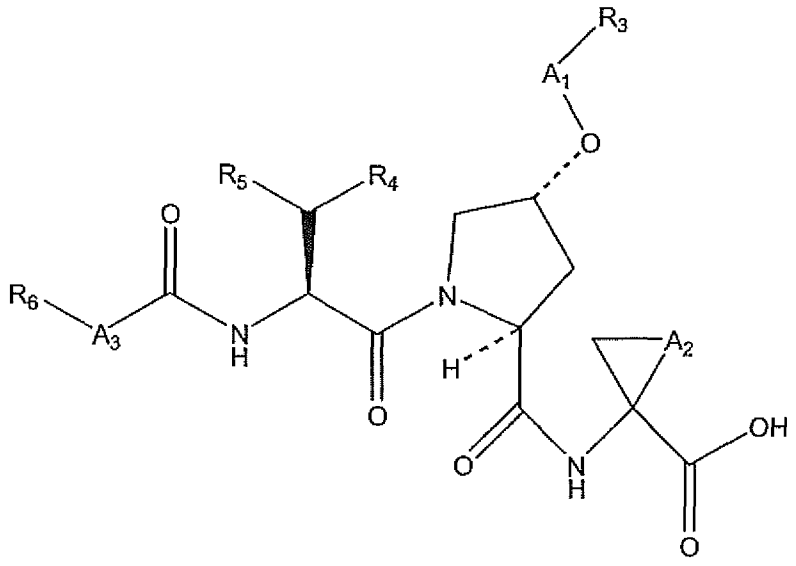
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



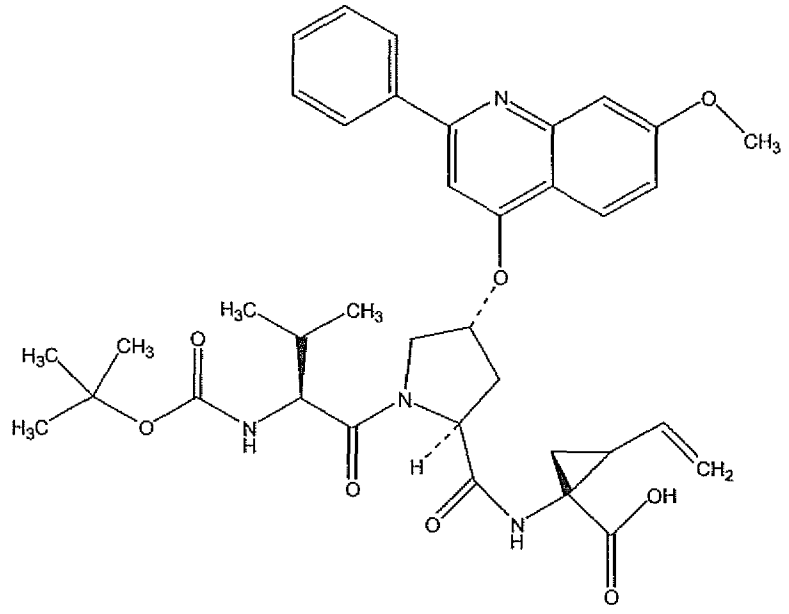
where the various elements are defined therein. An illustrative compound of that series is:



Reference is also made to WO 00/09543 (equal to US2002016442 and US 2002037998; Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:

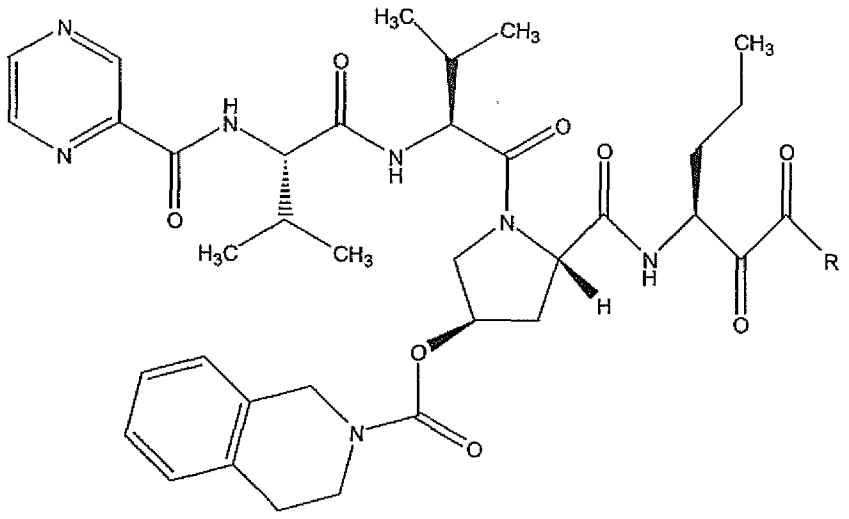


where the various elements are defined therein. An illustrative compound of that series is:

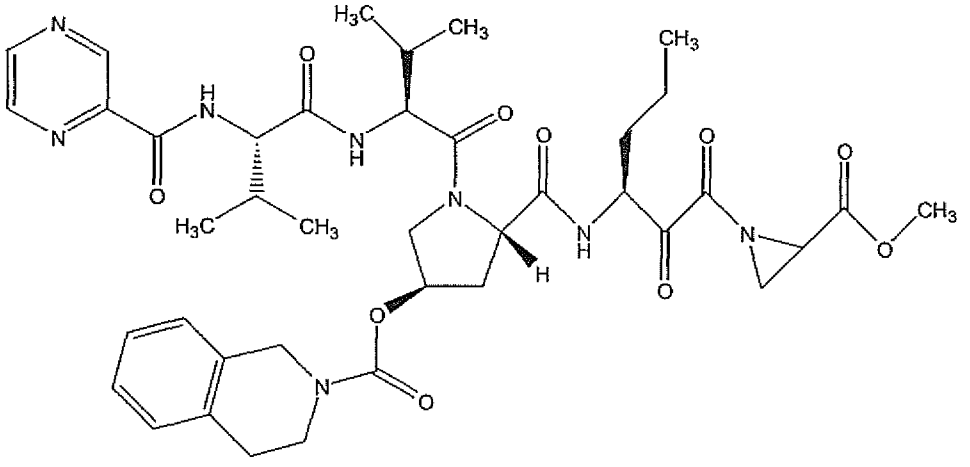


Current therapies for hepatitis C include interferon-α (INF_{α}) and combination therapy with ribavirin and interferon. *See*, e.g., Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2):98-112. These therapies suffer from a low sustained response rate and frequent side effects. *See*, e.g., Hoofnagle et al. (1997) N. Engl. J. Med. 336:347. Currently, no vaccine is available for HCV infection.

Reference is further made to WO 01/74768 (equal to US 2003236242; Assignee: Vertex Pharmaceuticals Inc) published October 11, 2001, which discloses certain compounds of the following general formula (R is defined therein) as NS3-serine protease inhibitors of Hepatitis C virus:



A specific compound disclosed in the afore-mentioned WO 01/74768 has the following formula:



PCT Publications WO 01/77113; WO 01/081325; WO 02/08198; WO 02/08256; WO 02/08187; WO 02/08244; WO 02/48172; WO 02/08251; and pending U.S. patent application, Serial No. 10/052,386, filed January 18, 2002, disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of hepatitis C virus. The disclosures of those applications are incorporated herein by reference thereto.

There is a need for new treatments and therapies for HCV infection. There is a need for compounds useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis C.

There is a need for methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

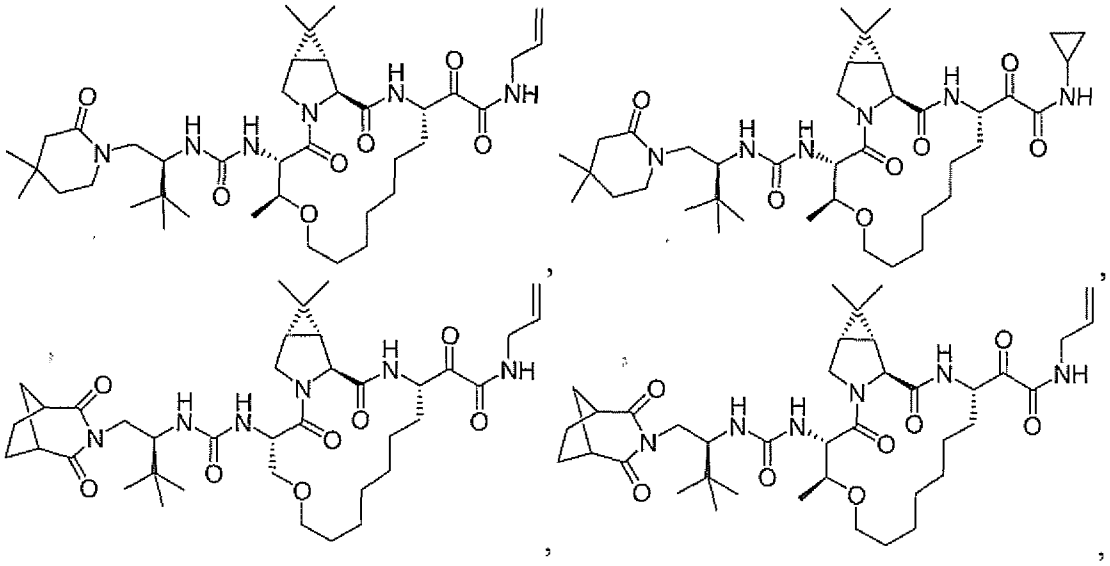
There is a need for methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

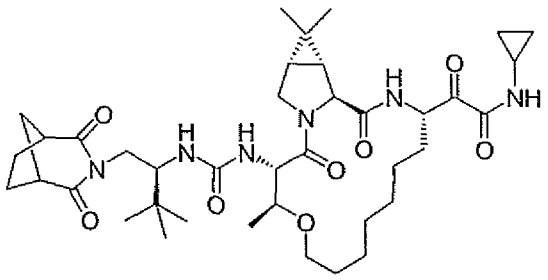
There is a need for methods of modulating the processing of the HCV polypeptide using the compounds provided herein.

Summary of the Invention

U.S. patent application, Serial No. 10/948367, filed February 24, 2005 (which published as 2005/0119168 on June 2, 2005), the entire dislosure of which, is incorporated herein, by reference.

In its many embodiments, the present invention provides novel compounds as inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more of such compounds, methods of treatment or prevention of HCV or amelioration of one or more of the symptoms of hepatitis C using one or more of such compounds or one or more of such formulations, and methods of modulating the interaction of an HCV polypeptide with HCV protease using one or more of such compounds or one or more of such formulations. The present invention discloses compounds, as well as pharmaceutically acceptable salts, solvates or esters of said compounds, said compound being selected from the compounds of structures listed below:

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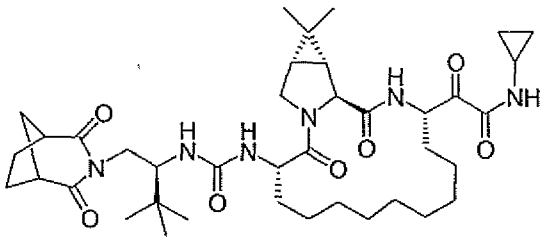
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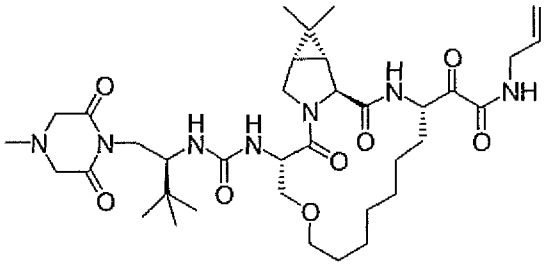
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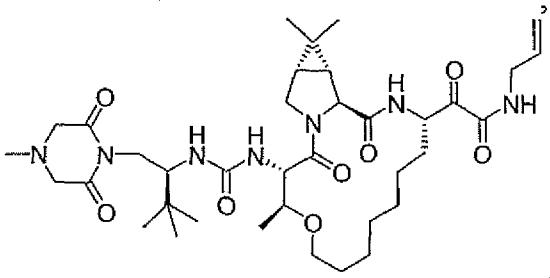
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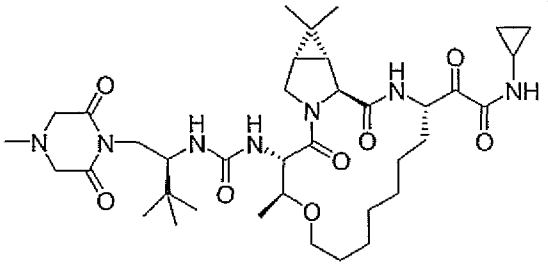
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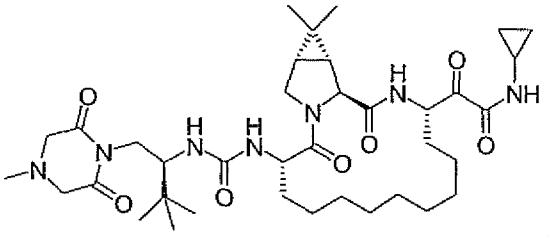
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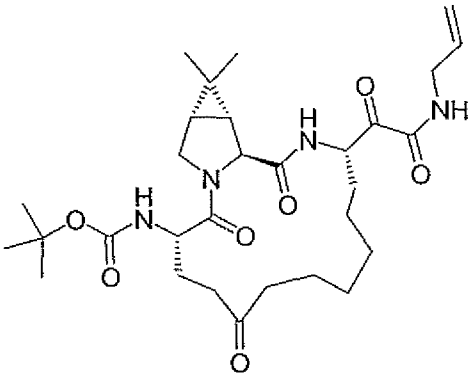
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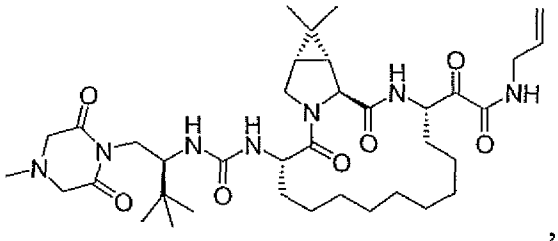
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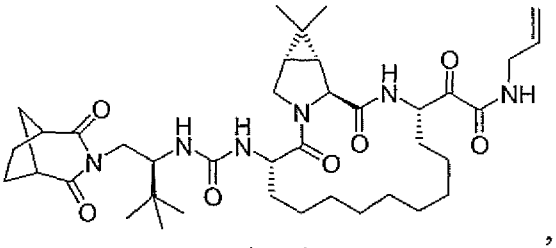
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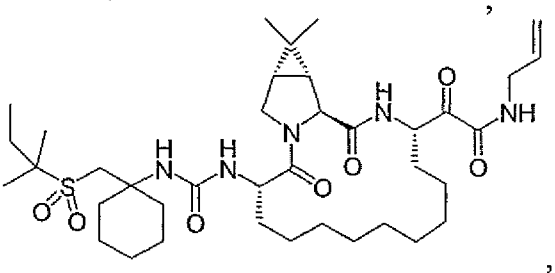
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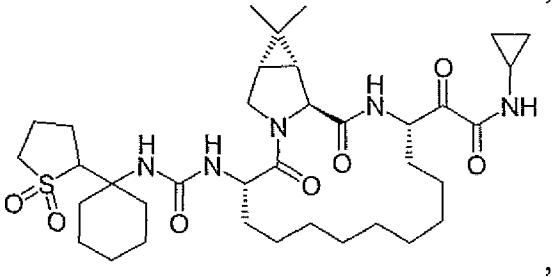
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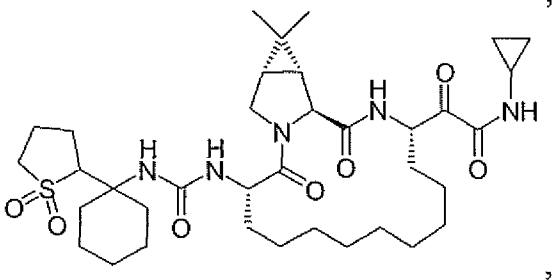
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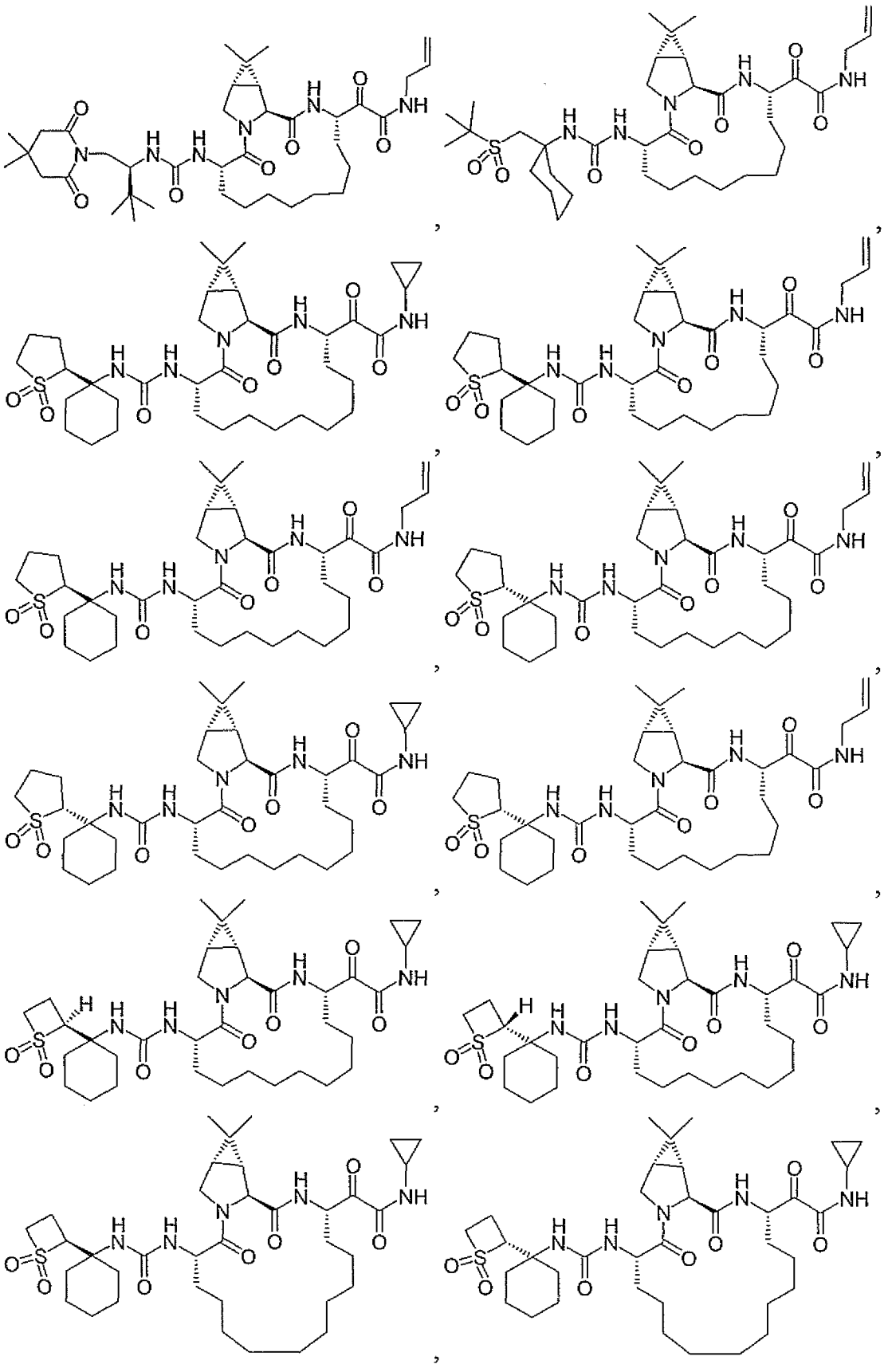

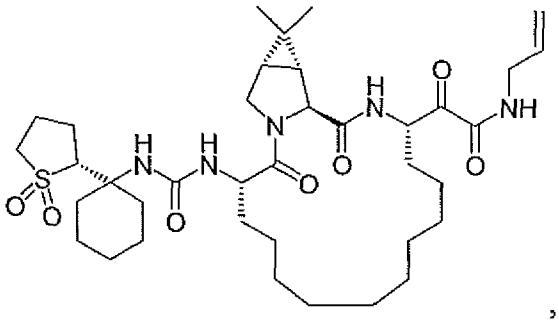
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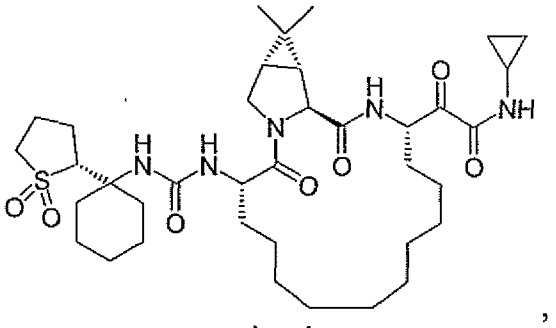
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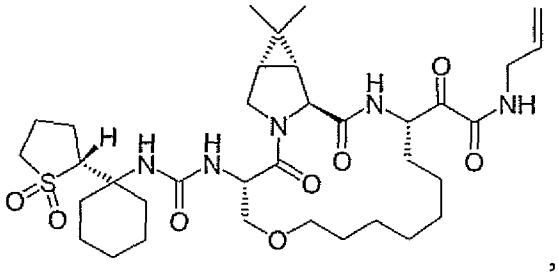
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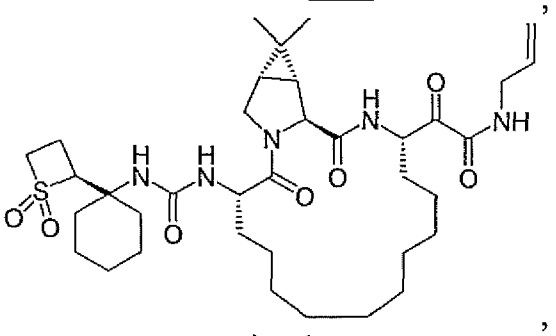
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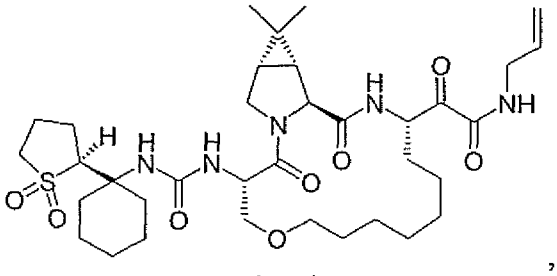
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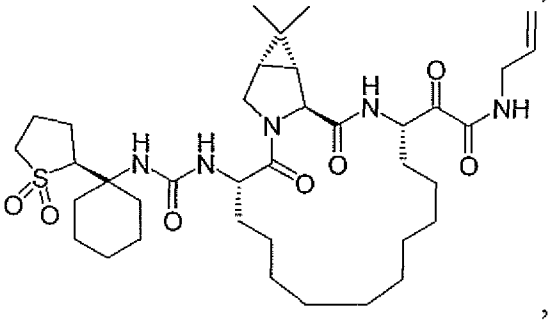
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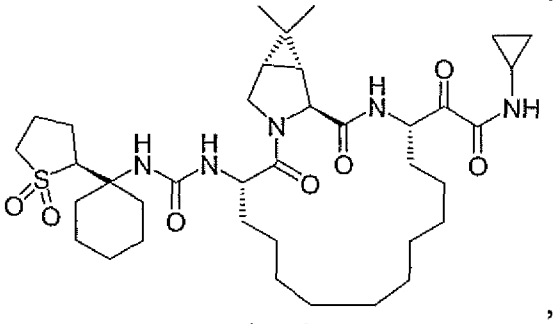
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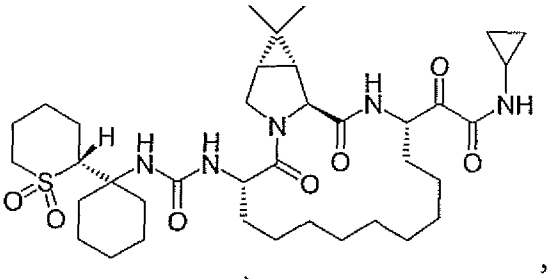
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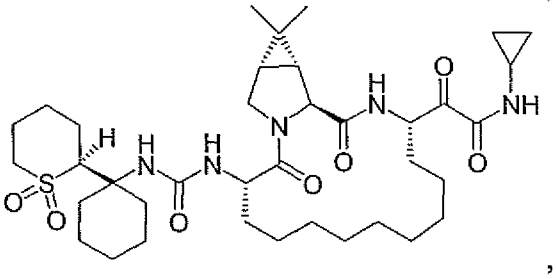
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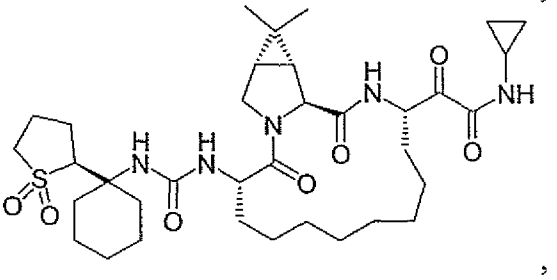
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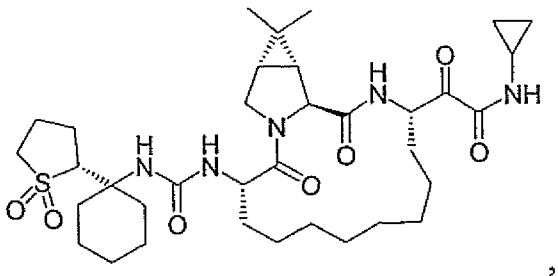
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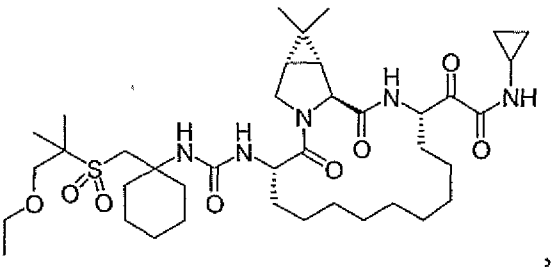
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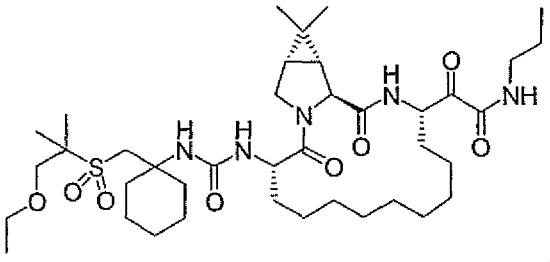
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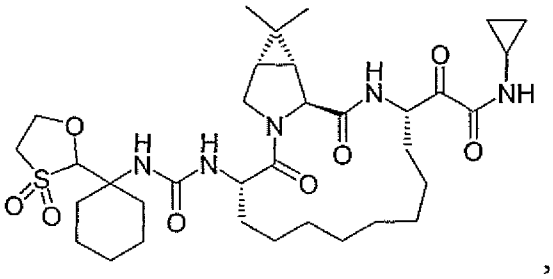
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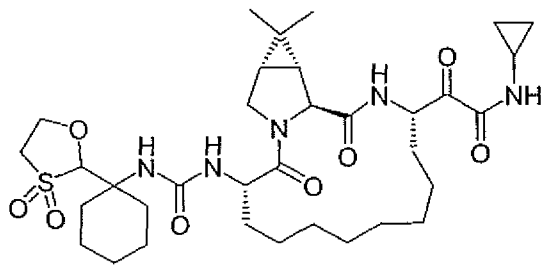
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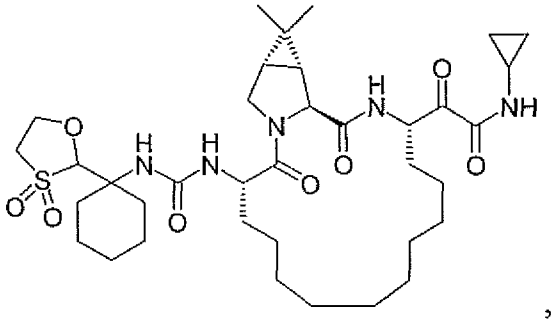
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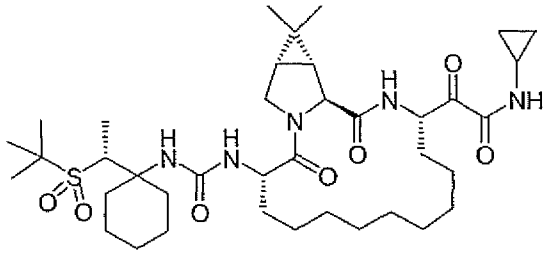
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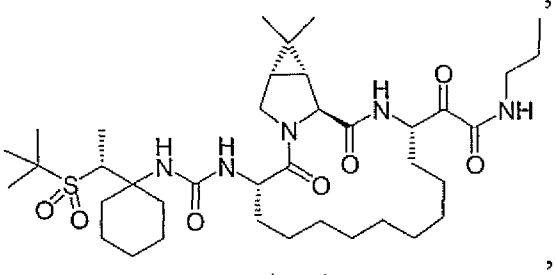
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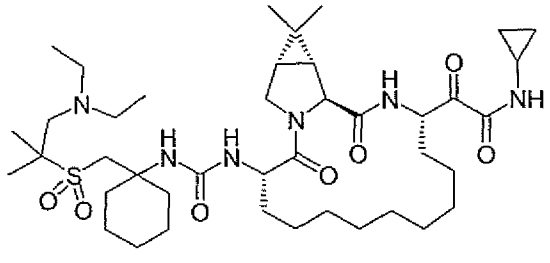
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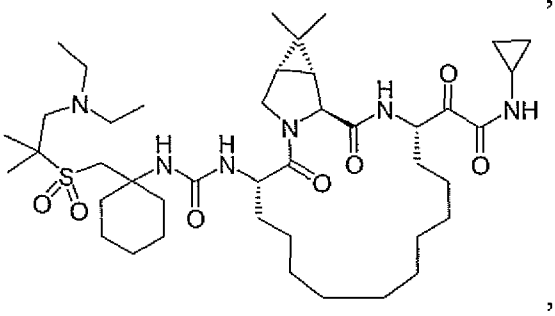
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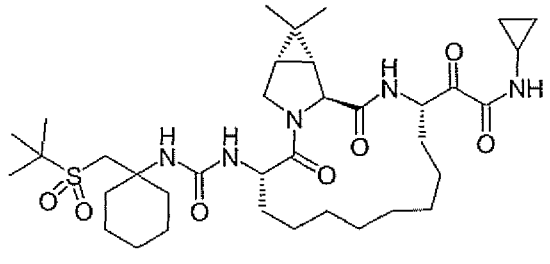
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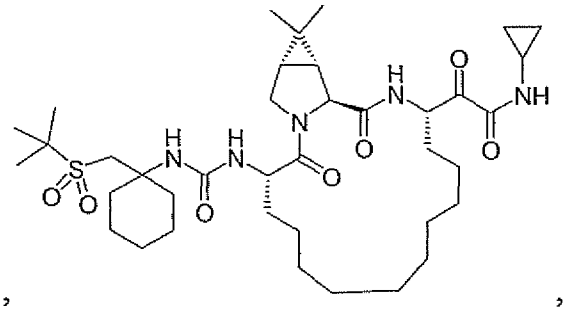
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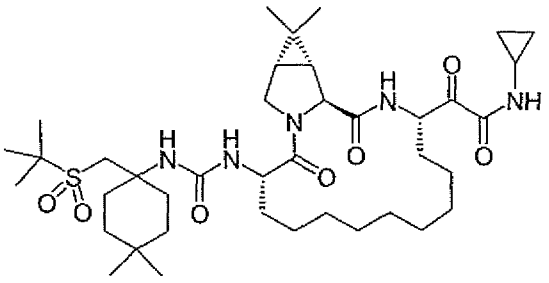
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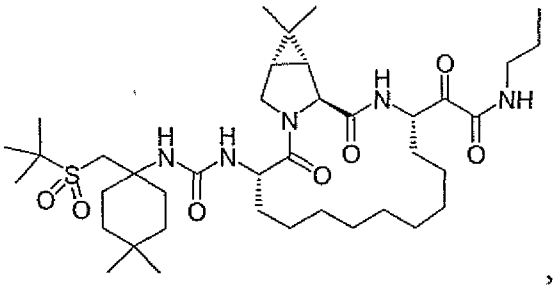
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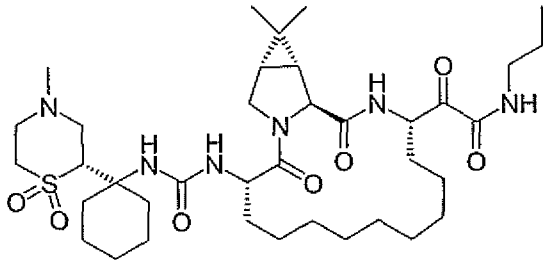
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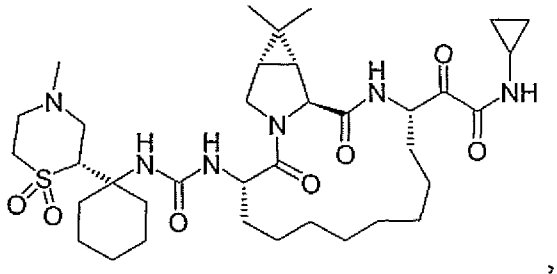
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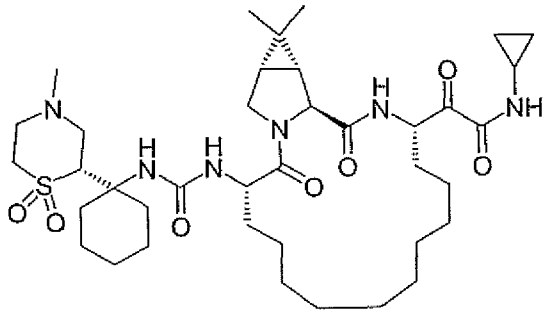
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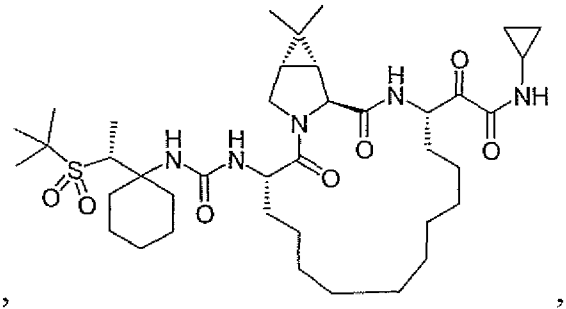
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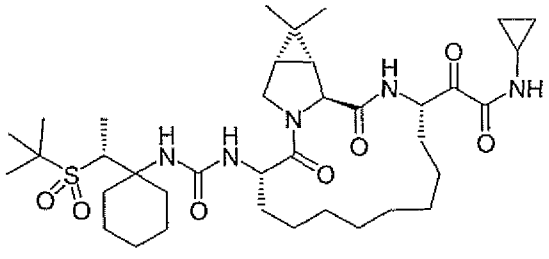
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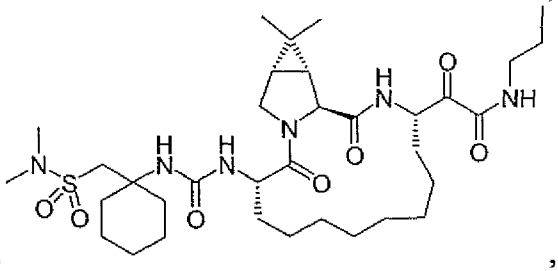
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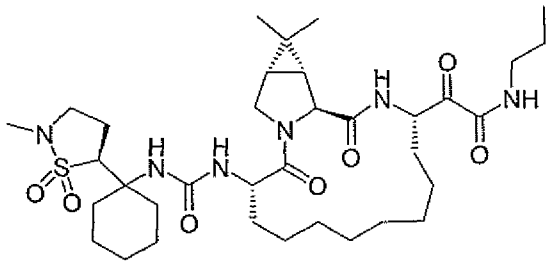
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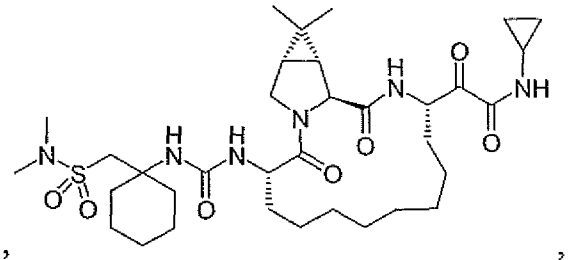
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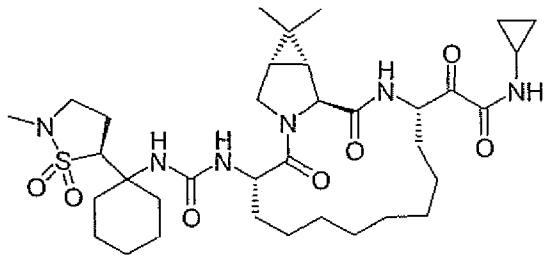
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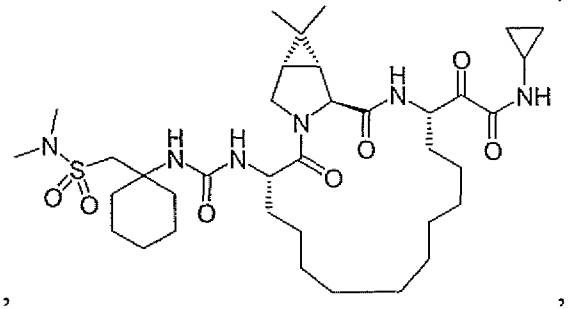
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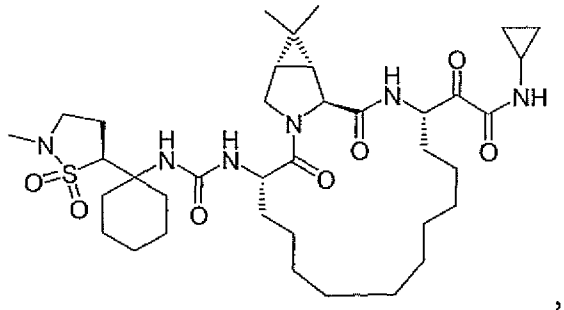
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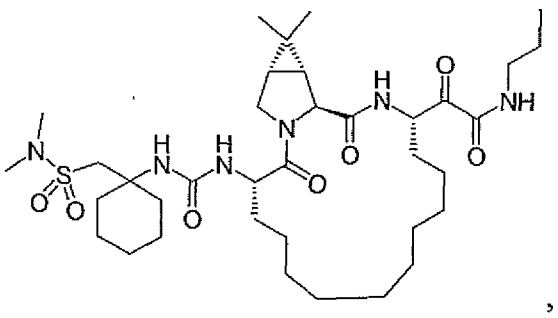
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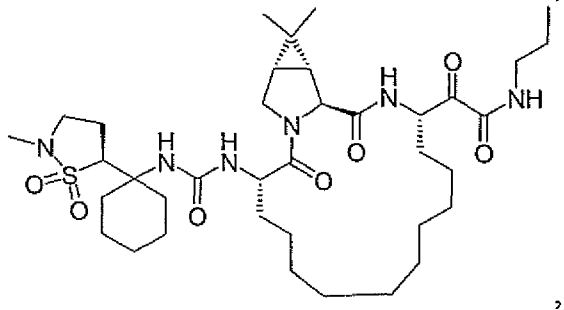
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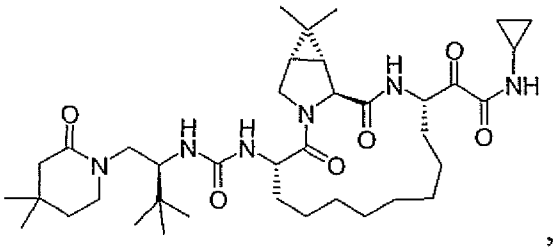
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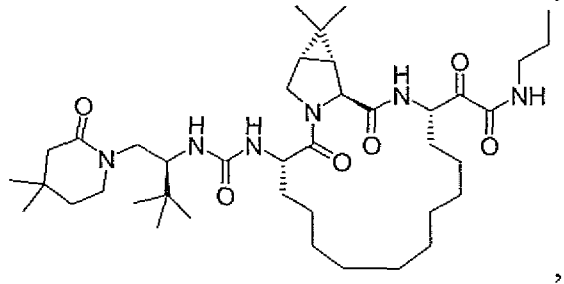
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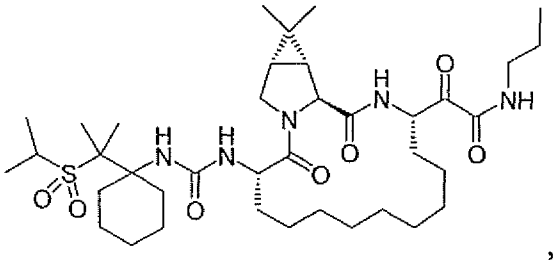
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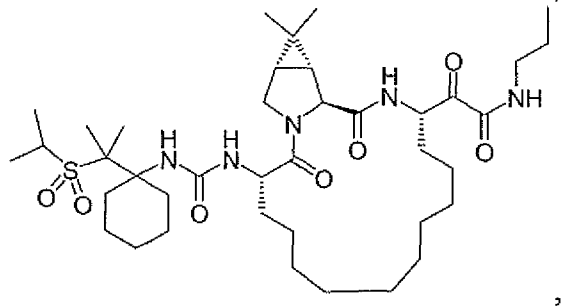
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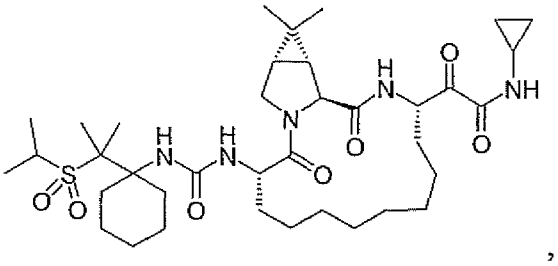
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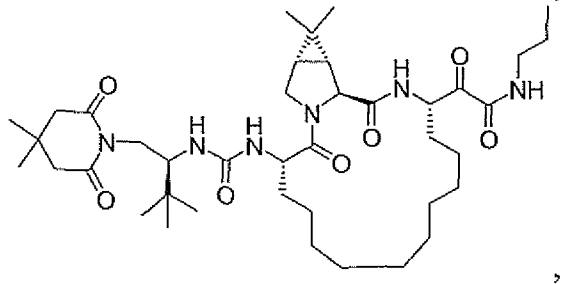
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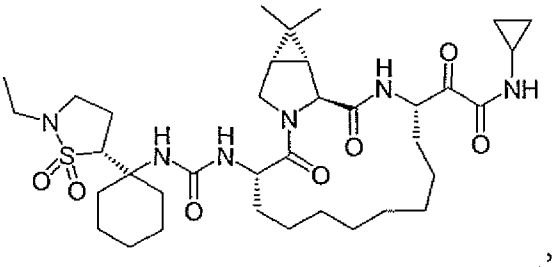
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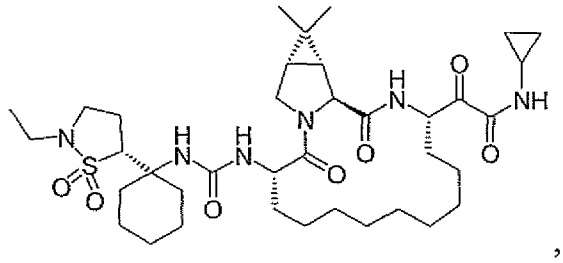
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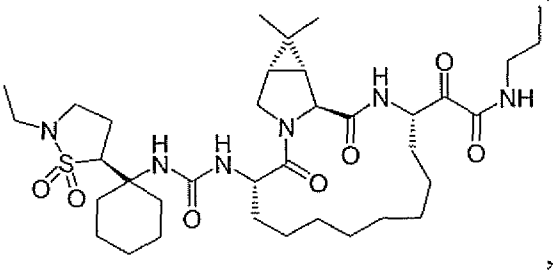
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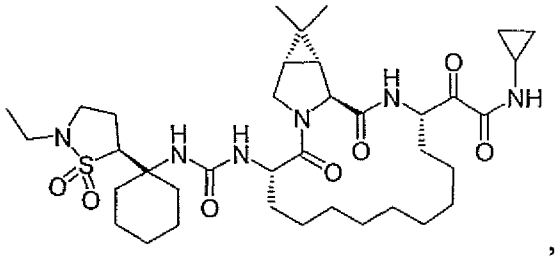
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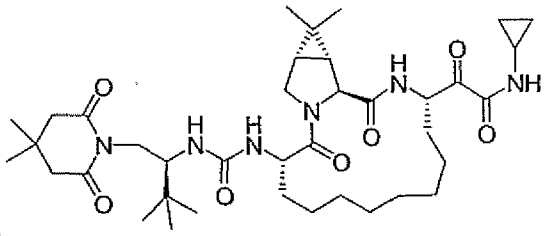
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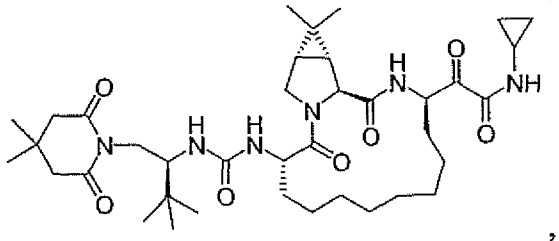
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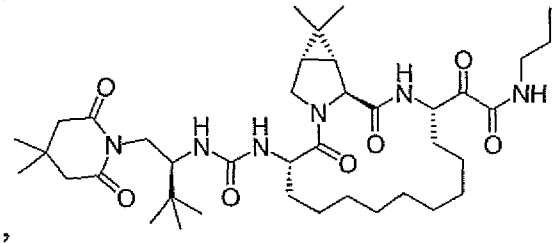
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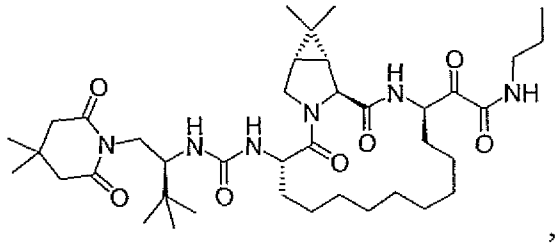
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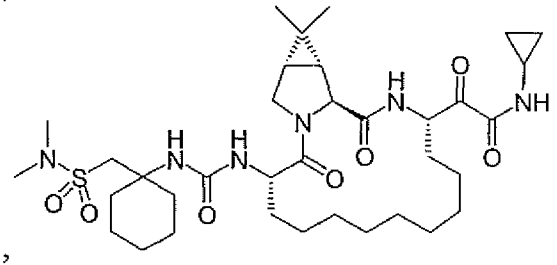
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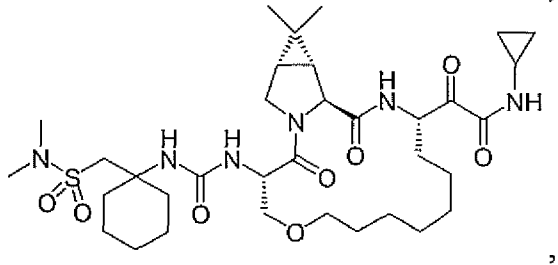
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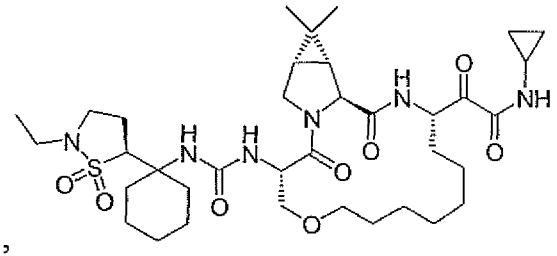
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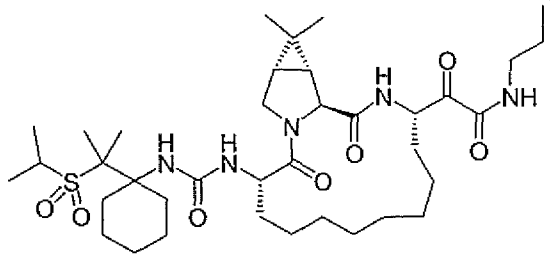
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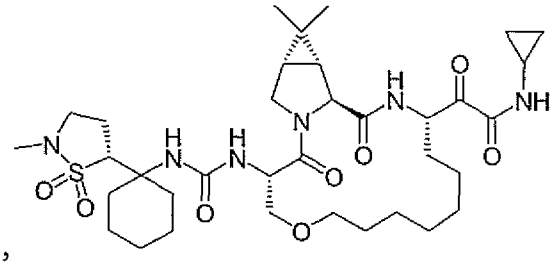
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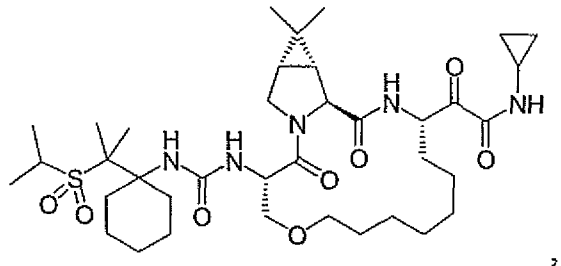
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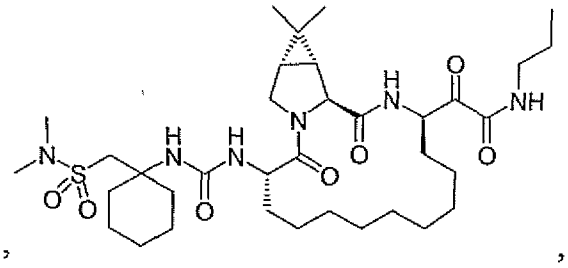
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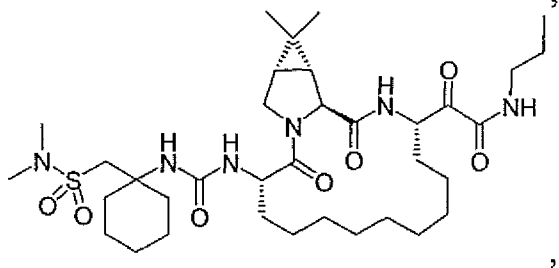
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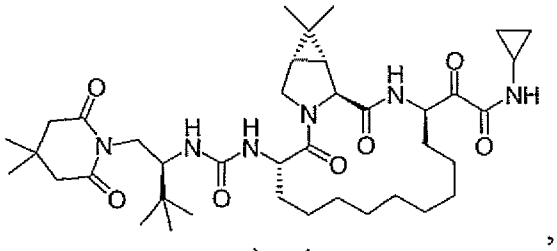
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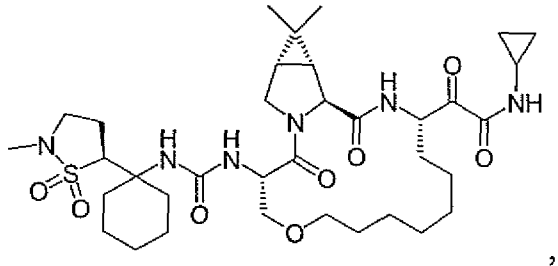
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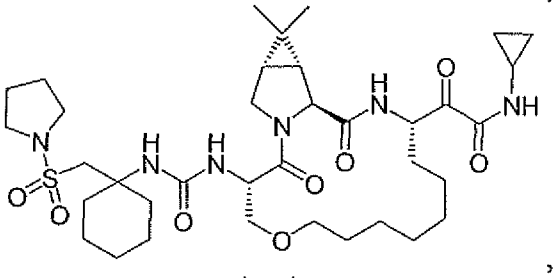
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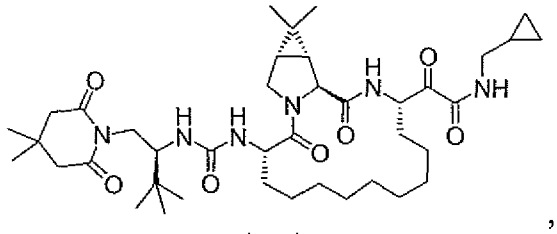
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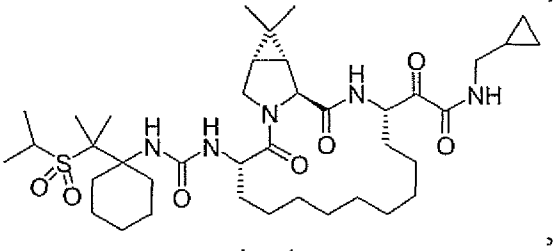
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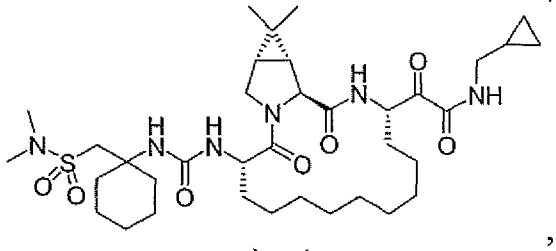
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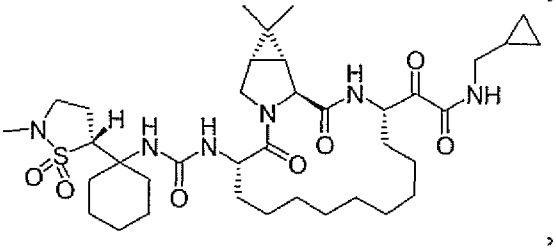
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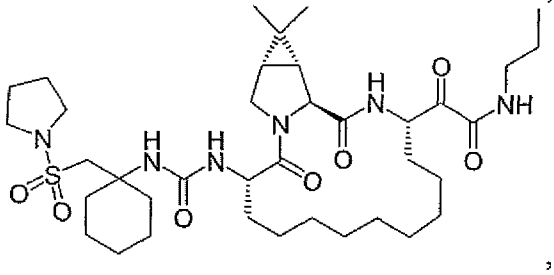
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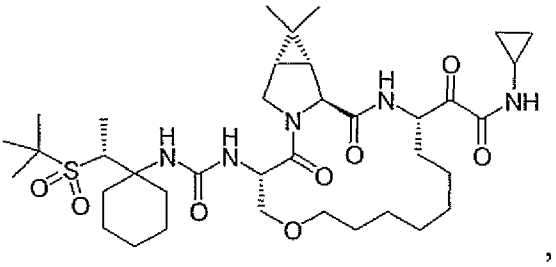
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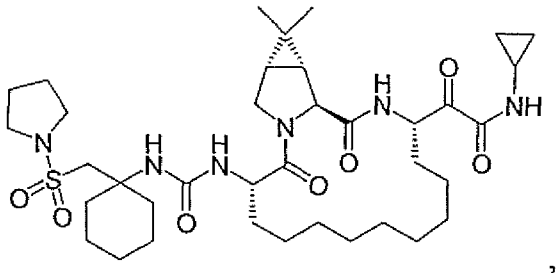
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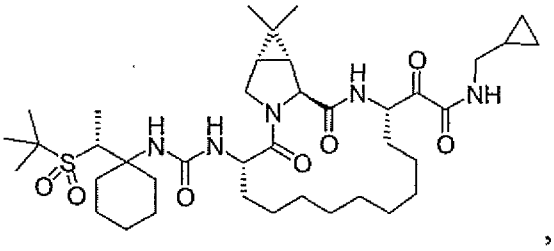
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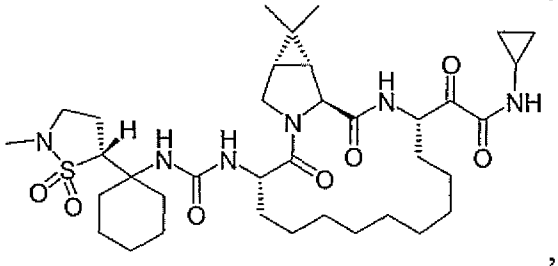
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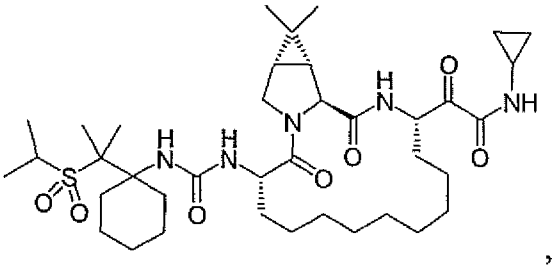
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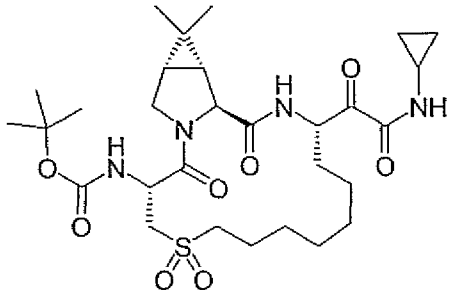
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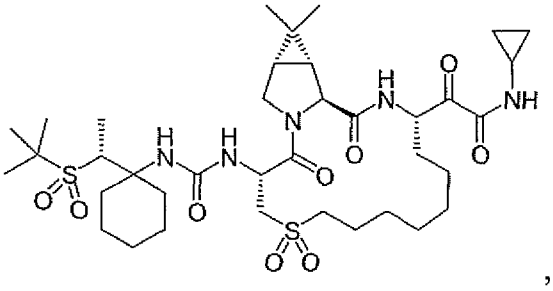
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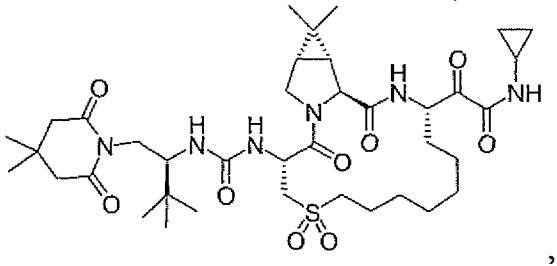
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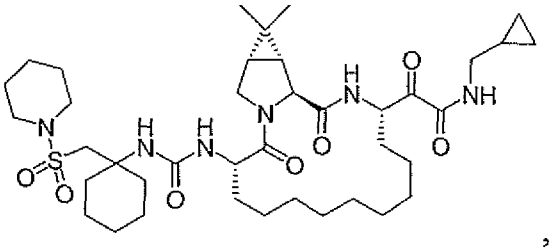
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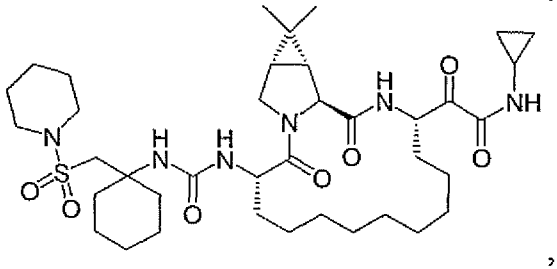
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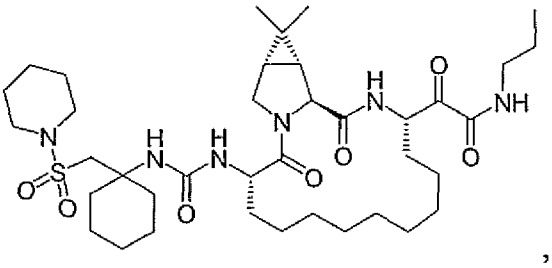
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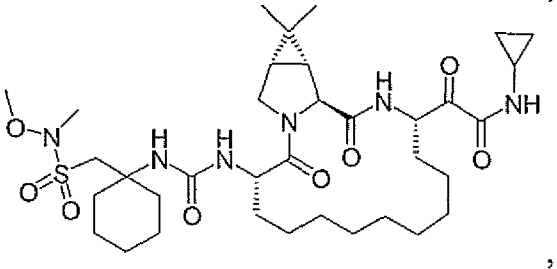
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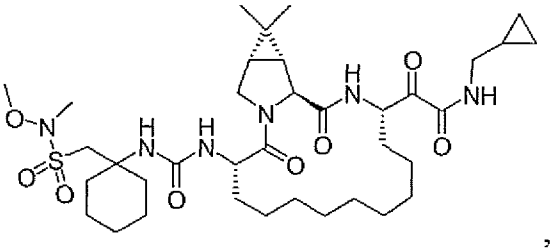
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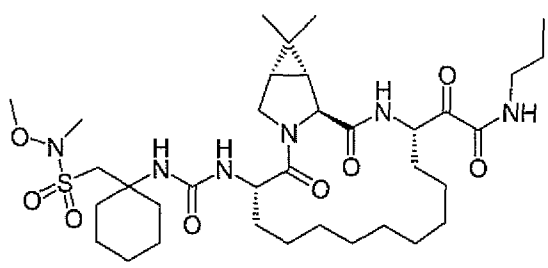
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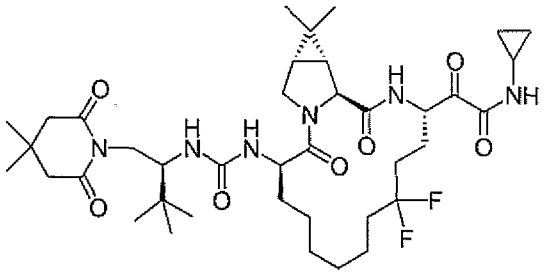
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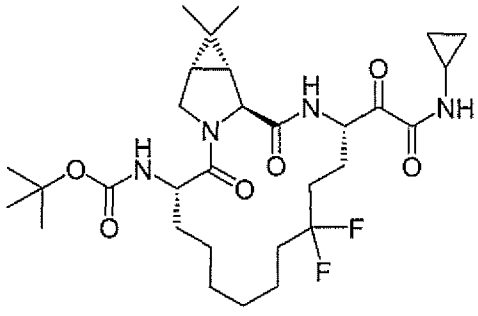
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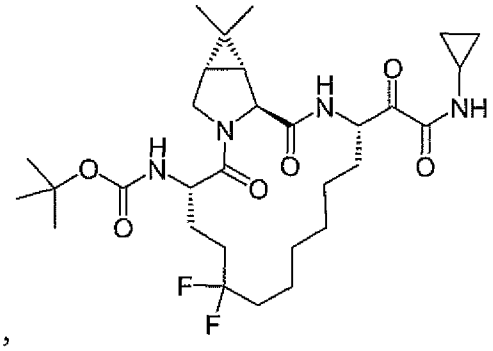
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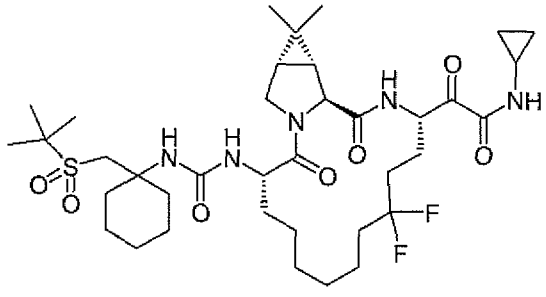
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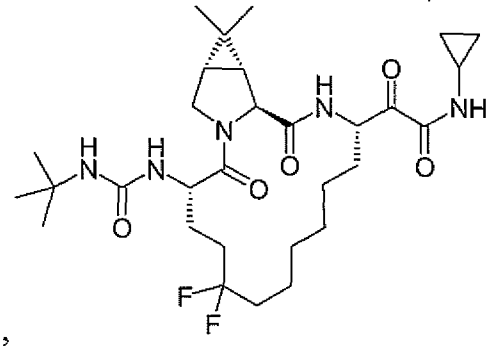
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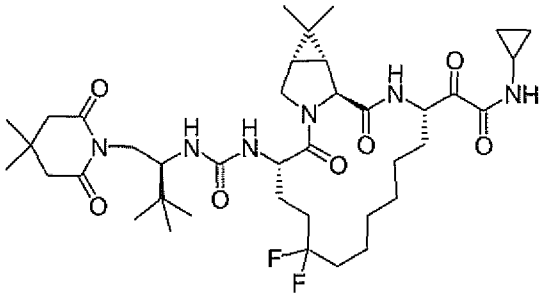
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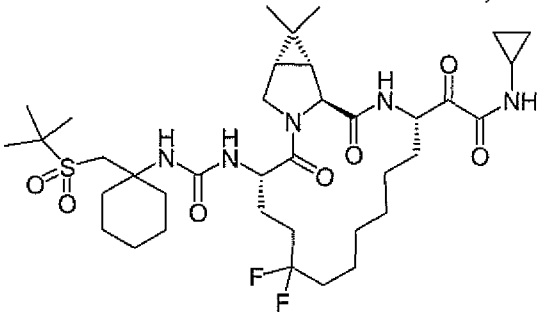
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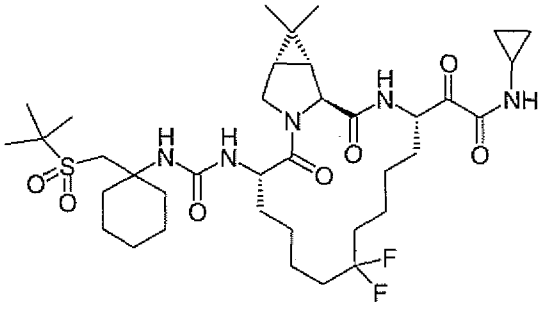
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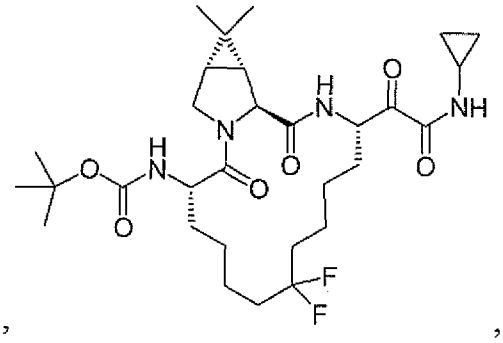
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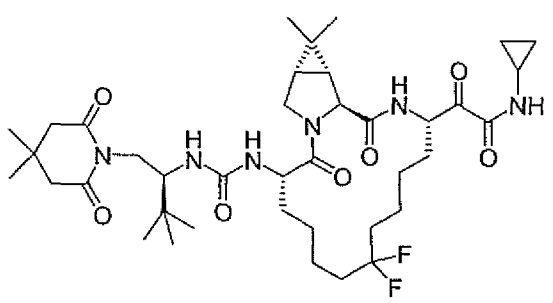
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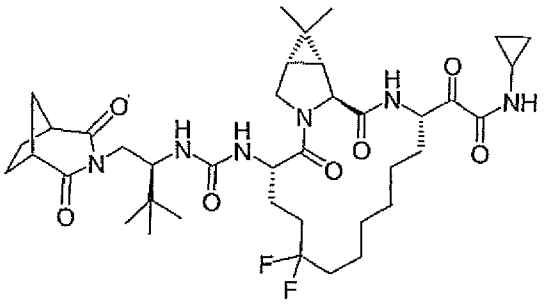
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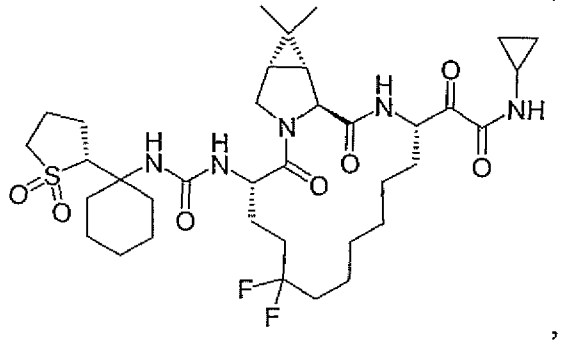
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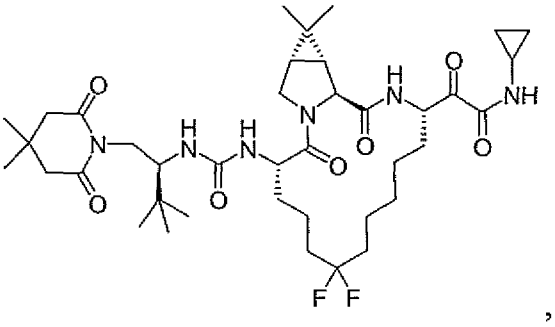
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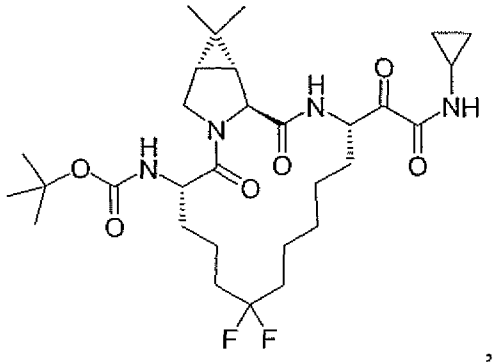
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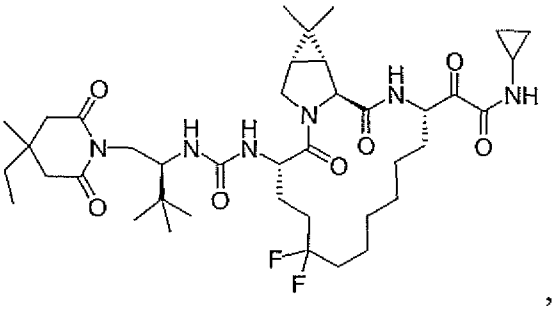
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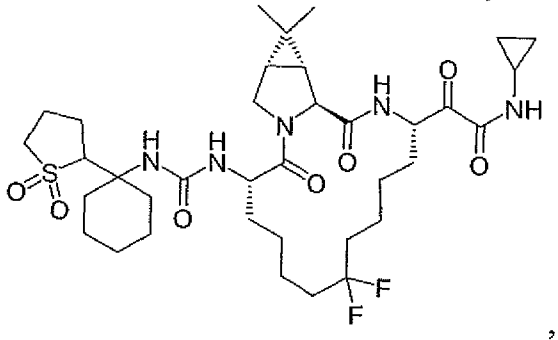
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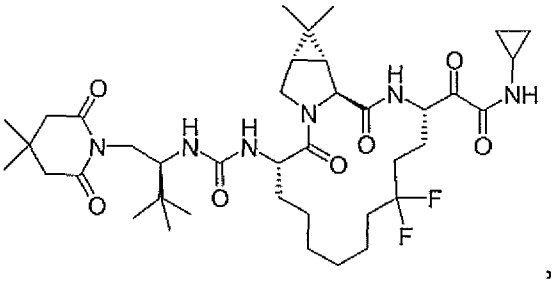
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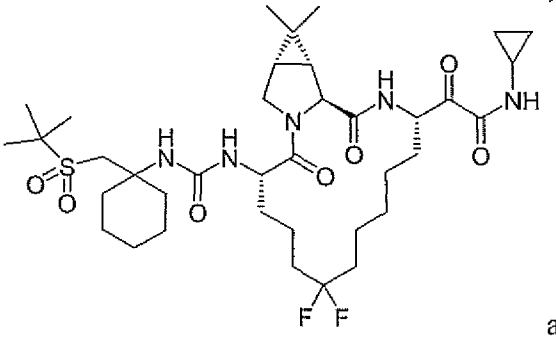
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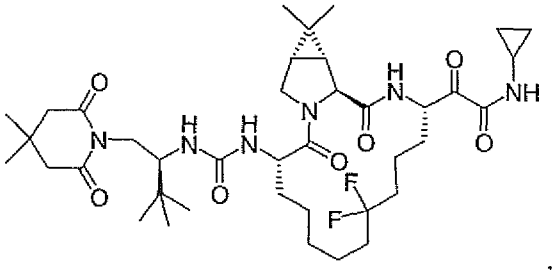
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A further feature of the invention is pharmaceutical compositions containing as active ingredient at least one compound of the present invention (or its salts, esters, solvate or isomers) together with a pharmaceutically acceptable carrier or excipient.

The invention also provides methods for preparing compounds of the present invention as well as methods for treating diseases such as, for example, HCV, AIDS (Acquired Immune Deficiency Syndrome), and related disorders. The methods for such treatment comprise administering to a patient suffering from one or more of the above diseases or one or more related diseases a therapeutically effective amount of at least one compound of the present invention or a pharmaceutical composition comprising at least one compound of the present invention.

Also disclosed is the use of at least one compound of The present invention for the manufacture of a medicament for treating HCV, AIDS, and related disorders.

Further disclosed is a method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more of the inventive compounds.

In still yet further embodiments there is provided methods of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more inventive compounds as well as methods of treating or preventing HCV, or ameliorating one or more symptoms of hepatitis C, comprising administering an effective amount of one or more of the inventive compounds. Such modulation, treatment, prevention or amelioration can also be done with the inventive pharmaceutical compositions or formulations. Without being limited to theory, it is believed that the HCV protease may be the NS3 or NS4a protease. The inventive compounds can inhibit such protease. They can also modulate the processing of hepatitis C virus (HCV) polypeptide.

Description of the Invention

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

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred

alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The alkyl group may be optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aliphatic" means and includes straight or branched chains of paraffinic, olefinic or acetylenic carbon atoms. The aliphatic group can be optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of H, halo, halogen, alkyl, aryl, cycloalkyl, cycloalkylamino, alkenyl, heterocyclic, alkynyl, cycloalkylaminocarbonyl, hydroxyl, thio, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, carboxyl, –C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, heteroalkyl, carbonyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, amino, amido, ester, carboxylic acid aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio,

heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, carbamate, urea, ketone, aldehyde, cyano, sulfonamide, sulfoxide, sulfone, sulfonyl urea, sulfonyl, hydrazide, hydroxamate, S(alkyl)Y_1Y_2N-alkyl-, Y_1Y_2N-alkyl-, Y_1Y_2NC(O)- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

"Heteroaliphatic" means an otherwise aliphatic group that contains at least one heteroatom (such as oxygen, nitrogen or sulfur). The term heteroaliphatic includes substituted heteroaliphatic.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroalkyl" means an alkyl as defined above, wherein one or more hydrogen atoms are substituted by a heteroatom selected from N, S, or O.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated

heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

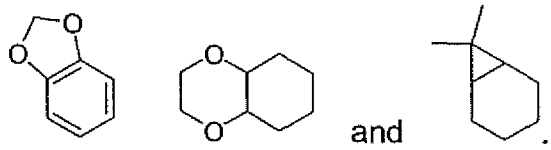
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent"

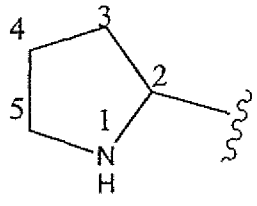
may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:



and

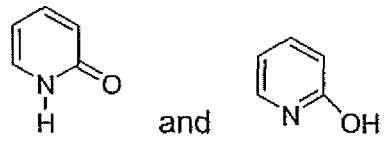
"Heterocyclyl" or "heterocycloalkyl" or "heterocyclic" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include

benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in the present invention, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the present invention or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the *A.C.S. Symposium Series*, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B.

Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the desired diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of the present invention can form salts which are also within the scope of this invention. Reference to a compound of the present invention herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of the present invention contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the the present invention may be formed, for example, by reacting a compound of the present invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates,

toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

One or more compounds of the invention may also exist as, or optionally converted to, a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by

standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

Compounds of the present invention, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of the present invention and of the salts, solvates and prodrugs of the compounds of the present invention, are intended to be included in the present invention.

In one embodiment, the present invention discloses compounds of the present invention as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

In another embodiment, R^1 is ketoamide, acid, ketoacid, ketoester, ketoaldehyde, diketone, boronic acid or trifluoroketone.

In still yet another aspect of the invention there is provided a pharmaceutical composition comprising as an active ingredient a compound of the present invention which is for use in treating disorders associated with HCV. The composition would generally include a pharmaceutically acceptable carrier. The composition may contain

one or more additional agents such as, for example, an antiviral agent, an interferon or pegylated interferon and the like. A preferred antiviral agent is ribavirin and a preferred interferon is α-interferon.

A method of treating disorders associated with the HCV protease comprises administering to a patient in need of such treatment therapeutically effective amounts of a compound of the present invention, or a pharmaceutical composition which comprises therapeutically effective amounts of a compound of the present invention. The administration may be oral or subcutaneous.

The compounds of the present invention may be used for the manufacture of a medicament to treat disorders associated with the HCV protease, for example, the method comprising bringing into intimate contact a compound of the present invention a pharmaceutically acceptable carrier. These and other aspects of the invention are described in further detail below.

In embodiments described above, the present invention discloses compounds of the present invention as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

In another embodiment, this invention provides pharmaceutical compositions comprising the inventive peptides as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders. The HCV inhibitory activity can also lead to use of the inventive compounds and/or compositions for treating diseases (e.g., AIDS, etc) that are associated or connected with HCV.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices.

For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like.

Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. HCV inhibitory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and pacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous

mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of the invention may also be administered orally, intravenously, intranasally or subcutaneously.

The compounds of the invention may also comprise preparations which are in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The

capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gel- refers to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powder for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrant - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate;

cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for

making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

Another embodiment of the invention discloses the use of the pharmaceutical compositions disclosed above for treatment of diseases such as, for example, hepatitis C and the like. The method comprises administering a therapeutically effective amount of the inventive pharmaceutical composition to a patient having such a disease or diseases and in need of such a treatment.

In yet another embodiment, the compounds of the invention may be used for the treatment of HCV in humans in monotherapy mode or in a combination therapy (e.g., dual combination, triple combination etc.) mode such as, for example, in combination with antiviral and/or immunomodulatory agents. Examples of such antiviral and/or immunomodulatory agents include Ribavirin (from Schering-Plough Corporation, Madison, New Jersey) and Levovirin™ (from ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (from Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (from ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (from Ribozyme Pharmaceuticals, Boulder, Colorado), VX 497™ (from Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (from SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), mycophenolate mofetil (from Hoffman-LaRoche, Nutley, New Jersey), interferon (such as, for example, interferon-alpha, PEG-interferon alpha conjugates) and the like. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, from Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (e.g., as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, from Boehringer Ingelheim, Ingelheim, Germany) or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, from Amgen, Thousand Oaks, California).

As stated earlier, the invention includes tautomers, rotamers, enantiomers and other stereoisomers of the inventive compounds also. Thus, as one skilled in the art

appreciates, some of the inventive compounds may exist in suitable isomeric forms. Such variations are contemplated to be within the scope of the invention.

Another embodiment of the invention discloses a method of making the compounds disclosed herein. The compounds may be prepared by several techniques known in the art. Representative illustrative procedures are outlined in the following reaction schemes. The invention disclosed herein is then further exemplified by preparative examples and example compounds which should not be construed to limit the scope of the invention which is defined in the appended claims. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

It is to be understood that while the following illustrative schemes describe the preparation of a few representative inventive compounds, suitable substitution of any of both the natural and unnatural amino acids will result in the formation of the desired compounds based on such substitution. Such variations are contemplated to be within the scope of the invention.

For the procedures described below, the following abbreviations are used:

AcOH: Acetic acid

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

Boc means t-butyloxy or tert-Butyloxycarbonyl

^{t}Bu, TBu or Bu^{t}: *tert*-Butyl

Cbz: Benzyloxycarbonyl

Bop: Benzotriazol-1-yl-oxy-tris(dimethylamino)hexafluorophosphate

Bn or Bzl: Benzyl

Bz: Benzoyl

Chg: Cyclohexylglycine

Cp: Cylcopentyldienyl

DCM means diclhloromethane;

DCC: 1,3-Dicyclohexylcarbodiimide

DEAD: Diethylazodicarboxylate

DMAP: 4-N,N-Dimethylaminopyridine

DMF means *N,N*-dimethylformamide;

DMSO means dimethyl sulfoxide;

EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

Et: Ethyl;

EtOAc means ethyl acetate;

Et_2O: Diethyl ether;

HATU means O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium;

HOOBt: 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one;

HOBt: N-Hydroxybenzotriazole;

iBoc: isobutoxycarbonyl;

iPr: isopropyl;

KHMDS means Potassium hexamethyl disilylamide;

LiHMDS means hexamethyldisilazide;

Me: Methyl;

MS means mass spectrum;

nBuLi means n-butyl lithium;

NMM means N-methyl morpholine;

NMR means nuclear magnetic resonance;

Phg: Phenylglycine;

Ph: Phenyl;

Pd/C means palladium on charcoal catalyst;

PyBrOP: Bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate;

TBuNCO means t-butyl isocyanate;

TEMPO: 2,2,6,6-Tetramethyl-1-piperidinyloxy;

THF means tetrahydrofuran;

THP means tetrahydrofuran;

TMSI means trimethyl silyl iodide;

T_3N means triethylamine;

Ts: p-toluenesulfonyl.

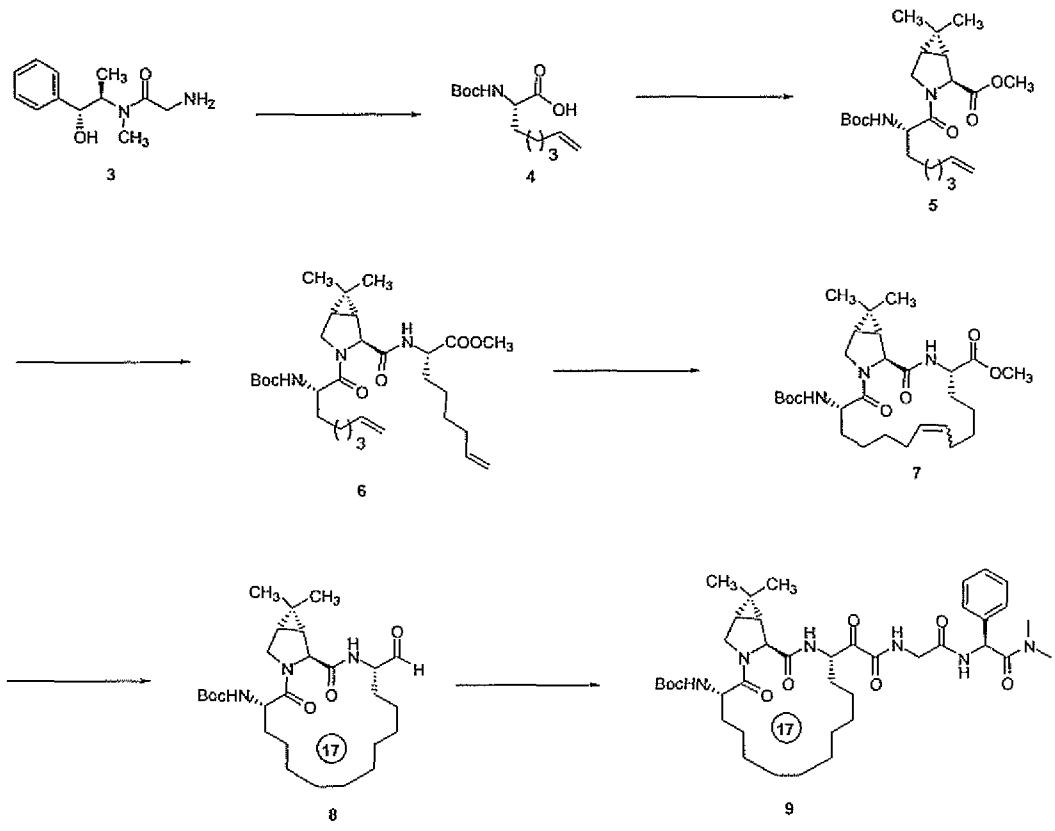
Several of the intermediates and/or preparative examples used in the following synthetic procedures have been disclosed in WO 01/77113; WO 01/081325; WO 02/08198; WO 02/08256; WO 02/08187; WO 02/08244; WO 02/48172; WO 02/08251; and pending U.S. patent application, Serial No. 10/052,386, filed January 18, 2002. The disclosures of those applications are incorporated herein by reference thereto.

The compounds of the present invention can be synthesized using the schemes and procedures for preparative examples disclosed in U.S. patent

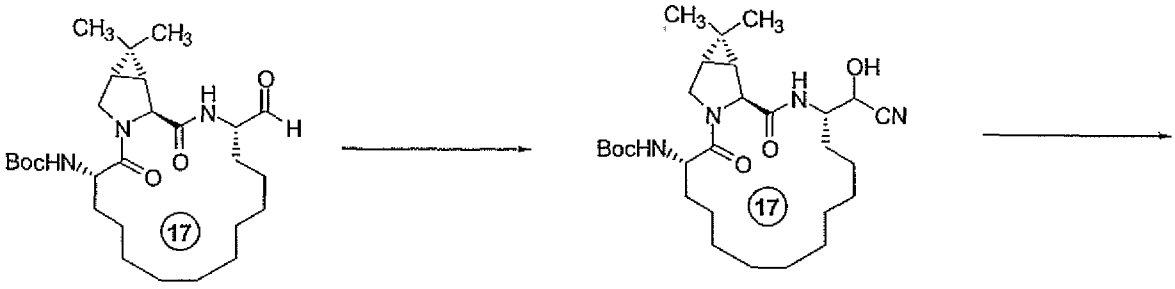
application, Serial No. 10/948367, filed February 24, 2005 (which published as 2005/0119168 on June 2, 2005), the entire dislosure of which, is incorporated herein, by reference.

General Preparative Schemes and Procedures for Preparative Examples

SCHEME 1



SCHEME 2



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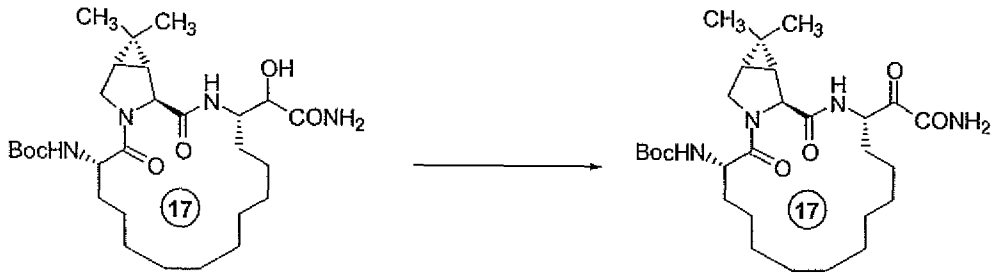

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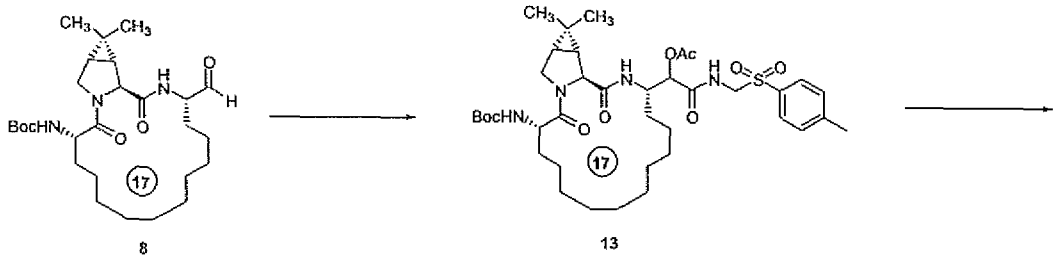
SCHEME 3



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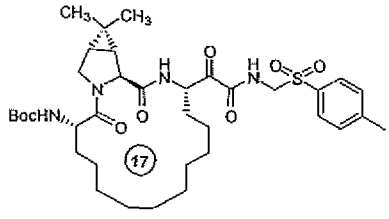

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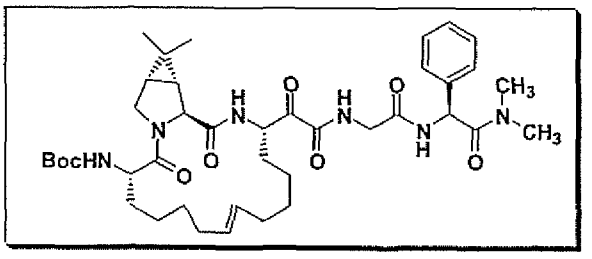
Procedures For Preparative Examples

Preparative Example 1



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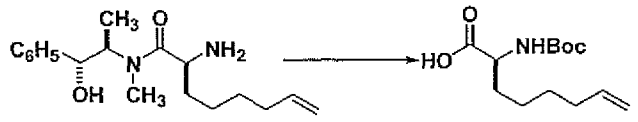
Step A

1a **1b**

The synthesis of **1b** can be accomplished using the procedure of (1) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W.; *J. Am. Chem. Soc* **1997,** *119* , 656; (2) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W.; *J. Org. Chem.*, **1999**, 64, 3322.; or (3) Myers, A. G.; Gleason, J. L.; *Org. Synth.* **1998**, *76*, 57.

A solution of amine **1a** (24 g, 120 mmol) in THF (300 mL) was treated with anhydrous LiCl (16.80 g, 400 mmol) over 0.5 h and stirred till the reaction mixture turns homogeneous. The reaction mixture was cooled to 0° C and treated with a THF solution of LiHMDS (66.80 g , 400 mmol in 300 ml of THF) over 20 min. The reaction mixture was stirred at 0° C for 0.5 h and treated with 6-bromohexene (19.44 g, 120 mmol) and stirred at rt. for 24 h. The reaction mixture was dissolved in aq. 1 M HCl and concentrated in *vacuo* to remove THF. The mostly aq. layer was further diluted with 3M aq HCl (300 mL) and extracted with ether (2x200 mL). The aqueous layer was basified to pH 14 using aq. NaOH (50%) and extracted with CH_2Cl_2 (3x 300 mL). The combined organic layers were dried with $MgSO_4$ filtered concentrated in *vacuo* to yield crude **1b** (15.1 g) that was used in next step without further purification.

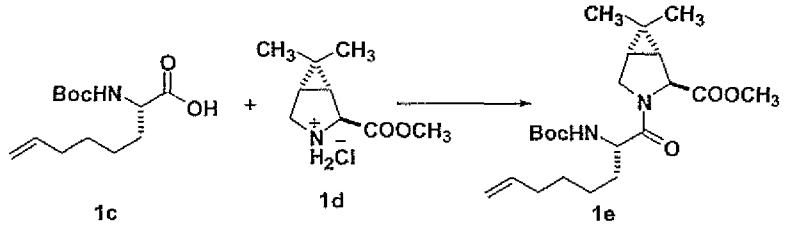
Step B



1b **1c**

A solution of **1b** (12.5 g, 41.2 mmol) was dissolved in aq. NaOH (1 M, 88.0 mL, 88 mmol) and heated at reflux for 3 h. The reaction mixture was cooled to rt. and extracted with CH2Cl2 (3x100 mL). The aq. layer was treated with 100 mL of dioxane followed by $NaHCO_3$ (8.00 g, 95.2 mmol) and di-tertbutyl dicarbonate (8.95 g, 41 mmol) and stirred at rt. for 5 h. The reaction mixture was extracted with ether (2x250 mL) and the aqueous layer was acidified to pH~2 with aq. HCl and extracted with CH_2Cl_2 (2x200 mL). The combined organic layers were dried with MgSO4, filtered concentrated in *vacuo* to yield acid **1c** (10.8 g) as a colorless oil.

Step C



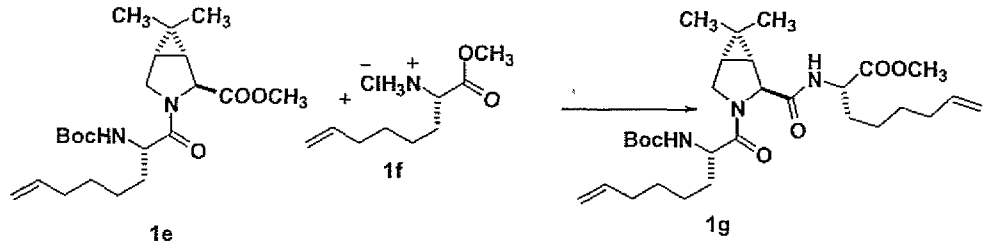
1c **1d** **1e**

A solution of acid **1c** (5g, 19.44 mmol) and amine **1d** (3.98 g, 19.44 mmol) in CH_2Cl_2 (30 mL), DMF (30 mL) at 0° C was treated with HATU (8.87 g, 23.31 mmol) and NMM (4.91 g, 5.33 mL) and stirred overnight at 0° C. The reaction mixture was concentrated in *vacuo* and diluted with 650 mL of CH_2Cl_2. The aqueous layer was washed with aq. HCl (1M, 2x300 mL), aq. $NaHCO_3$ (1M, 2x300 mL). The organic layers were dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 5:1) to yield **1e** as a colorless oil (5.5 g).

^{1}H NMR: (CD_3OD, 300 MHz) δ5.87-5.76 (m, 1 H), 4.97-4.92 (dd, 2 H), 4.26 (bt, 1 H, J=7.8 Hz), 3.98 (d, 1 H, J= 10.2 Hz), 3.61 (dd, 2 H, J=5.1, 5.1 Hz), 3.73 (s, 3 H), 2.14-2.07 (m, 2 H), 1.74-1.42 (m, 9 H), 1.41 (s, 9 H), 1.12 (s, 3 H), 0.92 (s, 3 H).

^{13}C NMR: (CD_3OD, 75 MHz), d 173.8, 173.2, 158.0, 139.8, 115.0, 80.4, 60.91, 53.42, 52.80, 34.7, 33.5, 32.3, 31.4, 29.8, 28.7, 26.4, 26.1, 20.6, 12.9.

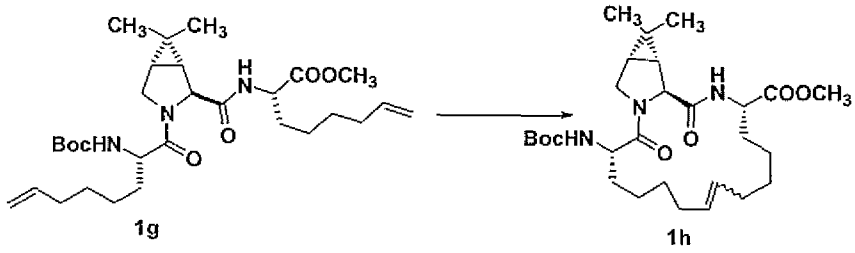
Step D



A solution of ester **1e** (4g, 9.79 mmol) in THF (20 mL), H_2O (20 mL) and MeOH (10 mL) was treated with $LiOH{\cdot}H_2O$ (575 mg, 14 mmol) and stirred at rt. for 4h. The reaction mixture was concentrated in *vacuo* to remove THF and MeOH. The mostly aqueous layer was acidified with aq. HCl and extracted into CH_2Cl_2 (3x100 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated in *vacuo* and used as it is.

A solution of acid obtained from hydrolysis of **1e**, amine segment **1f** (2.02 g, 9.79 mmol) in DMF (40 mL), CH_2Cl_2 (40 mL) at 0 °C was treated with HATU (4.46 g, 11.84 mmol) and NMM (3.5 g, 35 mmol) and stirred at 0° C for 24 h. The reaction mixture was concentrated in *vacuo* and diluted with aq. HCl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3x75 mL). The combined organic layers were washed with aq saturated $NaHCO_3$ (3x100 mL), brine dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by silica gel chromatography (EtOAc/Hex 1:3) to yield **1g** (4.5 g) as a colorless foam.

Step E

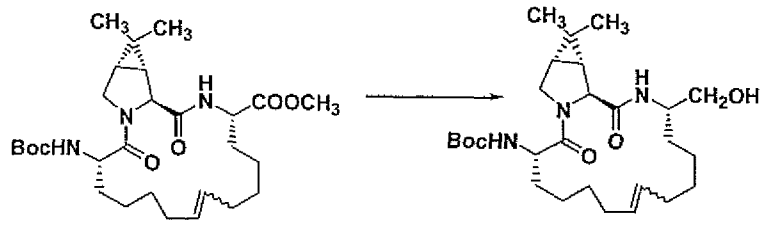


A solution of diene **1g** (1.1 g, 2.0 mmol) in dry CH_2Cl_2 (20 mL) was treated with Grubbs catalyst $[(Cy)_3RuCl_2{=}CHC_6H_5$, 83.8 mg, 0.1 mmol) and stirred at rt. for 24 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:3) to yield **1h** (501 mg) as a colorless solid and mixture of *E/Z* isomers.

^{1}H NMR ($CDCl_3$, 300 MHz) δ, 7.38 (d, 1 H, J=8.1 Hz), 5.30-5.18 (m, 2 H), 4.55 (dt, 1 H, J= 2.4, 9.6 Hz), 3.92 (bs, 1 H), 3.77 (s, 3 H), 3.79-3.77 (bm, 1H), 2.06-2.1 (bm, 3 H). 1.95-1.81 (m, 2 H), 1.79-1.77 (m, 13 H), 1.31 (s, 9 H), 1.05 (s, 3 H), 0.85 (s, 3H).

MS (ESI), m/z, relative intensity 542 [(M+Na)$^+$ 45], 464 (20), 448 (25) 420 (100) .

Step F

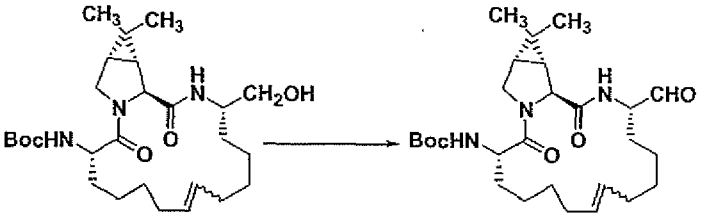


A solution of ester **1h** (100 mg, 0.19 mmol) in dry THF (1 mL) was treated with $LiBH_4$ (2M soln. in THF, 0.2 mL) and stirred at rt. for 16 h. The reaction mixture was quenched with aqueous HCl (1M, 30 mL) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with aq. $NaHCO_3$ (100 ml) brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **1i** (70 mg) as an amorphous solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (d, 1 H, J=8.1 Hz), 5.32-5.21 (m, 2 H), 4.43-4.37 (m, 2 H) 4.01-3.93 (m, 1 H), 3.77 (dd, 1 H, J=5.7, 4.8 Hz), 3.65 (dd, 1 H, J= 3.9, 6.6 Hz), 3.53 (dd, 1 H, J= 6.0, 10.8 Hz), 2.11-1.77 (m, 6 H), 1.55-1.31 (m, 12 H), 1.45 (s, 9 H), 1.05 (s, 3 H), 0.87 (s, 3 H).

MS (ESI), m/z, relative intensity 530 [(M+K)$^+$, 10], 514 [(M+Na)$^+$, 70], 492 [(M+1)$^+$, 20], 392 (100).

Step H



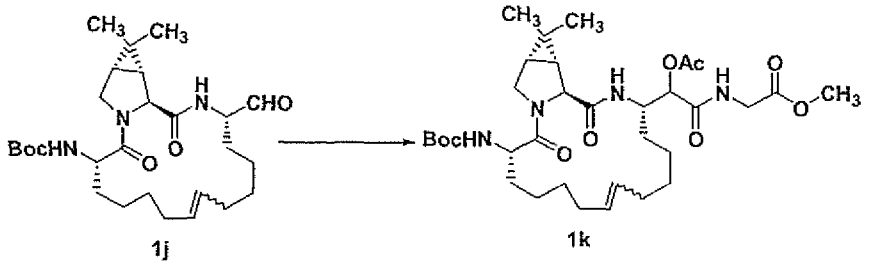
1i 1j

A solution of alcohol **1i** (70 mg, 0.15 mmol), in CH_2Cl_2 (3 mL) was treated with Dess Martin reagent (85 mg, 0.2 mmol) and stirred at rt. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ solution (10%, 10 mL) and saturated $NaHCO_3$ solution (10 mL) and stirred at rt. for 0.5 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL). The organic layer was dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 4:1) to yield **1j** (50 mg) as a colorless fluffy solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ9.54 (s, 1 H), 7.43 (d, 1 H, J = 7.8 Hz), 5.30-5.19 (m, 2 H), 4.55-4.40 (m, 2 H), 3.93 (d, 1 H, J=10.2 Hz), 3.77 (dd, 1 H, J=5.4, 5.1 Hz), 2.04-1.78 (m, 4 H), 1.55-1.27 (m, 14), 1.31 (s, 9 H), 1.02 (s, 3 H), 0.95 (s, 3 H).

MS (ESI), m/z, relative intensity 512 [$(M+Na)^+$, 80], 490 [$(M+1)^+$, 10], 434 (20), 390 (100).

Step I

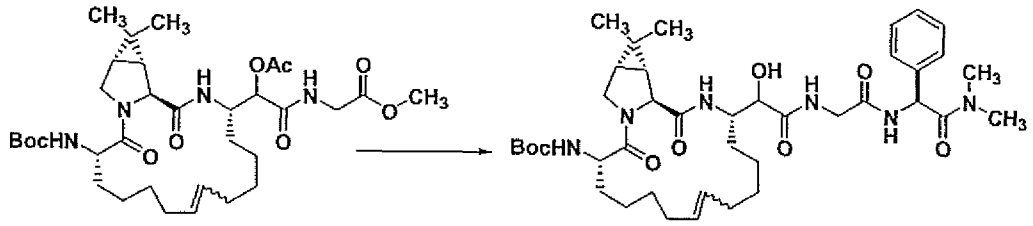


1j 1k

A solution of aldehyde **1j** (50 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) was treated with CH_3COOH (19 mg, 0.31 mmol) and methylisocyanoacetate (31 mg, 0.31 mmol). The reaction mixture was stirred at rt. for 48 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **1k** (50 mg) as a mixture of diastereomers.

MS (ESI), m/z, relative intensity 671 [$(M+Na)^+$, 45], 649 [$(M+1)^+$, 30], 549 (100).

Step J

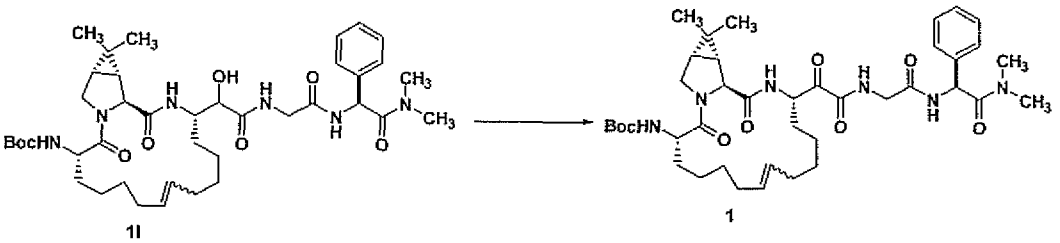


1k 1l

A solution of methyl ester **1k** (50 mg, 0.078 mmol) in THF (2 mL), H_2O (2 mL) and CH_3OH (2 mL) was treated with $LiOH{\cdot}H_2O$ (20 mg, 0.5 mmol) and stirred at rt. for 2 h. After the completion of the reaction it was acidified with aq. HCl (2 mL) and concentrated in *vacuo*. The residue was dried in *vacuo* and used as it with out further purification.

The acid was dissolved in CH_2Cl_2 (2 mL), DMF (2 mL) and treated with H-Phg-$N(CH)_2$ ·HCl (26 mg, 0.12 mmol), NMM (32 mg, 0.32 mmol) HATU (45 mg, 0.12 mmol) and stirred at 0 °C for 24 h. The yellow colored solution was concentrated in *vacuo* and diluted with CH_2Cl_2 (70 mL). The organic layers were washed with saturated aq. $NaHCO_3$, aq. HCl and brine. The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and used as it is in next step (47 mg).

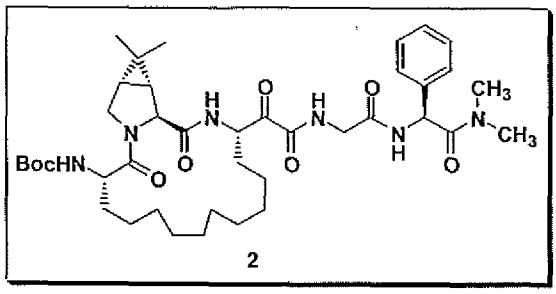
Step K



1l 1

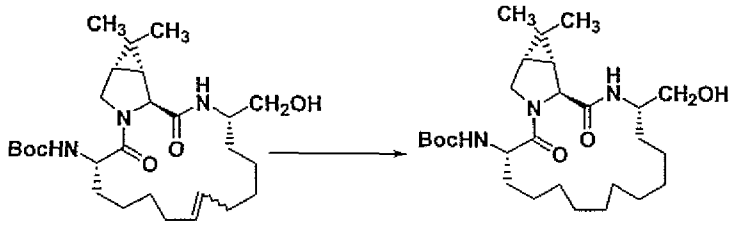
A solution of alcohol **1l** (50 mg, 0.066 mmol) in CH_2Cl_2 (2 mL) was treated with Dess-Martin reagent (60 mg, 0.14 mmol) and stirred at rt. for 2 h. The reaction was diluted with aq Na2S2O3 solution and aq. $NaHCO_3$ solution (20 mL each) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with satd. $NaHCO_3$, brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (acetone/hexanes 2:3) to yield **1** (22 mg) as a colorless solid. **MS** (ESI), m/z, relative intensity 773 $[(M+Na)^+$, 80], 751 $[(M+1)^+$, 60], 651 (100).

Preparative Example 2



2

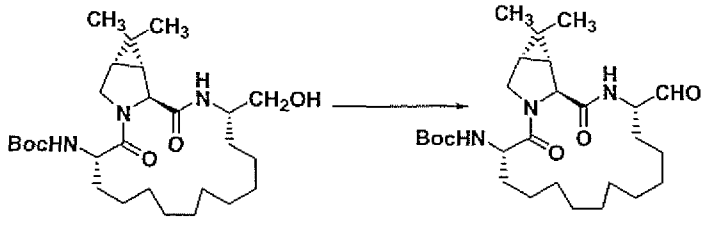
Step A



1i 2a

A solution of alcohol **1i** (1.1g, 2.25 mmol) in methanol (30 mL) was treated with Pd/C (10% w/w, 100 mg) and hydrogenated at 60 psi for 3 h. The reaction mixture was filtered through a plug of celite, concentrated in *vacuo* to yield **2a** which was used in the next step without further purification.

Step B

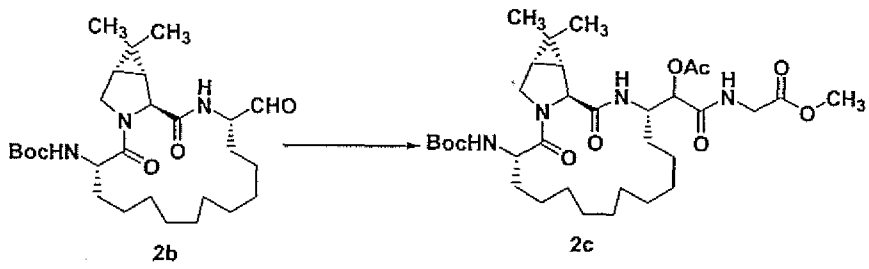


2a 2b

Crude **2a** from step A was oxidized using Dess-Martin reagent (1.14 g, 2.68 mmol) following the procedure similar to step H (preparative example 1) to yield **2b** (760 mg) as a colorless foam.

MS (ESI), m/z, relative intensity 1005 [$(2M+Na)^+$, 10], 530 [$(M+K)^+$, 20], 514 [$(M+Na)^+$, 90], 492 [$(M+1)^+$, 30], 436 (40), 392 (100).

Step C



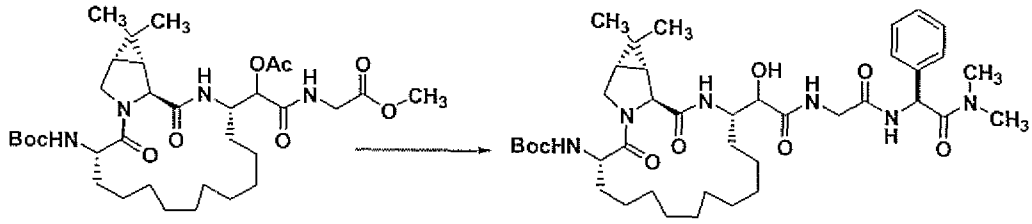
2b 2c

Compound **2b** (200 mg, 0.41 mmol) from step B was converted to **2c** (250 mg) using CH_3COOH (60 mg) and methylisocyanoacetate (99 mg, 1 mmol) following the procedure similar to step I (preparative example 1) as a mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) 8.05, 7.93 (d, 1 H), 6.60 (d, 1 H, J=7.8 Hz), 5.20, 5.09 (d, 1 H), 4.58-4.49 (bt, 1 H), 4.34 (s, 1H), 4.34-4.31 (bt, 1H), 4.11-4.06 (m, 1H), 3.95-3.86 (m, 3 H), 3.73, 3.71 (s, 3 H), 2.21, 2.19 (s, 3H), 1.99-1.06 (m, 31 H), 0.99-0.94 (6 H).

MS (ESI), m/z, relative intensity 689 [$(M+K)^+$, 5], 673 [$(M+Na)^+$, 30], 651 [$(M+1)^+$, 35], 551 (100).

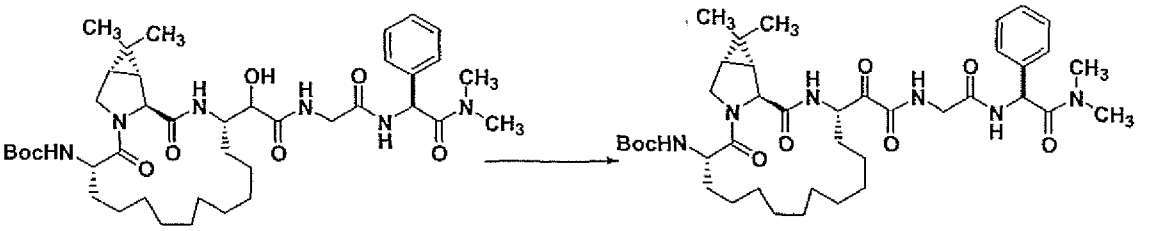
Step D



2c 2d

Methyl ester **2c** (250 mg, 0.39 mmol) was hydrolyzed to acid using $LiOH \cdot H_2O$ (42 mg, 1 mmol) and coupled to H-Phg-$N(CH)_2$ ·HCl (90 mg, 0.42 mmol) using NMM (126 mg, 1.26 mmol) and HATU (160 mg, 0.42 mmol) as outlined in preparative example 1, step J to yield crude **2d** directly used for oxidation.

Step E

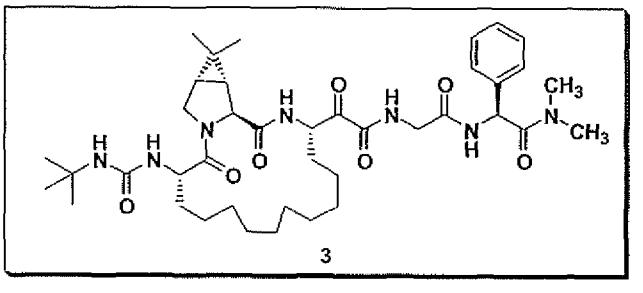


2d 2

Hydroxy amide **2d** was oxidized using Dess-Martin reagent (200 mg, 0.48 mmol) which was purified by chromatography (SiO_2, acetone/CH_2Cl_2 1:4) to yield **2** (110 mg) as colorless solid.

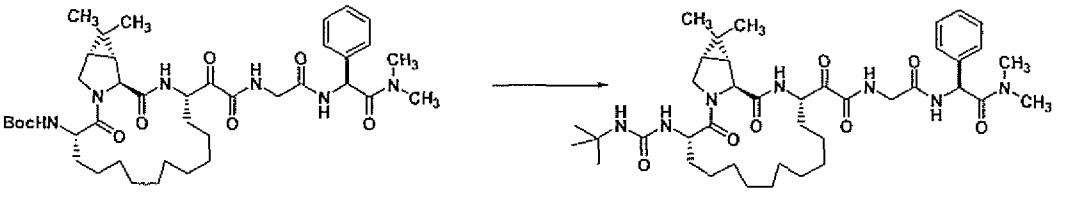
MS (ESI), m/z, relative intensity 775 [$(M+Na)^+$, 60], 753 [$(M+1)^+$, 50], 653 (100), 277 (80), 232 (60), 162 (30), 162 (40), 148 (80), 217 (95).

Preparative Example 3



3

Step A

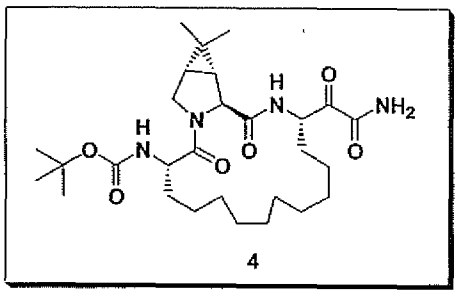


2 3

A solution of **2** (40 mg, 0.0053 mmol) in HCOOH (2 mL) was stirred at rt. for 2 h and concentrated in *vacuo*. The residue was repeatedly dissolved in toluene and dried in *vacuo* to remove residual formic acid. The residue was dissolved in CH_2Cl_2/DMF (1 mL each) and treated with ^{t}BuNCO (10 µL) and NMM (15 µL) at 0° C and left in the refrigerator for 12 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **3** (21 mg) as a colorless solid.

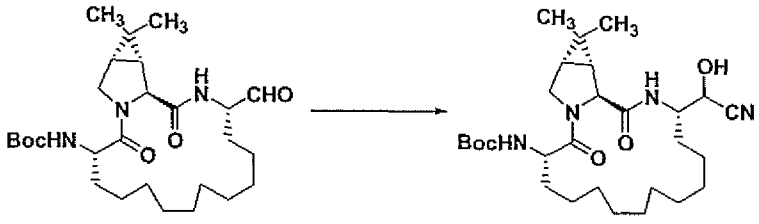
MS (ESI), m/z, relative intensity 774 [$(M+Na)^+$, 50], 752 [$(M+1)^+$, 70], 653 (90), 420 (30), 297 (30), 148 (100), 134 (40).

Preparative Example 4



4

Step A

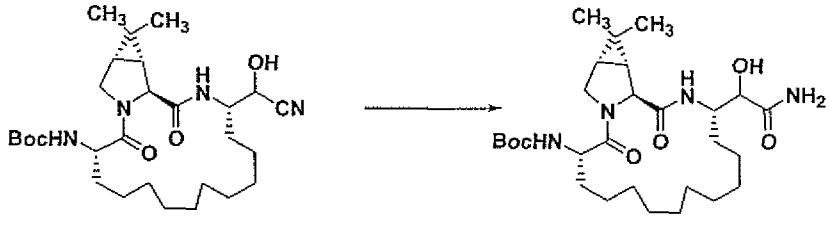


2b 4a

A solution of aldehyde **2b** (100 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was treated with Et_3N (50 mg, 0.5 mmol) and acetone cyanohydrin (43 mg, 0.5 mmol). The reaction mixture was stirred at rt. for 2 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO2, acetone/hexanes 1:4) to yield **4a** (100 mg) as a colorless solid.

MS (ESI), m/z, relative intensity 541 [$(M+Na)^+$, 60], 519 [$(M+1)^+$, 10], 463 (30), 419 (100).

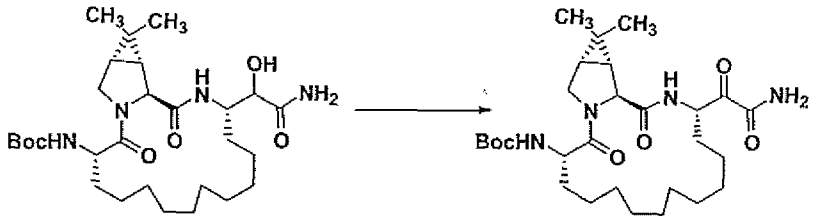
Step B



4a 4b

A solution of cyanohydrin **4a** (100 mg, 0.2 mmol) in DMSO (3 mL) was treated with H_2O_2 (35%, 0.3 mL) and K_2CO_3 (43 mg, 0.3 mL) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with aq. $Na_2S_2O_3$ solution (10%, 30 mL) and brine (30 mL). The reaction mixture was dried (MgSO4) filtered concentrated in *vacuo* and directly used in step C without further purification.

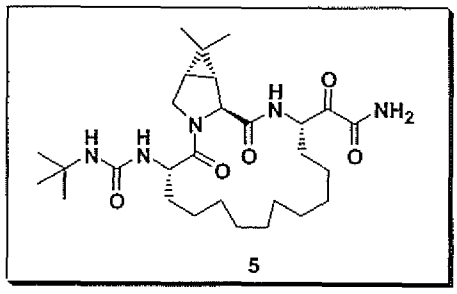
Step C



4b 4

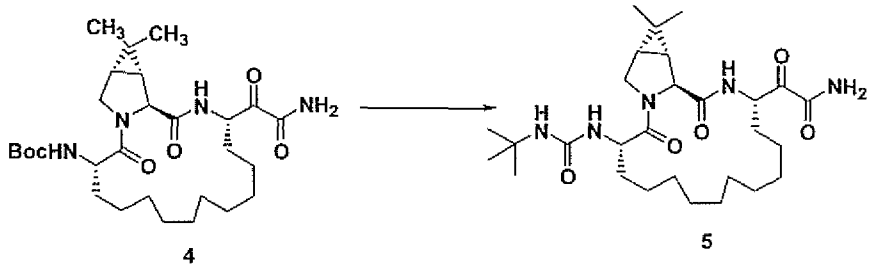
A solution of hydroxy amide **4b** (100 mg, 0.18 mmol) in toluene/DMSO (1:1, 5 mL) at 0 °C was treated with EDCI (356 mg, 1.86 mmol) and $Cl_2CHCOOH$ (120 mg, 0.93 mmol) and stirred at 0 °C for 3 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with satd. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The ethyl acetate layer was dried ($MgSO_4$), concentrated and purified by chromatography (SiO_2, acetone/hexanes 2:3) to yield **4** (20 mg) as colorless solid **MS** (ESI), m/z, relative intensity 435 $[(M+1)^+$, 85], 390 (100).

Preparative Example 5



5

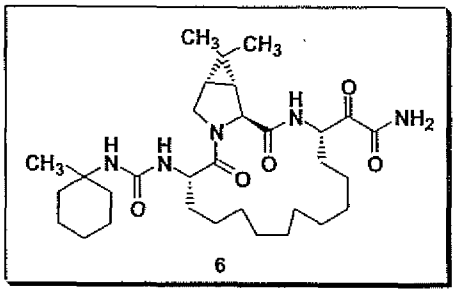
Step A



4 5

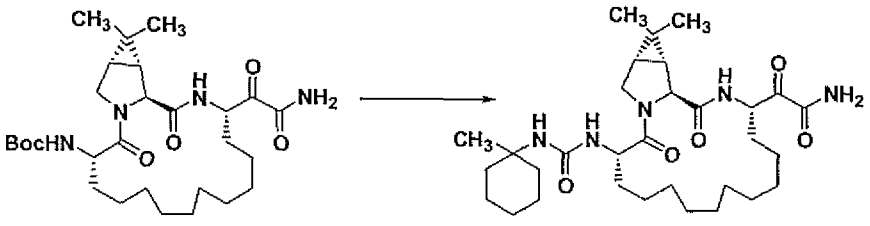
Carbamate **4** (40 mg, 0.1 mmol) was converted to urea **5** (7.5 mg) following the procedure similar to preparative example 3, Step A.

Preparative Example 6



6

Step A

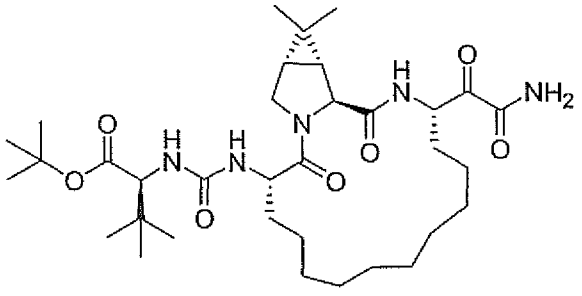


4 6

The synthesis of **6** was achieved using the similar procedure so synthesis of **5**. A solution of **4** (180 mg 0.34 mmol) in HCOOH (3.0 mL) was stirred at rt. for 3 h an concentrated in *vacuo*. The residue was dried in *vacuo* and taken in CH_2Cl_2 (4 mL) and treated with methyl cyclohexylisocyanate (72 mg, 0.52 mmol) and Et_3N (52 mg, 0.52 mmol). The reaction mixture was stirred at 0 °C for 16 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **6** (10 mg) as colorless solid

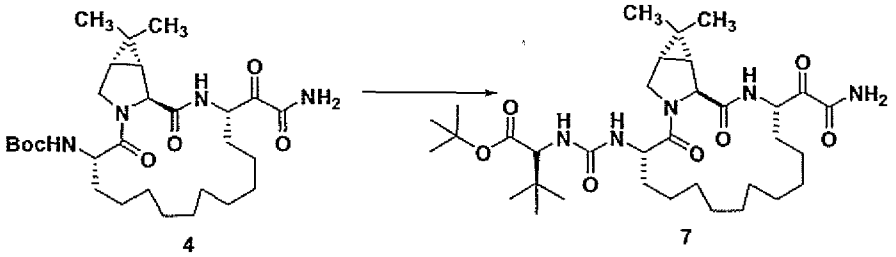
MS (ESI), m/z, relative intensity 574 [$(M+1)^+$, 20], 435 (100), 390 (50).

Preparative Example 7



7

Step A

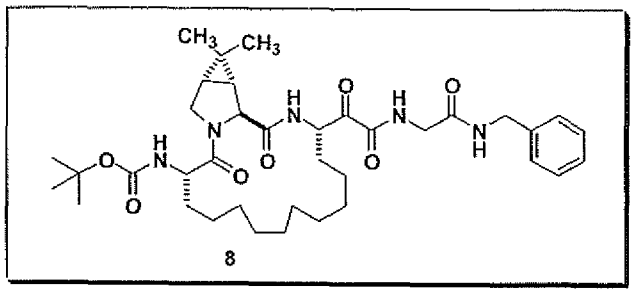


4 7

The synthesis of **7** was achieved using the similar procedure so synthesis of **5**. A solution of **4** (180 mg 0.34 mmol) in HCOOH (3.0 mL) was stirred at rt. for 3 h and concentrated in *vacuo*. 50 mg (0.12 mmol) of this residue was dried in *vacuo* and taken in CH_2Cl_2 (4 mL) and treated with isocyanate of *tert*-butyl glycine *tert*butyl ester (74mg, 0.0.35 mmol) and Et_3N (35 mg, 0.0.35 mmol). The reaction mixture was stirred at 0 °C for 16 h and concentrated in *vacuo*. The residue was diluted with CH_2Cl_2 and washed with aq HCl, aq satd. $NaHCO_3$ and brine. The organic layers were dried ($MgSO_4$) and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **7** (15 mg) as colorless solid.

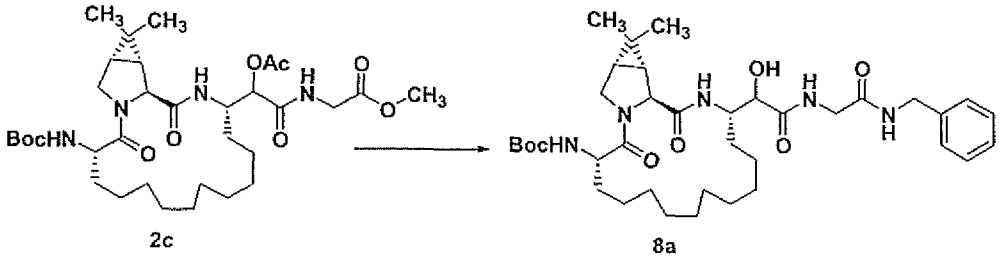
MS (ESI), m/z, relative intensity 648 $[(M+1)^+$, 45], 592 (25), 435 (100).

Preparative Example 8



8

Step A



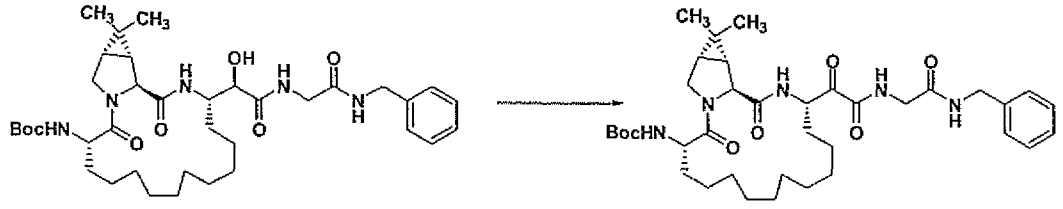
2c 8a

A solution of methyl ester **2c** (100 mg, 0.15 mmol) in THF (2 mL), H_2O (2 mL) and CH_3OH (2 mL) was treated with $LiOH{\cdot}H_2O$ (41 mg, 1.0 mmol) and stirred at rt. for 2 h. After the completion of the reaction it was acidified with aq. HCl (2 mL) and

concentrated in *vacuo.* The residue was dried in *vacuo* and used as it with out further purification.

The acid was dissolved in CH_2Cl_2 (2 mL), DMF (2 mL) and treated with benzyl amine (107 mg, 0.22 mmol), NMM (42 mg, 0.42 mmol) HATU (53 mg, 0.14 mmol) and stirred at 0 °C for 24 h. The yellow colored solution was concentrated in *vacuo* and diluted with CH_2Cl_2 (100 mL). The organic layers were washed with saturated aq. $NaHCO_3$, aq. HCl and brine. The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and used as it is in next step (63 mg).

Step B

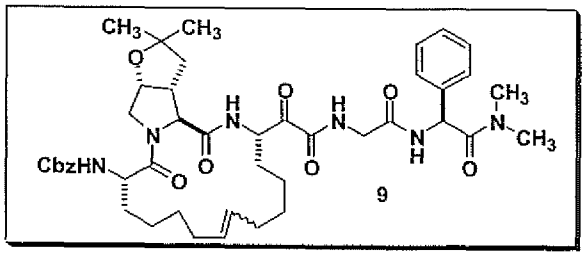


8a 8

Hydroxyamide **8a** (62 mg) in CH_2Cl_2 (3 mL) was treated with Dess-Martin reagent (62 mg, 0.15 mmol) and stirred at rt. for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and treated with aq. soln of $Na_2S_2O_3$ (10%, 25 mL) and satd. $NaHCO_3$ (25 mL) and stirred for 20 min. The aqueous layer was separated and extracted once again with CH2Cl2. The combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **8** as a colorless solid (21 mg).

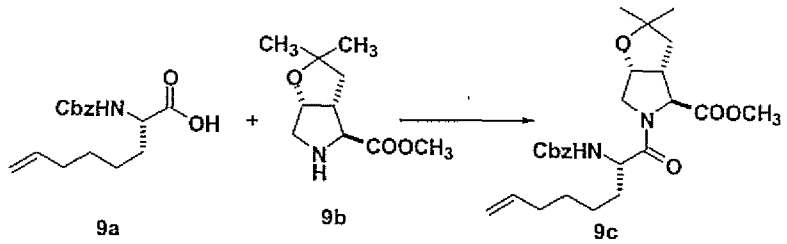
MS (ESI), m/z, relative intensity 704 [$(M+Na)^+$, 40], 682 [$(M+1)^+$, 20], 582 (100), 150 (70), 117 (30).

Preparative Example 9



9

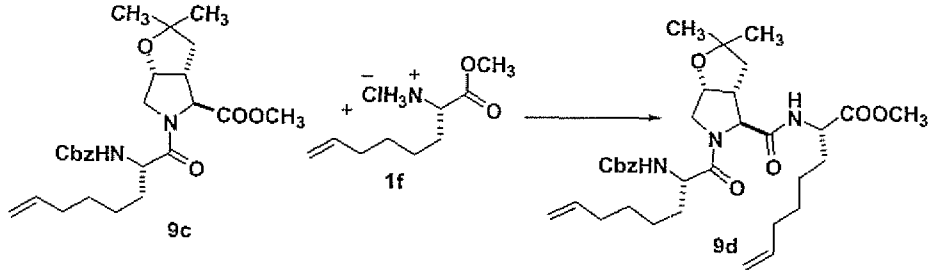
Step A



A solution of acid **9a** (3.6 g, 18.1 mmol), amine **9b** (5.53 g, 18.1 mmol) HATU (8.59 mmol, 22.62 mmol) and NMM in CH_2Cl_2 (50 mL), DMF (50 mL) was stirred at 0°C overnight. The reaction mixture was concentrated in *vacuo* and diluted with aq. HCl (1M, 500 mL) and extracted with CH_2Cl_2 (3x250 mL). The combined organic layers were washed with aq. HCl 500 ml), aqueous saturated $NaHCO_3$ (500 mL) brine (300 mL) and purified by chromatography (SiO_2, acetone/hexanes 1:4) to yield **9c** (6.7 g) as colorless solid.

MS (ESI), m/z, relative intensity 495 $(M+Na)^+$, 90], 473 $[(M+1)^+$, 60], 429 (70), 391 (40), 200 (100), 140 (30).

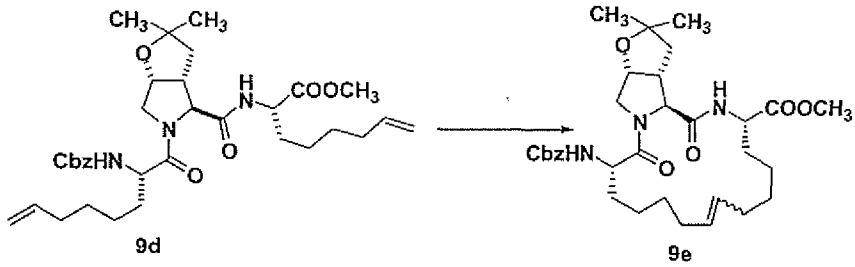
Step B



A solution of methyl ester **9c** (5.5 g, 11.59 mmol) in $CH_3OH/THF/H_2O$ (300 mL) was treated with $LiOH.H_2O$ (700 mg, 16.7 mmol) and stirred at rt. for 1.5 h. The reaction mixture was diluted with aq. HCl and extracted into CH_2Cl_2 (700 mL). The organic layer was dried with $MgSO_4$ filtered concentrated in *vacuo* and used as it is in subsequent steps.

A solution of crude acid in CH_2Cl_2 (50 mL), DMF (50 mL) was treated with HATU (5.5 g, 17.35 mmol), NMM (4.07 g, 40.32 mmol) and stirred at 0 °C for 24 h. The reaction mixture was concentrated in vacuo and taken in aq. HCl (300mL). The acidic layers was extracted into CH_2Cl_2 (2x200 mL) and the combined organic layers were washed with saturated NaHCO3, brine and purified by chromatography (SiO_2, acetone/hexanes 4:1) to yield **9d** (7.1 g) as a colorless solid.

Step C

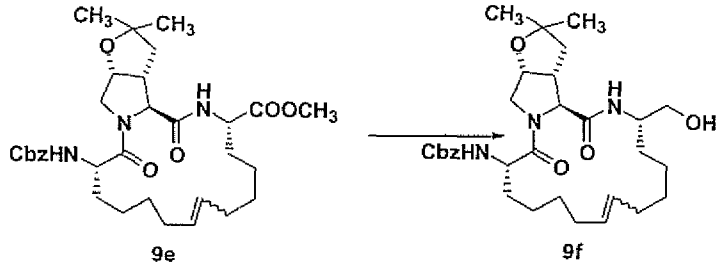


A solution of diene **9d** (2.0 g, 3.2 mmol) in CH2Cl2 (64 mL) was treated with Grubbs catalyst ($[(Cy)_3RuCl_2=CHC_6H_5$, 404 mg, 0.48 mmol) and stirred at rt. for 24 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:3) to yield **9e** (1.1 g) as a brown solid and mixture of *E/Z* isomers.

^{1}H NMR ($CDCl_3$, 300 MHz) □, 7.36 (bm, 5 H), 7.13 (d, 1 H, 4.5 Hz), 5.73 (d, 1 H, J=8.1Hz), 5.28 (m, 2 H), 5.10 (s, 2 H), 4.75 (m, 1 H), 4.65 (m, 2 H), 4.52- 4.46 (m, 1 H), 3.90 (bd, 1 H), 3.74 (s, 3 H), 3.61 (dd, 1 H, J= 15.6, 11.1 Hz), 3.44 (dd, 1 H, J=6.9, 7.2 Hz), 2.12-2.01 (m, 5 H), 1.79-1.67 (m, 3 H), 1.49-1.43 (m, 3 H), 1.36-1.34 (m, 4 H), 1.26 (bs, 5 H), 1.16 (bs, 3 H).

MS (ESI), m/z, relative intensity 606 [$(M+Na)^+$ 70], 584 (100), 540 (30).

Step D

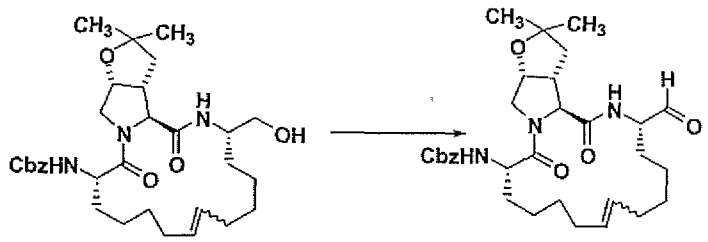


A solution of ester **9e** (200 mg, 0.32 mmol) in dry THF (5 mL) was treated with $LiBH_4$ (2M soln. in THF, 0.32 mL) and stirred at rt. for 3 h. The reaction mixture was quenched with aqueous HCl (1M, 100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with aq. $NaHCO_3$ (100 ml) brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **9f** (2.1 g).

^{1}H NMR ($CDCl_3$, 300 MHz) δ.

MS (ESI), m/z, relative intensity 578 [$(M+Na)^+$, 40], 556 [$(M+1)^+$, 80], 512, (30), 295 (100).

Step E



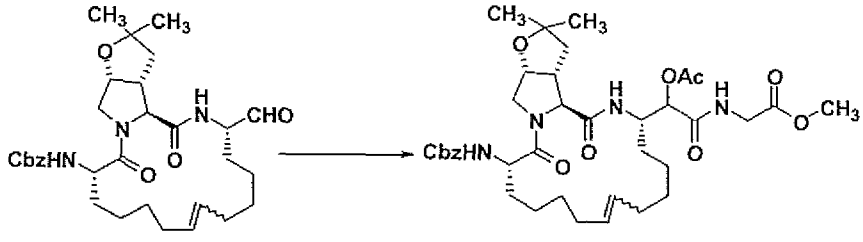
9f 9g

A solution of alcohol **9f** (100 mg, 0.19 mmol), in CH_2Cl_2 (3 mL) was treated with Dess Martin reagent (106 mg, 0.25 mmol) and stirred at rt. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ solution (10%, 10 mL) and saturated $NaHCO_3$ solution (10 mL) and stirred at rt. for 0.2 h. The reaction mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 3:1) to yield **9g** (80 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.52 (s, 1 H), 7.36 (bs, 5 H), 7.11 (d, 1 H, J=7.2 Hz), 5.67 (d, 1 H, J=7.8 Hz), 5.24-5.11 (m, 2 H), 5.11 (s, 2 H), 4.77-4.45 (m, 5 H), 3.92 (d, 1 H, J=12 Hz), 3.58 (dd, 1 H, J=6.6, 5.5 Hz), 3.51-3.46 (m, 1 H), 2.17-1.00 (m, 25 H).

MS (ESI), m/z, relative intensity 576 $[(M+Na)^+$, 15], 554 $[(M+1)^+$, 100], 510 (40).

Step F

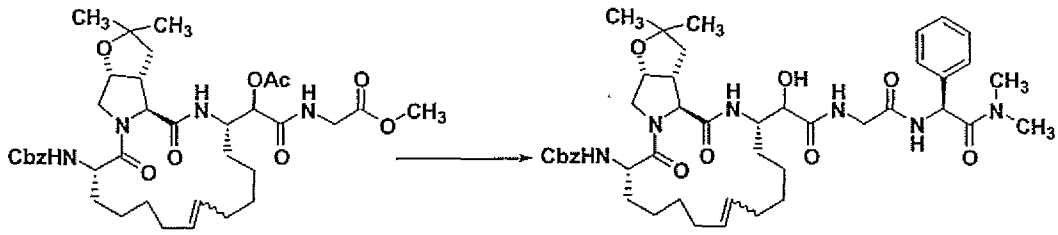


9g 9h

A solution of aldehyde **9g** (80 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was treated with CH_3COOH (30 mg, 0.50 mmol) and methylisocyanoacetate (50 mg, 0.50 mmol). The reaction mixture was stirred at rt. for 24 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **9h** as a mixture of diastereomers.

MS (ESI), m/z, relative intensity 735 $[(M+Na)^+$, 70], 713 $[(M+1)^+$, 100].

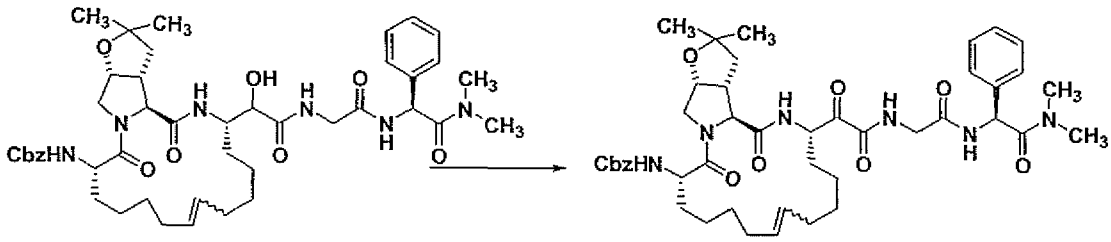
Step F



9h 9i

Methyl ester **9h** (600 mg, 0.92 mmol) was hydrolyzed to acid using $LiOH \cdot H_2O$ and coupled to H-Phg-$N(CH)_2$ ·HCl (235 mg, 1.09 mmol) using NMM (303 mg, 3.0 mmol) and HATU (437 mg, 1.15 mmol) as outlined in preparative example 1, step J to yield **9i** that was directly used for oxidation.

Step G

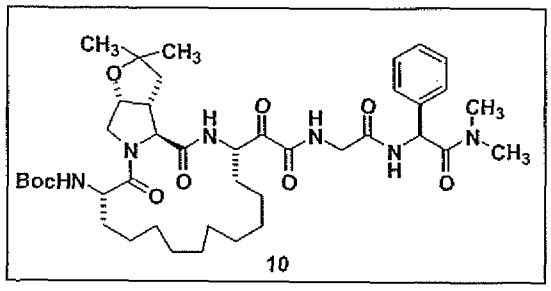


9i 9j

Crude **9j** (470 mg, 0.58 mmol) from step F was oxidized using Dess-Martin reagent (424 mg, 1.00 mmol) following the procedure similar to step H (preparative example 1) to yield **9j** (310 mg) as a colorless solid.

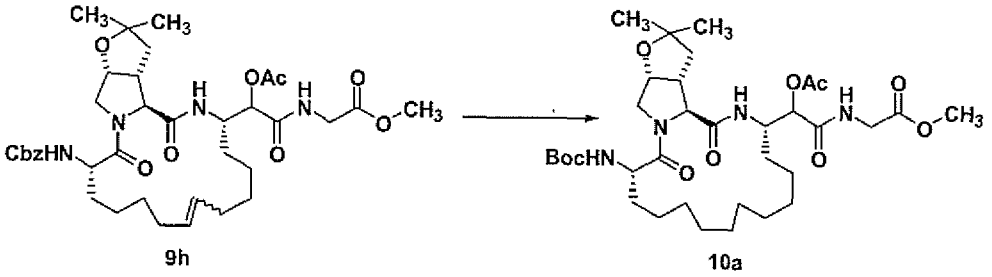
MS (ESI), m/z, relative intensity 869 [$(M+CH_3OH+Na)^+$, 100], 815 [$(M+1)^+$, 40], 770 (30).

Preparative Example 10



10

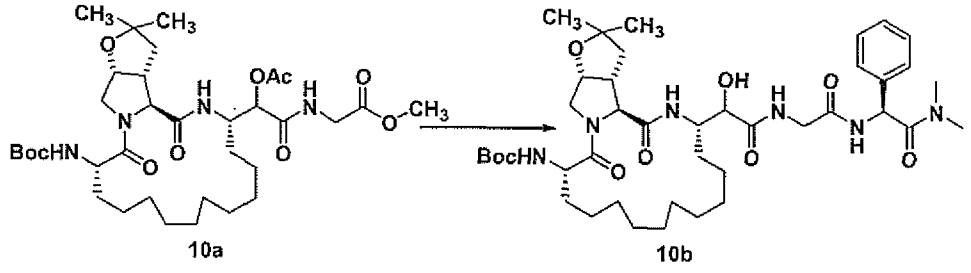
Step A



9h 10a

A solution of **9h** (200 mg, 0.3 mmol) in methanol (5 ml) was treated with Pd(OH)2/C (wet, 10%) and hydrogenated for 3h. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated in vacuo. The residue was dissolved in methylene chloride and treated with ditertbutyldicarbonate (200 mg, 0.92 mmol). The reaction mixture was stirred at rt. for 24 h and purified by chromatography (SiO_2, acetone/Hexanes 1:2) to yield **10a** (85 mg) as a colorless solid.

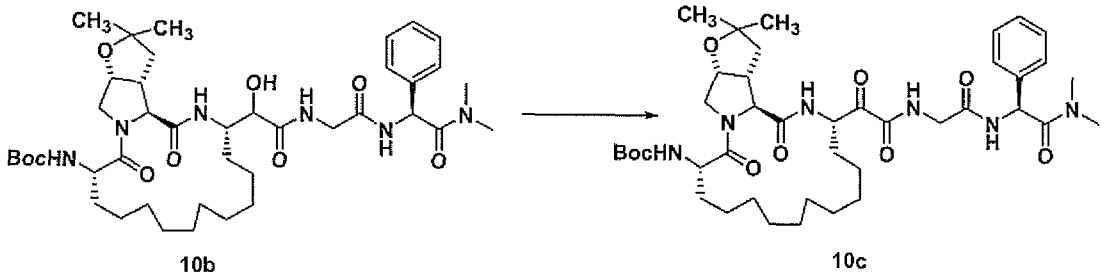
Step B



10a 10b

Methyl ester **10a** (80 mg, 0.15 mmol) was hydrolyzed to acid using $LiOH{\cdot}H_2O$ (41 mg, 1 mmol) and coupled to H-Phg-$N(CH)_2$ ·HCl (32 mg, 0.15 mmol) using NMM (40 mg, 0.40 mmol) and HATU (64.6 mg, 0.17 mmol) as outlined in preparative example 1, step J to yield **10b** directly used for oxidation.

Step C

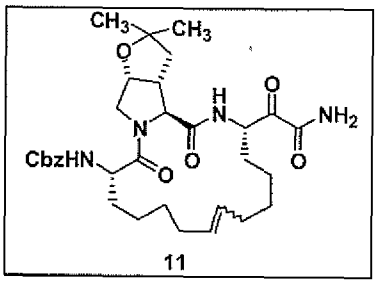


10b 10c

Hydroxy amide **10b** (60 mg, 0.08 mmol) was oxidized using Dess-Martin reagent (60 mg, 0.14 mmol) which was purified by chromatography (SiO_2, acetone/CH_2Cl_2 1:2) to yield **10c** (21 mg) as colorless solid.

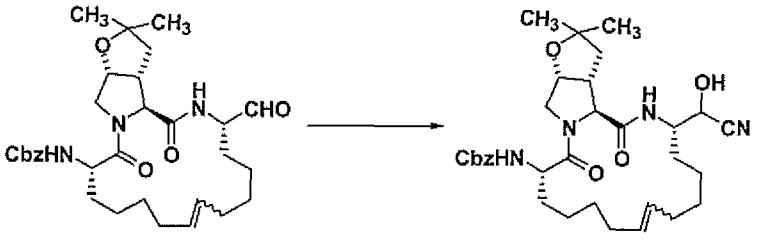
MS (ESI), m/z, relative intensity 805 [$(M+Na)^+$, 20], 783 [$(M+1)^+$, 20], 683 (30), 369 (40), 210 (70), 116 (100).

Preparative Example 11



11

Step A

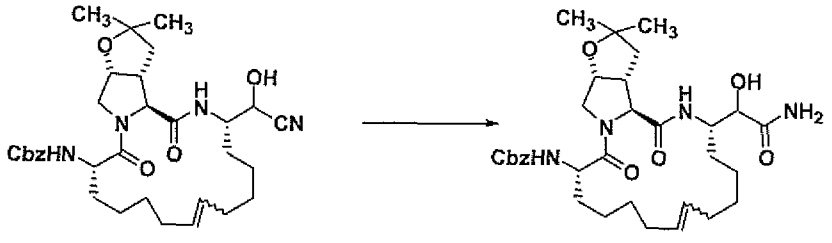


9g 11a

A solution of aldehyde **9g** (400 mg, 0.73 mmol) in CH_2Cl_2 was treated with Et_3N (150 mg, 1.5 mmol) and acetone cyanohydrin (170 mg, 1.5 mmol). The reaction mixture was stirred at rt. for 3 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:4) to yield **4a** (286 mg) as a colorless solid.

MS (ESI), m/z, relative intensity 603 $[(M+Na)^+$, 60], 581 $[(M+1)^+$, 70], 464 (50), 420 (100).

Step B

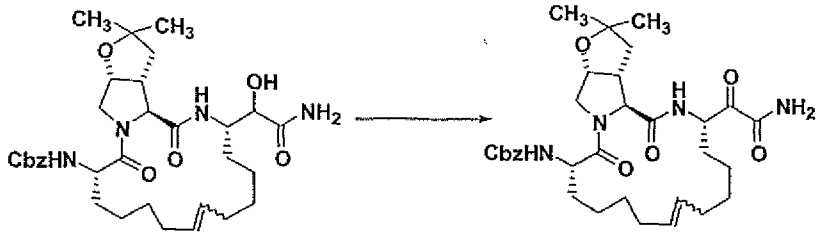


11a 11b

A solution of cyanohydrin **11a** (600 mg, 1.1 mmol) in DMSO (12 mL) was treated with H_2O_2 (35%, 1.0 mL) and K_2CO_3 (43 mg, 0.3 mL) and stirred at rt. for 8 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with aq. $Na_2S_2O_3$ solution (10%) and brine (30 mL). The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and directly used in step C without further purification.

MS (ESI), m/z, relative intensity 621 $[(M+Na)^+$, 70], 599 $[(M+1)^+$, 100], 554 (40).

Step C

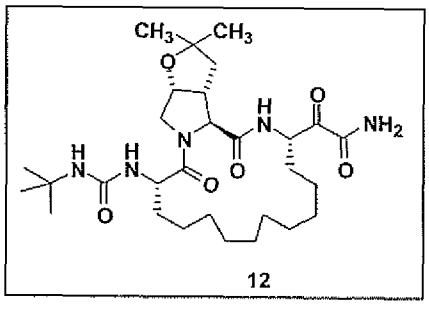


11b 11

A solution of hydroxy amide **11b** (320 mg, 0.54 mmol) in toluene/DMSO (1:1, 10 mL) at 0 °C was treated with EDCI (1.1 g, 5.40 mmol) and $Cl_2CHCOOH$ (350 mg, 2.7 mmol) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with satd. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **11** (173 mg) as colorless solid.

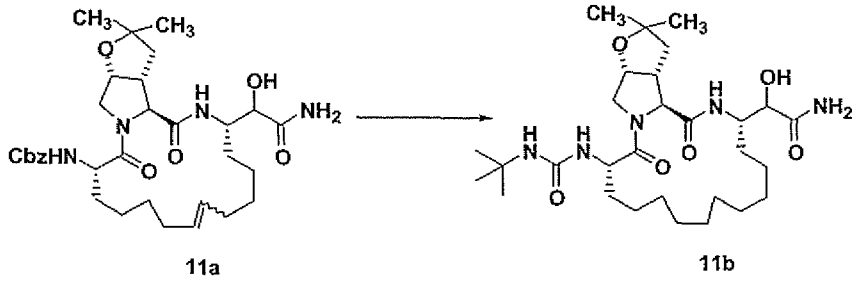
MS (ESI), m/z, relative intensity 619 [$(M+1)^+$, 20], 597 (100).

Preparative Example 12



12

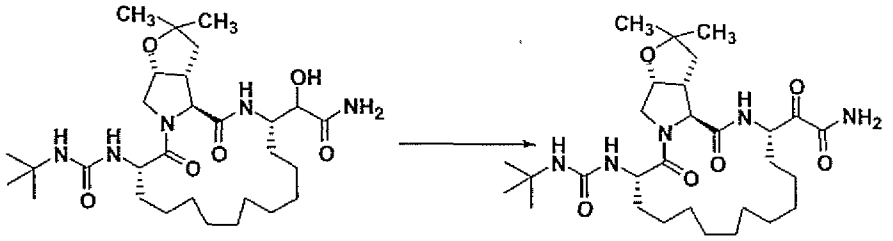
Step A



11a 11b

A solution of **11a** was hydrogenated using Pd/C and the amine obtained was dissolved in CH_2Cl_2 and treated with tert-butylisocyanide at 0 °C. The reaction mixture was stirred at rt. for 12 h and diluted with water. The reaction mixture was extracted with CH_2Cl_2 (30 mL) and combined organic layers were dried ($MgSO_4$) filtered concentrated in vacuo to obtain **11b** that was used in oxidation without further purification.

Step B

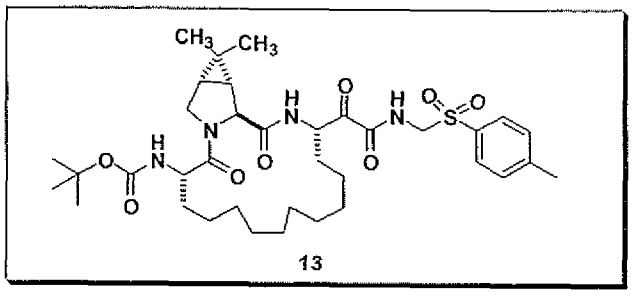


11b 12

A solution of hydroxy amide **11b** (320 mg, 0.54 mmol) in toluene/DMSO (1:1, 10 mL) at 0 °C was treated with EDCI (1.1 g, 5.40 mmol) and $Cl_2CHCOOH$ (350 mg, 2.7 mmol) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with satd. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **11** (173 mg) as colorless solid.

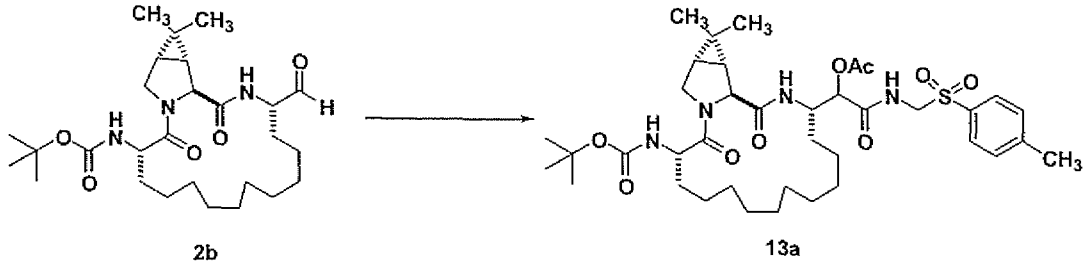
MS (ESI), m/z, relative intensity 619 $[(M+1)^+$, 20], 597 (100).

Preparative Example 13



13

Step A

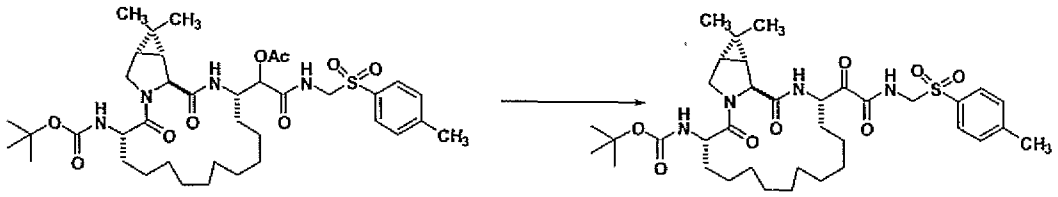


2b 13a

A solution of aldehyde **2b** (50 mg, 0.1 mmol) in dry CH_2Cl_2 (5 mL) was treated with CH_3COOH (21 mg, 0.3 mmol) and TOSMIC (59 mg, 0.3 mmol, 3.0 eq.). The reaction mixture was stirred at rt. for 40 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, EtOAc/hexanes 2:3) to yield **1k** (60 mg) as a mixture of diastereomers.

MS (ESI), m/z, relative intensity 769 $[(M+Na)^+$, 30], 747 $[(M+1)^+$, 20], 647 (100).

Step B



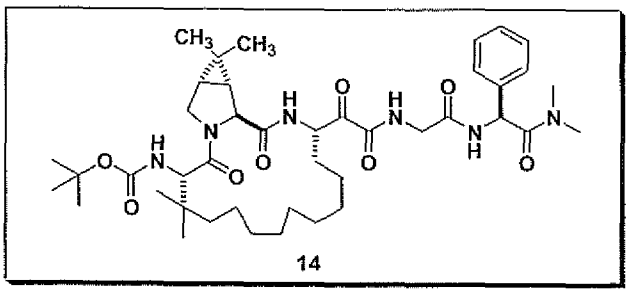
13a 13

A solution of **13a** (60mg, 0.08 mmol) in methanol was treated with a 8 drops of concentrated HCl and stirred at rt for 12 h. The acetate ester was hydrolyzed with partially deprotection of Boc group which was reprotected with ditertbutyldicarbonate (16 mg, 0.073 mmol).

The hydroxyamide (46 mg, 0.07 mmol) in CH_2Cl_2 was treated with Dess-Martin reagent (55 mg, 0.13 mmol) and stirred at rt for 10 min. Satd aq. $Na_2S_2O_3$ was added and reaction mixture was extracted into CH_2Cl_2 . The reaction mixture was dried ($MgSO_4$) filtered concentrated in vacuo and purified by chromatography to yield **13** (61 mg).

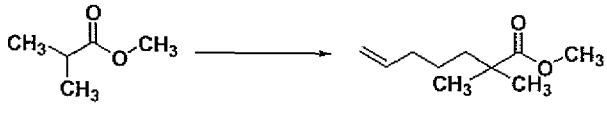
MS (ESI), m/z, relative intensity 703 [$(M+1)^+$, 11], 603 (100).

Preparative Example 14



14

Step A



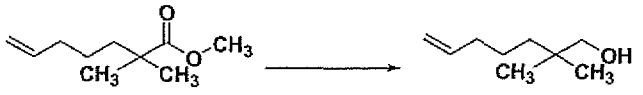
14a

A solution of methylisobutyrate (2.0g, 19.5 mmol) in THF was added dropwise to a solution of KHMDS in THF (4.65 g, 23.5 mmol) at –78 °C and stirred for 0.5 h. The reaction mixture was treated with 5-bromo-1-pentene (3.5 g, 23.5 mmol) and shirred at rt. for 1 h. The reaction mixture was quenched with aq. HCl and extracted into ether (150 mL). The organic layer was dried ($MgSO_4$) filtered concentrated in

vacuo and purified by chromatography (EtOAc/Hexane 1:19) to yield 2.1 g of **14b** as colorless liquid.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ, 5.83-5.70 (m, 1 H), 5.00-4.91 (dd, 2 H), 3.65 (s, 3 H), 2.01 (dt, 2 H), 1.53-1.48 (m, 2 H), 1.35-1.30 (m, 2 H), 1.1 (s, 9 H).

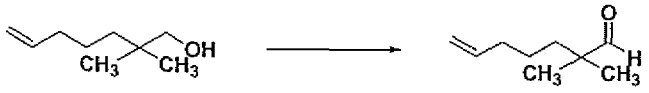
Step B



14b 14c

A solution of ester (2. 6 g, 16 mmol) in ether (30 mL) was treated with $LiAlH_4$ (1M soln in THF, 20 mL) at –78 °C and warmed to rt. The reaction mixture was quenched with a solution of $KHSO_4$ and filtered through a plug of celite and $MgSO_4$. The filtrate was concentrated in vacuo and used as it is in the next step.

Step C

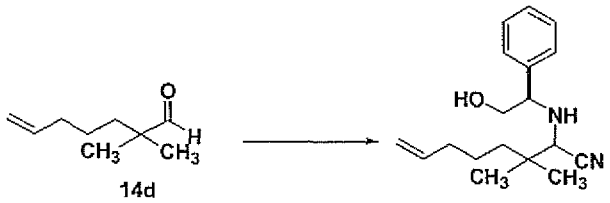


14c 14d

A solution of oxalyl chloride (1.48 g, 11.7 mmol) in dry CH_2Cl_2 was treated with DMSO (1.53 g, 19.5 mmol) at –78 °C and stirred for 15 min. To this mixture was added alcohol **14c** (1.1 g, 7.8 mmol) and stirred at –78 °C for 15 min. Triethyl amine (5.0 mL, 35.5 mmol) was added and the reaction mixture was warmed to rt. The reaction mixture was acidified and extracted with EtOAc (200 mL). The combined organic layers were washed with aq. HCl, dried (MgSO4) filtered, concentrated in vacuo and used in next reaction.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.42 (s, 1 H), 5.82-5.68 (m, 1 H), 5.00-4.91 (m, 2 H), 2.03 (dt, 2 H), 1.48-1.23 (m, 4 H), 1.03 (s, 3 H).

Step D

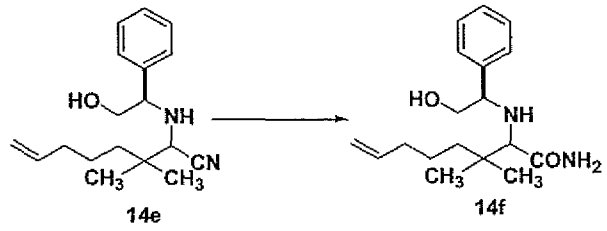


14d 14e

A solution of aldehyde **14d** (18g, 129 mmol) in CH_2Cl_2 (150 mL) was treated with (R)-phenyglycinol (20.33 g, 148.3 mmol) and stirred at 0 °C for 1 h. The reaction mixture was treated with TMS-CN (25.6g, 258 mmol) and stirred at rt. for 12 h. The

reaction mixture was quenched with saturated aqueous NaHCO3 and extracted with EtOAc (3x150 mL). The combined organic layers were dried ($MgSO_4$) filtered concentrated in vacuo and the residue was dissolved in THF (100 mL) and treated with aq HCl (100 mL). The aqueous layer was basified with aq. NaOH (1 M) and extracted with (EtOAc, 450 mL). The combined organic layers were dried, filtered concentrated in vacuo and purified with chromatography (SiO_2, EtOAc/Hexanes 6:1) to yield **14e** 21 g as a colorless oil.

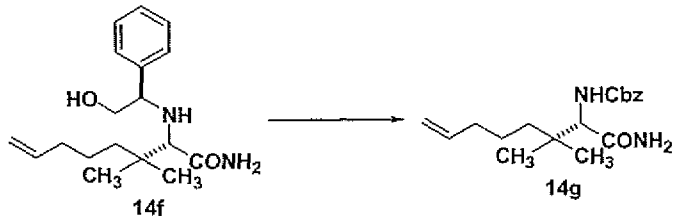
Step E



A solution of **14e** (20 g) in CH_3OH (200 mL) was treated with H_2O_2 (60 mL) and $LiOH.H_2O$ (5.88 g, 209.6 mmol) at 0 °C. The reaction mixture was stirred at rt. for 12 h and cooled to 0°C and carefully quenched with aq. $Na_2S_2O_3$ solution (10%). The reaction mixture was concentrated in vacuo and the aq. layer was extracted with EtOAc (600 mL). The combined organic layers were washed extensively with aq. $Na_2S_2O_3$, dried ($MgSO_4$) concentrated in vacuo and purified by crystallization (EtOAc/Hexanes) to yield pure diastereomer directly used in the next reaction.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (bs, 5 H), 6.25 (s, 1 H), 6.17 (s, 1 H), 5.79-5.66 (m, 2 H), 4.98-4.89 (m, 2 H), 3.71-3.60 (m, 3 H), 2.68 (bs, 1 H), 1.98-1.90 (3 H), 1.03 (s, 3 H), 0.99 (s, 3 H), 1.03-0.99 (m, 1 H).

Step F



A solution of amide **14f** (8.00g, 26.3 mmol) in CH_2Cl_2 (160 mL), CH3OH (80 mL) at 0°C was treated with $Pb(OAc)_4$ (13.45 mmol, 30.3 mmol), at 0° C for 1 h. the yellow solution was treated with aq. $NaHCO_3$ (250 mL, and stirred for 15 min. The reaction mixture was filtered and concentrated in vacuo. The mostly aqueous layer

was extracted in CH_2Cl_2 (3x300 mL) concentrated in vacuo and directly used in further reaction.

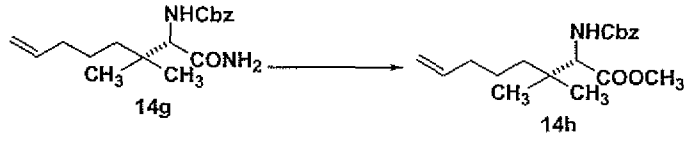
A solution of the crude imine was taken in THF (200 mL) and treated with aq HCL (1 M, 200 mL) and stirred at rt. for 1 h. The reaction mixture was concentrated in vacuo and extracted with Ether (2x250 mL). The aqueous layer was basified with aq. NaOH (50%) at 0 °C and extracted with CH_2Cl_2 (600 mL). The combined organic layers were extracted with brine, dried (MgSO4) filtered concentrated in vacuo and directly used in the next reaction.

The residue was dissolved in CH_2Cl_2 (200 mL) and cooled to –78°C and treated with NMM (4.2 g, 40 mmol) and Cbz-Cl (5.4g, 31.58 mmol). The reaction mixture was stirred at rt. for 12 h and washed with aq. HCl . The organic layer was separated and the aq. layer was extracted with CH_2Cl_2 (200 mL) The combined organic layers were extracted with brine, dried and purified by chromatography (SiO_2, EtOAc/Hexanes 2:3) to yield **14g** (6.8 g) as a colorless solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.30 (m, 5 H), 6.23 (bs, 1 H), 5.86 (bs, 1 H), 5.82-5.64 (m, 1 H), 5.63 (d, 1 H, J= 9.3 Hz), 5.12-4.93 (m, 4 H), 4.07 (d, 1 H, J=9 Hz), 2.0-1.9(m, 2 H), 1.42- 1.30 (m, 4 H), 0.96 (s, 6 H).

MS (ESI), m/z, relative intensity 341[M+Na)$^+$, 100], 319 [(M+1)+, 30], 274 (50), 230 (70), 213 (30), 140 (30).

Step G

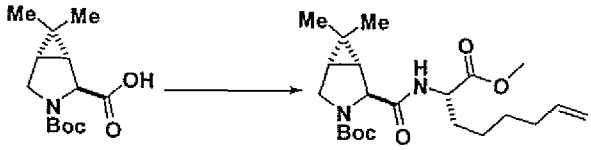


A solution of amide **14 g** (6.8 g, 21.4 mmol) in CH_2Cl_2 (200 mL) was treated with Me_3OBF_4 (10.36 g, 69.9 mmol) and K_3PO_4 (12.11 g, 69.52 mmol) and stirred at rt. for 12 h. The reaction mixture was concentrated in vacuo and dissolved in CH_3OH (280 mL) and aq. HCl (140 mL, 1 M) and heated at reflux for 1 h. The reaction mixture was concentrated and the aqueous layer was further extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were dried ($MgSO_4$), filtered concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hexanes 1:19) to yield **14h** (5.6g) as colorless oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (bs, 5 H), 5.85-5.71 (m, 1 H), 5.32 (d, 1 H, J=9.9 Hz), 5.10 (dd, 2 H, J= 12, 3.9 Hz), 5.03-4.93 (m, 2 H), 4.27 (d, 1 H, J=9.9 Hz), 3.72 (s, 3 H), 2.05—1.98 (m, 2 H), 1.47-1.24 (m, 4 H), 0.93 (s, 9 H).

MS (ESI), m/z, relative intensity 356 $[M+Na)^+$, 95], 334 [(M+1)+, 10], 290 (100), 230 (60), 213 (20).

Step H

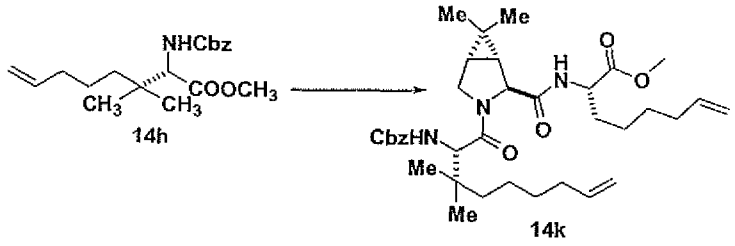


A solution of acid **14i** (4.5g, 17.64 mmol) and amine **1f** (3.66 g, 17.64 mmol) in CH_2Cl_2 (50 mL), DMF (50 mL) at 0° C was treated with HATU (8.39 g, 22.05 mmol) and NMM (5.35 g, 52.92 mmol) and stirred overnight at 0° C. The reaction mixture was concentrated in *vacuo* and diluted with 450 mL of CH_2Cl_2. The aqueous layer was washed with aq. HCl (1M, 2x300 mL), aq. $NaHCO_3$ (1M, 2x300 mL). The organic layers were dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 5:1) to yield **14j** as a colorless oil (5.8 g).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03, 6.39 (d, 1 H, J = 7.5 Hz), 5.8-5.7 (m, 1 H), 4.99-4.90 (m, 2 H), 4.66 –4.54 (m, 1 H), 3.72 (s, 3 H), 3.62-3.42 (m, 2 H), 2.01 (bs, 2 H), 1.88-1.63 (m, 4 H), 1.61, 1.43 (s, 9 H), 1.6-1.3 (m, 4 H), 1.02 (s, 3 H), 0.90 (s, 3H).

MS (ESI), m/z, relative intensity 431 $[(M+Na)^+$, 60], 409 $[(M+1)^+$, 40], 353 (40), 309 (100), 110 (80).

Step I



A solution of ester **14h** (5.4g, 16.2 mmol) in H_2O (30 mL), THF (30 mL) and CH_3OH (30 mL) was stirred with $LiOH{\cdot}H_2O$ (1.36 g, 32.42 mmol) for 24 h and concentrated in vacuo. The aqueous layer was acidified with aq. HCl (1M) and extracted into CH_2Cl_2 (400 mL). The combined organic layers were dried ($MgSO_4$), filtered concentrated in vacuo and used as it is in further reactions.

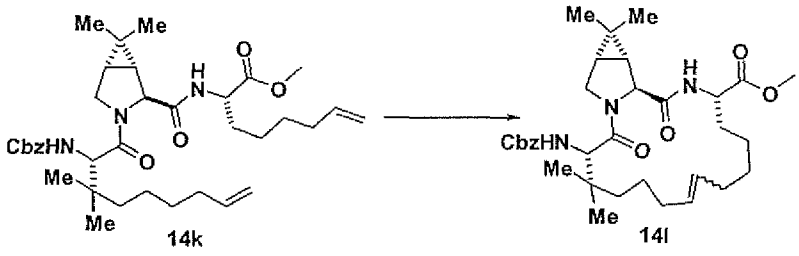
A solution of acid (4.0 g, 12.5 mmol) and deprotected amine* in CH_2Cl_2 (30 mL), DMF (30 mL) at 0° C was treated with HATU (7.15 g, 18.79 mmol) and NMM (4.5 g, 45.0 mmol) and stirred at 0° C for 48 h, and 25°C for 24 h. The reaction mixture was concentrated in *vacuo* and diluted with 300 mL of CH_2Cl_2. The aqueous layer was washed with aq. HCl (1M, 3x100 mL), aq. $NaHCO_3$ (satd, 3x100 mL). The organic layers were dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hexanes 3:1) to yield **14k** as a colorless oil (4 g of pure 14k and 2 g of partially impure 14k).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.32 (bs, 5 H), 6.92 (d, 1H, J=7.5Hz), 5.48-5.69 (m, 2 H), 5.37 (d, 1 H, J=9.9 Hz), 5.08-4.92 (m, 6 H), 4.56-4.33 (M, 1 h), 3.97-3.93 (m, 2 H), 3.84-3.80 (m, 2 H), 3.74 (s, 3 H), 2.03-1.97 (m, 4 H), 1.86-1.87-1.39 (m, 12 H), 1.12 (s, 3 H), 0.98 (s, 6 H), 084 (s, 3 H)

MS (ESI), m/z, relative intensity 632 [$(M+Na)^+$, 20], 610 [$(M+1)^+$, 100], 309 (60).

* Amine was obtained by the deportation of **14j** with 4 M HCl in dioxane.

Step J

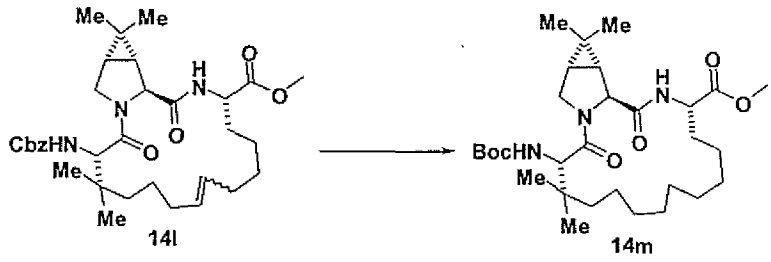


A solution of diene **14k** (4.00 g, 6.57 mmol) in CH_2Cl_2 (65.0 mL) at rt. was saturated with N_2 and treated with Grubbs catalyst (551 mg, 0.657 mmol) and stirred for 24 h. The reaction mixture was concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hexanes 1:3) to yield **14l** (1.7 g) as a tan colored solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.31 (bs, 5 H), 7.08 (d, 1 H, J = 7.8 Hz), 5.43 (d, 1 H, J = 10.2 Hz), 5.28 (m, 2 H), 5.13-5.02 (m, 2 H), 4.56-4.32 (m, 1 H), 4.49-4.28 (m, 2 H), 3.96-3.79 (m, 2 H), 3.74 (s, 9 H), 2.05-1.29 (m, 16 H), 1.0 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H), 0.86 (s, 3 H).

MS (ESI), m/z, relative intensity 550 [$(M+1)^+$, 50], 450 (100).

Step K

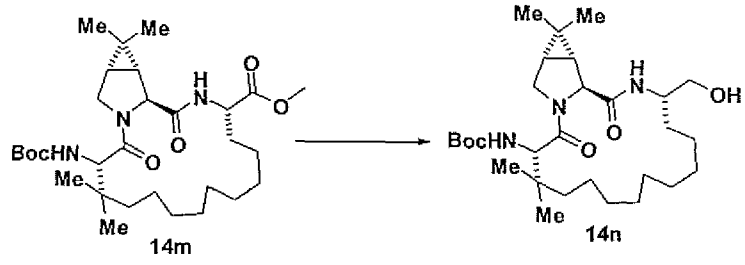


A solution of alkene **14l** (200 mg, 0.35 mmol) in CH3OH (2 0 mL) was treated with Pd/C (5%, 200 mg), ditertbutyldicarbonate (200 mg, 0.92 mmol) and hydrogenated at rt. for 12 h. The reaction mixture was filtered through a plug of celite and concentrated in vacuo. The reaction mixture was purified by chromatography (SiO_2, acetone/hexanes 1:5) to yield **14m** (81 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (d, 1 H, J=7.8 Hz), 5.14 (d, 1 H), 4.61-4.55 (m, 1 H), 4.31 (s, 1 H), 4.22 (d, 1 H, J=10 Hz), 4.03 (d, 1 H, J=10.5 Hz), 3.88-3.85 (m, 1 H), 3.75(s, 3 H), 1.89-1.76 (m, 1 H), 1.59-1.76 (m, 28 H), 1.02 (s, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.86 (s, 3 H).

MS (ESI), m/z, relative intensity 610 [$(M+AcOH+1)^+$, 40], 550 [$(M+1)^+$, 50], 450 (100), 309 (20).

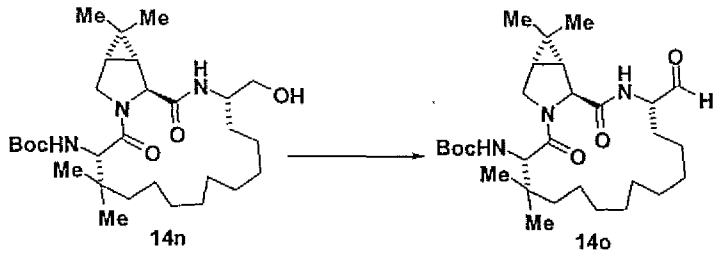
Step L



A solution of ester **14m** (80 mg, 0.15 mmol) in dry THF (2 mL) was treated with $LiBH_4$ (2M soln. in THF, 0.1 mL) and stirred at rt. for 4 h. The reaction mixture was quenched with aqueous HCl (1M, drops) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with aq. $NaHCO_3$ (100 ml) brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **14n** (70 mg) as an amorphous solid.

MS (ESI), m/z, relative intensity 544 [$(M+Na)^+$, 30], 522 [$(M+1)^+$, 40], 422 (100).

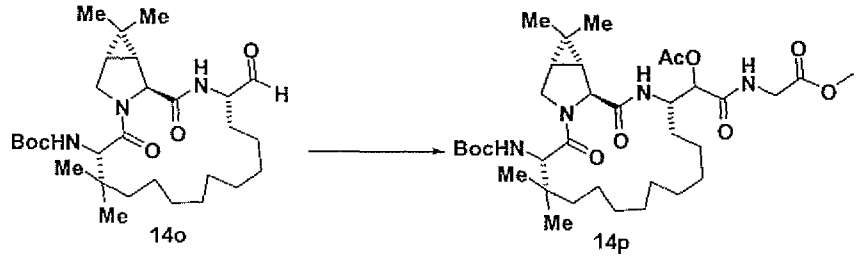
Step M



A solution of alcohol **14n** (30 mg, 0.05 mmol), in CH_2Cl_2 (2 mL) was treated with Dess Martin reagent (30 mg, 0.07 mmol) and stirred at rt. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ solution (10%, 10 mL) and saturated $NaHCO_3$ solution (10 mL) and stirred at rt. for 0.5 h. The reaction mixture was extracted with CH_2Cl_2 (3x10 mL). The organic layer was dried with $MgSO_4$, filtered concentrated in *vacuo* and used as it is in further reaction.

MS (ESI), m/z, relative intensity 552 [$(M+1)^+$, 100], 248 (40).

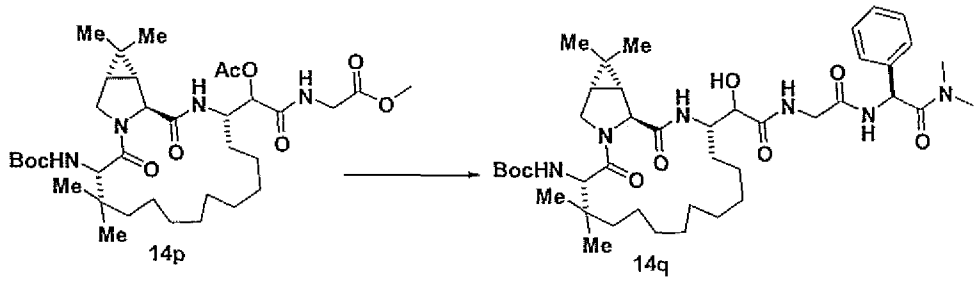
Step N



Compound **14o** from step **M** was converted to **14p** (40 mg) using CH_3COOH (20 □L) and methylisocyanoacetate (20 □L) following the procedure similar to step I (preparative example 1) as a mixture of diastereomers.

MS (ESI), m/z, relative intensity 711 [$(M+1)^+$, 100], 240 (20).

Step O

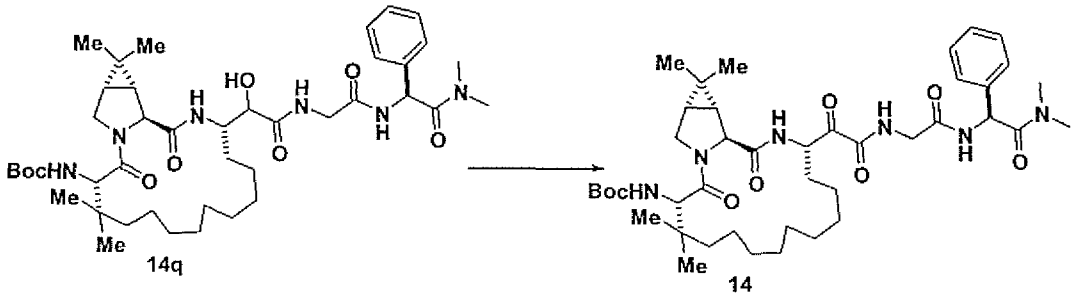


A solution of methyl ester **14p** (80 mg, 0.12 mmol) in THF (3 mL), H_2O (3 mL) and CH_3OH (3 mL) was treated with $LiOH{\cdot}H_2O$ (41 mg, 1 mmol) and stirred at rt. for 2 h. After the completion of the reaction it was acidified with aq. HCl (15 mL) and extracted with CH2Cl2 (3x30 mL). The combined organic layers were dried (MgSO4),

filtered and concentrated in *vacuo.* The residue was dried in *vacuo* and used as it with out further purification.

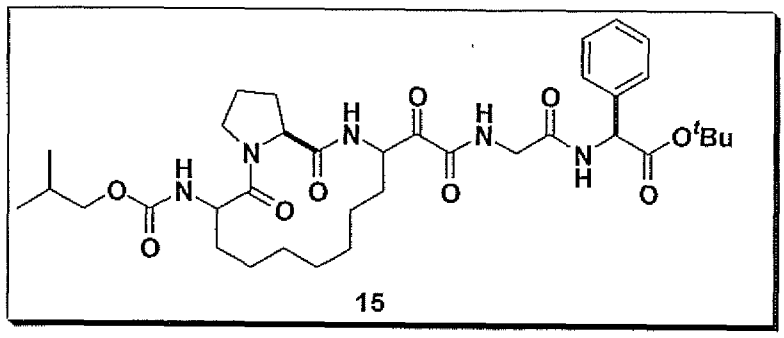
The acid was dissolved in CH_2Cl_2 (2 mL), DMF (2 mL) and treated with H-Phg-$N(CH)_2$ ·HCl (40 mg, 0.2 mmol), NMM (40 mg, 0.4 mmol) HATU (68 mg, 0.16 mmol) and stirred at 0 °C for 24 h. The yellow colored solution was concentrated in *vacuo* and diluted with CH_2Cl_2 (75 mL). The organic layers were washed with saturated aq. $NaHCO_3$, aq. HCl and brine. The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and used as it is in next step (90 mg).

Step P



A solution of alcohol **14q** (90 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was treated with Dess-Martin reagent (100 mg, 0.24 mmol) and stirred at rt. for 2 h. The reaction was diluted with aq $Na_2S_2O_3$ solution (30 mL) and aq. $NaHCO_3$ solution (30 mL each) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with satd. $NaHCO_3$, brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (acetone/hexanes 2:3) to yield **14** (22 mg) as a colorless solid. **MS** (ESI), m/z, relative intensity 813 $[(M+1)^+$, 100], 768 (20).

Preparative Example 15



15

Step A

1a 15a

To 45 mL THF, diisopropylamine (4.70 mL, 33.51 mmol, 2 eq.) and LiCl (4.26 g, 6 eq) at –78 ^{0}C was added nBuLi (20.4mL, 1.95 eq) under nitrogen atmosphere. 10 min later, the solution of **1a**/30 mL THF was transferred to the above solution over 10 min. After 20 min, the brownish yellow mixture was warmed up to 0 ^{0}C. Another 20 min later, the solution became opaque bright yellow and 4-iodo-1-butene (3.35 g, 1.1 eq) was added in dropwise. The solution became even brighter and 60 min later 115 mL 1 M HCl was added to quench the reaction. The THF was removed and 150 mL EtOAc was added in for extraction. The organic layer was further washed with 115 mL 1M HCl. The aqueous layers were combined and adjusted to pH 14 by 6M NaOH at 0^{0}C. Extraction was done with dichloromethane 110 mL x 4. The organic layer was dried over sodium carbonate. Filtration through celite and removal of the solvent afforded 4 g of the oil which upon standing, became solid. Flash chromatography with 5:5:90 Et_3N/MeOH/DCM provided 2.63 g pure **15a** in 57 % yield. (R_f = 0.64, 5:5:90 Et_3N/MeOH/DCM)

^{1}H NMR (4: 1 rotamer ratio. * denotes minor rotamer peaks. $CDCl_3$): δ 0.96* (d, 3H, J = 6.7 Hz) 1.15 (d, 3H, J = 6.9 Hz) 1.45-1.55 (m, 2H) 2.05-2.20 (m, 2H) 2.80 (s, 3H) 2.92* (s, 3H) 3.55-3.60 (m, 2H) 4.00* (m, 1H) 4.35-4.45* (m, 1H) 4.60-4.65 (m, 2H) 4.92-5.02 (m, 2H) 5.68-5.80 (m, 1H) 7.20-7.40 (m, 5H).

^{13}C NMR($CDCl_3$): δ 11.26 15.68 31.11 35.67 47.17 52.22 76.92 116.46 127.50 128.67 129.34 138.60 143.19 178.08.

MS: $C_{16}H_{24}N_2O_2$: 277 $(M+H)^+$;

HRMS: calcd: 277.1916; found: 277.1917.

Step B

15a 15b

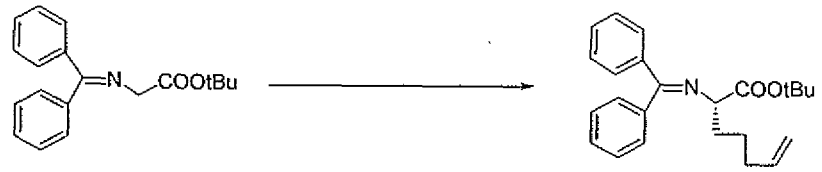
1.9 g of **15a** (6.88 mmol, 1 eq) was treated with 2N NaOH (7.0 mL, 2 eq), 7 mL of water and refluxed at 100 ^{0}C for 3 h. The mixture was cooled to room temperature. 20 mL of DCM, 10 mL of water was added and the organic layer was separated. The aqueous layer was washed with 20 mL of DCM. The combined organic layers were further washed with 10 mL of water. The combined aqueous layer was treated with 1.3 mL 12 N HCl. 20 mL of dioxane was added and the solution was adjusted to pH 8-9 by adding saturated $NaHCO_3$. 1.48 g of iBOC-OSU (1 eq) was added and the mixture was stirred for overnight. After decreasing the solvent volume to one half, 10 mL of water and 10 mL DCM was added for extraction. The aqueous layer was then treated with 12 N HCl dropwise until it precipitated (pH 2). Extraction with EtOAc 40 mL x 2 followed by $MgSO_4$ drying and celite filtration afforded 1.52 g colorless oil **15b** in 90 % yield.

^{1}H NMR($CDCl_3$): δ 0.88 (d, 6 H, J = 6.6 Hz) 1.78-2.00 (m, 3 H) 2.10-2.20 (m, 2 H) 3.80-3.82 (m, 2 H) 4.40 (m, 1 H) 5.00-5.06 (m, 2 H) 5.10 (m, 1 H) 5.80 (m, 1 H).

^{13}C NMR($CDCl_3$): δ 20.0 26.2 29.0 32.8 54.2 72.8 117.0 138.0 157.8 177.6.

MS for $C_{11}H_{19}NO_4$: 230 $(M+H)^+$.

Step C



15c 15d

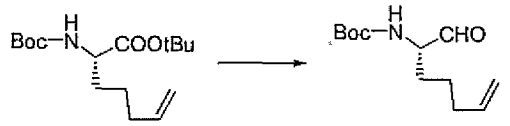
Imine **15c** (9.42 g, 31.88 mmol, 1 eq) was mixed with the Corey's catalyst (*J. Am. Chem. Soc.*, **1997**, *119*, 12414) (1.93 g, 0.1 eq), cesium hydroxide monohydrate (53.55 g, 10 eq) in 150 mL DCM. The solution was cooled down to –60 ^{0}C followed by addition of 5-iodo-1-pentene (25 g, 4 eq) under nitrogen. The crude was stirred for 60 h when 100 mL ethyl ether was added in. After washing with water 100 mL x 2 and brine 70 mL x 1, the organic layer was dried over $MgSO_4$. Celite filtration and removal of the solvent afforded the crude 28.56 g. 5.1 g of the crude was chromatographed with pure hexane first and then 1 : 40 to 1:20 EtOAc/hexane. A 2.56 g of a mixture of **15d**, 5-iodo-1-pentene and benzophenone (1 : 2.5 : 0.8) was obtained. (**15d**: R_f = 0.39, 1 : 20 EtOAc/hexane.)

Step D

15d 15e

0.5 g of the above crude **15 d** (2.56 g) was treated with 4 mL HOAc/THF/water 1 : 1 : 1 for 90 min when TLC shows disappearance of the starting material. Two pipetful of saturated $NaHCO_3$ was added. 10 mL water and 20 mL hexane was added for extraction. The aqueous layer was then further basified to pH 9-10. $(Boc)_2O$ (0.15 g) and dioxane 4 mL were added and after 2.5 h, the solvent was removed and the pH of the solution was adjusted to 3-4. Extraction with ether followed by chromatography with 1: 10 EtOAc/hexane afforded 0.16 g of **15e** in 48 % overall yield from **15c**. (R_f = 0.44, 1 : 10 EtOAc/hexane.)

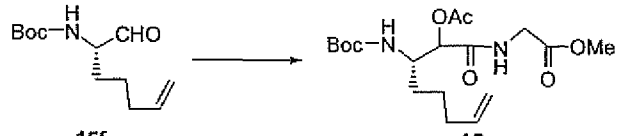
Step E



15e **15f**

4.88 g of **15e** (13.87 mmol) was dissolved in 20 mL of toluene at –78 ^{0}C and was treated with 21 mL $LiAlH_4$ (1 M in Et_2O, 1.6 eq) for 40 min. The mixture was warmed up to 0^{0}C and was quenched by EtOAc and 20 mL 5 % $NaHSO_4$. Extraction with ether, filtration through celite and removal of solvent afforded the residue which was chromatographed with 1/5 EtOAc/hexane. 2.8 g of the desired aldehyde **15f** (R_f = 0.4) along with the alcohol (1.43 g, R_f = 0.04) were obtained. The latter could be converted to the aldehyde by Dess-Martin reaction.

Step F



15f **15g**

1.26 g of **15f** (5.55 mmol, 1 eq), methyl isocyanoacetate (0.50 mL, 1 eq), acetic acid (0.32 mL, 1 eq) were mixed in 20 mL DCM and stirred for 80 h. Removal of the solvent and flash chromatography provided 1.10 g of **15g** in 51 % yield. (R_f = 0.29, 1:1 EtOAc/hexane).

^{1}H NMR($CDCl_3$): δ 1.42 (s, 9 H) 1.50-1.60 (m, 2 H) 1.99-2.20 (m, 4 H) 2.18 (s, 3 H) 3.76 and 3.78 (two singlets, 3 H, 1 : 1 diastereomers) 3.90-4.20 (m, 4 H) 4.90-5.00 (m, 2 H) 5.20 (br s, 1 H) 5.70 (m, 1 H) 6.62 (br s, 1 H).

^{13}C NMR($CDCl_3$): δ 21.93 26.26 29.46 31.25 34.41 41.99 52.53 53.50 75.57 80.41 115.74 139.14 156.28 168.91 169.38 170.79.

HRMS for $C_{18}H_{30}N_2O_7$: calcd: 387.2131 $(M+H)^+$; found 387.2133.

Step G

15g **15h**

Compound **15g** (1.08 g, 2.8 mmol, 1 eq), 60 mg K_2CO_3 (0.15 eq) in 6 mL MeOH were stirred at room temperature for 1 h and then another 2 h at 40^{0}C.

Removal of solid followed by flash chromatography afforded the desired product **15h** as white solid (0.65 g, 68 % yield).

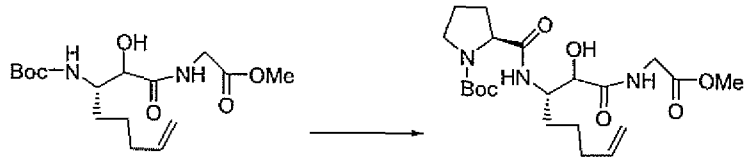
^{1}H NMR($CDCl_3$): δ 1.40 (s, 9 H) 1.40-1.70 (m, 4 H) 1.99-2.10 (m, 2 H) 3.70(s, 3 H) 3.80 (br, 1 H) 4.00-4.25 (m, 4 H) 4.90-5.00 (m, 2 H) 5.10 (br s, 1 H) 5.30 (m, 1 H) 5.78 (m, 1 H) 7.40 (br s, 1 H).

^{13}C NMR($CDCl_3$): δ 26.83 29.48 30.76 34.53 42.03 53.51 54.95 75.05 81.07 115.76 139.30 157.92 170.84 174.16.

$C_{16}H_{28}N_2O_6$: 345 $(M+H)^+$.

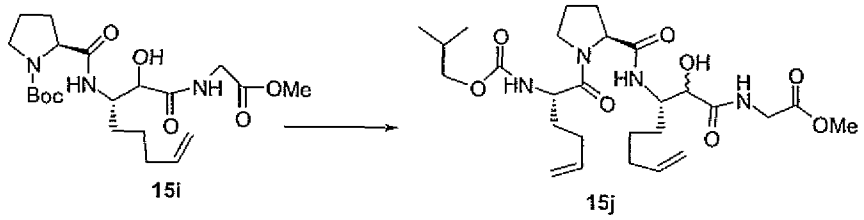
HRMS: calcd: 345.2026; found: 345.2033.

Step H



Compound **15h** (0.39 g, 1.13 mmol) was stirred with 4 M HCl in dioxane (4 mL) at room temperature for 2 h when solid precipitates formed. The solvent was removed and 20 mL DCM was added. The pH was adjusted to 7 by using Hunig's base. The solvent was then removed and the residue was treated with 10 mL THF, Boc-Pro-OH (0.73 g, 3 eq), HATU (1.29 g, 3 eq), Hunig's base (1.18 mL, 6 eq) and 1 mL DMF. After stirring at room temperature for 7 h, the solvent was removed in vacuo. The residue was dissolved in 20 mL EtOAc and washed with 10 mL saturated $NaHCO_3$, 10 mL 0.5 M HCl twice, water 20 mL and brine 5 mL. Chromatography provided 0.68 g **15i** (Rf = 0.31, 5 % MeOH in DCM).

Step I



15i was treated with 2 mL DCM, 3 mL 4 M HCl in dioxane for 1 h. 30mL DCM was added followed by neutralization with Hunig's base at 0 ^{0}C. The solvent was removed and the crude was dissolved in 5 mL DCM, 10 mL THF. After addition of **15b** (0.26 g, 1 eq), HATU (0.43 g, 1 eq) and Hunig's base (0.41 mL, 2.1 eq) and

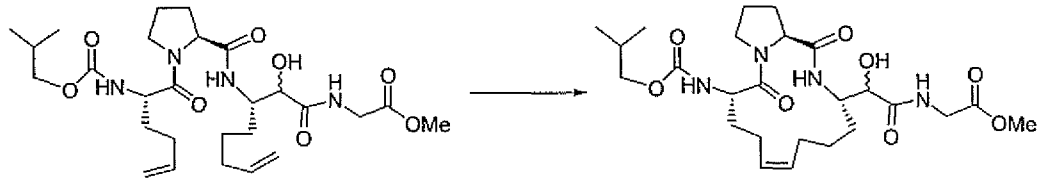
stirred for 4 h, the solvent was removed and 30 mL EtOAc was added. The solution was then washed with 10 mL saturated $NaHCO_3$, 10 mL 1 M HCl, 10 mL 0.5 M HCl, water 20 mL, brine 5 mL. Chromatography gave the desired product **15j** (0.3 g, 48 % from **15h**).

^{13}C NMR($CDCl_3$): δ 20.20 26.26 26.72 29.18 29.55 30.58 33.25 34.60 41.95 48.57 52.90 53.00 53.40 54.68 61.56 72.34 75.68 115.64 116.73 138.07 139.33 157.47 171.04 171.15 173.06 174.23

$C_{27}H_{44}N_4O_8$: 553 $(M+H)^+$.

HRMS: calcd: 553.3237; found: 553.3259.

Step J



15j 15k

Compound **15j** (0.37 g, 0.67 mmol) was treated with 0.138 g Grubbs' catalyst (0.25 eq) in 223 mL DCM under argon. After stirring at room temperature for 65 h, NMR shows the mixture contained the S.M. **15j**, the desired product **15k** (about 20 % yield) and $PO(C_6H_{11})_3$. The R_f for these three are 0.34, 0.24, 0.74, respectively in 5 % HOAc/EtOAc. Repeated flash chromatography could provide the pure sample of **15k**.

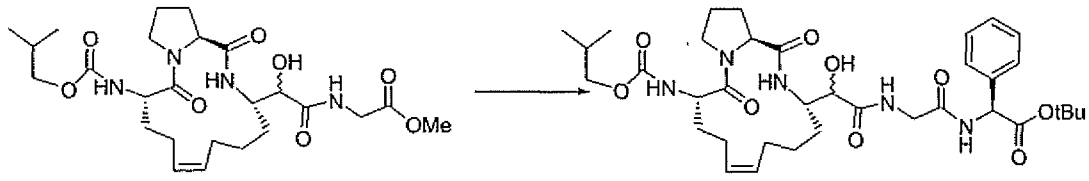
^{1}H NMR($CDCl_3$): δ 0.90 (d, 6 H, J = 6.6 Hz) 1.40-2.00 (m, 14 H) 2.05-2.50 (m, 3 H) 3.60(m, 1 H) 3.70 (s, 3 H) 3.75-4.00 (m, 3 H) 4.00-4.20 (m, 2 H) 4.50 (m, 1 H) 4.70 (d, 1 H, J = 7.5 Hz, diastereomer) 4.81 (d, 1 H, J = 7.9 Hz, another diastereomer) 5.38 (m, 1 H) 5.58 (m, 1 H) 5.65 (br s, 1 H) 7.20 (d, 1 H J = 7.0 Hz) 7.38 (d, 1 H, J = 7.1 Hz).

^{13}C NMR($CDCl_3$): δ 20.26 23.05 26.54 27.02 27.67 27.73 29.21 31.06 34.03 41.97 48.71 52.40 52.80 53..53 60.54 72.43 75.08 130.44 130.56 157.02 171.13 172.01 173.13 173.38.

LC/MS: Tr = 5.11min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) $C_{25}H_{40}N_4O_8$: 525 $(M+1)^+$

HRMS: calcd: 525.2924; found: 525.2908.

Step K



15k 15l

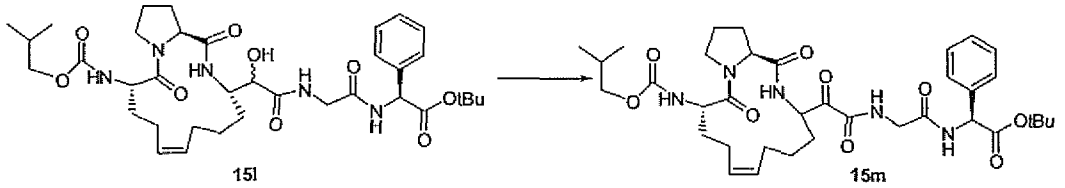
Compound **15k** (92 mg, 0.18 mmol, 1 eq), 60 mg K_2CO_3 (2.5 eq) in 5 mL MeOH were stirred at 40^0C for 2 h when TLC shows complete disappearance of S.M. After removal of the solvent, 44 mL 0.01 M HCl in DCM (2.5 eq) was added to neutralize the solution. The solvent was removed followed by addition of 10 mL THF, 1 mL DMF, PhG-O-tBu (HCl salt, 51 mg, 1.2 eq), 80 mg of HATU (1.2 eq), 0.11 mL of Hunig's base (3.5 eq). The mixture was stirred for 12 h. After removal of solvent, direct chromatography provided the product **15l** (97 mg, 79 % yield from **15j**. Rf = 0.32, 5 % MeOH/DCM).

^{1}H NMR($CDCl_3$): δ 0.90 (d, 6 H, J = 6.6 Hz) 1.30 (s, 9 H) 1.40-2.00 (m, 14 H) 2.15-2.20 (m, 1 H) 3.60(m, 1 H) 3.75-3.90 (m, 3 H) 4.00-4.09 (m, 1 H) 4.10-4.35 (m, 2 H) 4.50 (m, 1 H) 4.62 (d, 1 H, J = 7.5 Hz, diastereomer) 4.72 (d, 1 H, J = 7.9 Hz, another diastereomer) 5.20-5.38 (m, 1 H) 5.44 (d, 1 H, J = 6.6 Hz) 5.50 (m, 1 H) 5.98 (m, 1 H) 7.30 (m, 5 H) 7.45 (d, 1H, J = 7.0 Hz) 7.55 (d, 1 H, J = 7.1 Hz) 7.70 (br s, 1 H).

^{13}C NMR($CDCl_3$): δ 20.30 23.35 26.38 26.78 27.29 28.02 29.18 31.42 34.89 43.97 48.70 51.90 52.93 58.22 60.40 72.44 74.96 75.93 83.80 120.88 128.10 128.12 129.63 129.70 130.33 137.74 157.20 169.32 170.69 173.70 174.47.

LC/MS: Tr = 6.61min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) MS: $C_{36}H_{53}N_5O_9$: 700 $(M+H)^+$.

Step L



15l 15m

Compound **15l** (90 mg, 0.13 mmol) was treated with 109 mg of Dess-Martin reagent (2 eq) in 10 mL DCM at room temperature for 12 h. After removal of the solvent, direct chromatography with 7:3 EtOAc/hexane provided **15m** (40 %) as white solid.

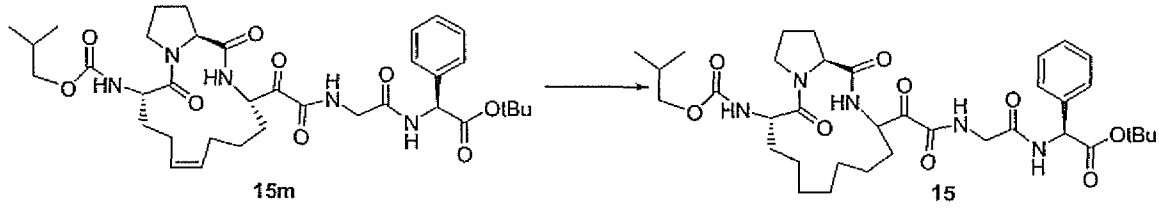
^{1}H NMR($CDCl_3$): δ 0.95 (d, 6 H, J = 6.6 Hz) 1.40 (s, 9 H) 1.50-2.10 (m, 14 H) 2.20-2.30 (m, 1 H) 3.60(m, 1 H) 3.75-3.90 (m, 3 H) 3.93 (dd, 1 H, J = 5.9, 16.8 Hz) 4.10 (m, 1 H) 4.50 (dd, 1 H, J = 8.0, 13.9 Hz) 4.80 (d, 1 H, J = 6.6 Hz) 5.20-5.40 (m, 3 H) 5.41 (d, 1 H, J = 6.6 Hz) 5.60 (dd, 1 H, J = 7.3, 10 Hz) 6.82 (d, 1 H, J = 7.3 Hz) 7.30 (m, 5 H) 7.50 (m, 1H) 7.80 (d, 1 H, J = 6.7 Hz).

^{13}C NMR($CDCl_3$): δ 20.29 23.65 26.34 26.75 29.02 29.20 30.37 30.95 31.56 35.07 43.71 48.83 52.95 54.20 58.14 60.23 72.54 84.15 128.03 129.41 129.68 129.87 130.62 137.60 156.99 160.33 167.41 171.37 173.84 187.26 196.36.

LC/MS: Tr = 6.81 min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) MS: $C_{36}H_{51}N_5O_9$: 698 $(M+H)^+$

HRMS: calcd 698.3765 found 698.3762.

Step M



15m 15

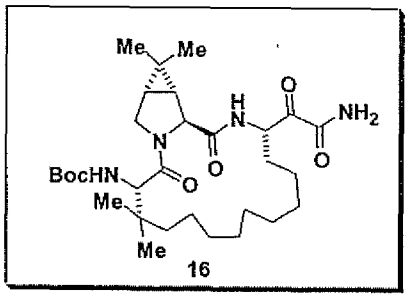
Compound **15m** (4 mg) was treated with 5 mL MeOH, 2 mg of Pd-C under hydrogen balloon for 1.5 h. The solution was filtered through celite. The filtrate was dried in vacuo and the NMR shows exclusive formation of **15**.

^{1}H NMR($CDCl_3$): δ 0.95 (d, 6 H, J = 6.6 Hz) 1.40 (s, 9 H) 1.50-2.10 (m, 16 H) 2.20-2.30 (m, 1 H) 3.60(m, 1 H) 3.75-3.90 (m, 3 H) 3.93 (dd, 1 H, J = 5.9, 16.8 Hz) 4.10 (m, 1 H) 4.50 (dd, 1 H, J = 8.0, 13.9 Hz) 4.80 (d, 1 H, J = 6.6 Hz) 5.30 (m, 1 H) 5.41 (d, 1 H, J = 6.6 Hz) 5.55 (d, 1 H, J = 7.0 Hz) 6.82 (d, 1 H, J = 7.3 Hz) 7.30 (m, 5 H) 7.50 (m, 1H) 7.80 (d, 1 H, J = 6.7 Hz).

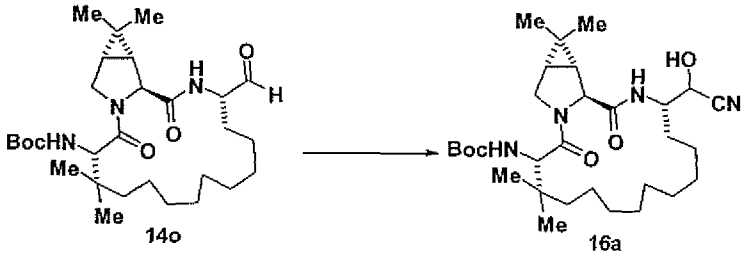
LC/MS: Tr = 5.26 min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) MS: $C_{36}H_{53}N_5O_9$: 700 $(M+H)^+$.

HRMS: calcd: 700.3922; found: 700.3925.

Preparative Example 16



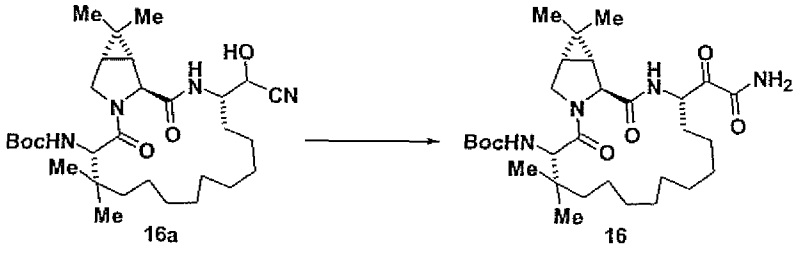
Step A



A solution of aldehyde **14o** (590 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (240 mg, 2.4 mmol) and acetone cyanohydrin (240 mg, 2.82 mmol). The reaction mixture was stirred at rt for 2 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:4) to yield **16a** (600 mg) as a colorless solid.

MS (ESI), m/z, relative intensity 569 [$(M+Na)^+$, 20], 547 [$(M+1)^+$, 40], 447 (100).

Step B



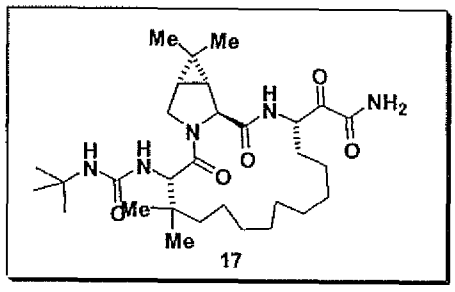
A solution of cyanohydrin **16a** (600 mg, 1.1 mmol) in DMSO (10 mL) was treated with H_2O_2 (35%, 1.5 mL) and K_2CO_3 (252 mg, 1.83 mmol) and stirred at rt. for 15 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with aq. $Na_2S_2O_3$ solution (10%, 50 mL) and brine (30 mL). The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and directly used in oxidation without further purification.

A solution of hydroxy amide in toluene/DMSO (2:1, 15 mL) was treated with EDCI (1.9 g, 10.00 mmol) and $Cl_2CHCOOH$ (317 mg, 2.49 mmol) and stirred at 0 °C

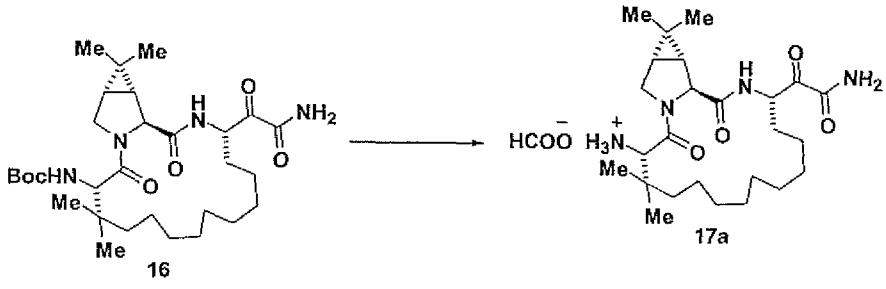
for 3 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with satd. aq. $NaHCO_3$ (2x100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (SiO_2, acetone/hexanes 1:5) to yield **16** as colorless solid.

MS (ESI), m/z, relative intensity 617 [$(M+CH_3OH+Na)^+$, 20], 595 [$(M+CH_3OH+1)^+$, 40], 507 [$(M+1)^+$, 20], 463 (100).

Preparative Example 17

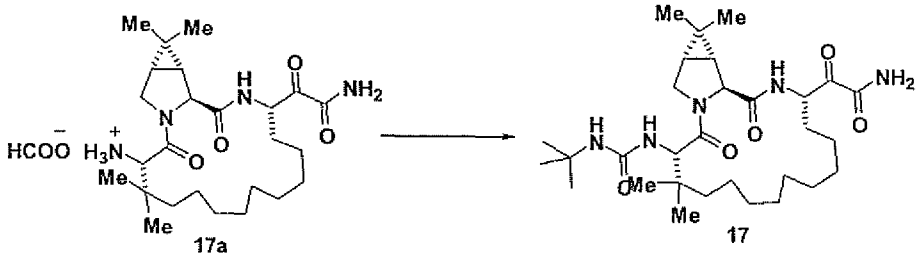


Step A



A solution of **16** (300 mg 0.54 mmol) in HCOOH (10.0 mL) was stirred at rt for 2 h and concentrated in *vacuo*. The residue was dried in *vacuo* and used in further reactions without further purification.

Step B

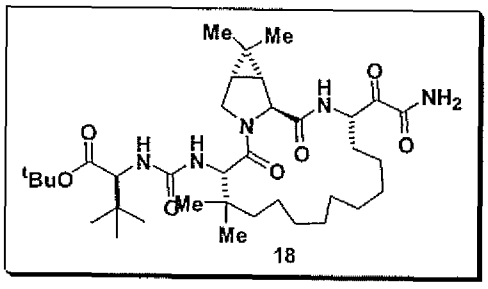


A solution of **17a** (100 mg) in DMF/CH_2Cl_2 (1:1, 3 mL) was treated with $^{t-}$BuNCO (50 □L and NMM (52 mg, 0.52 mmol). The reaction mixture was stirred at rt for 16 h and concentrated in *vacuo*. and diluted with CH_2Cl_2 (60 mL) and washed with

aq. HCl (1M, 2x30 mL), dried, concentrated in vacuo. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **17** (34 mg) as colorless solid.

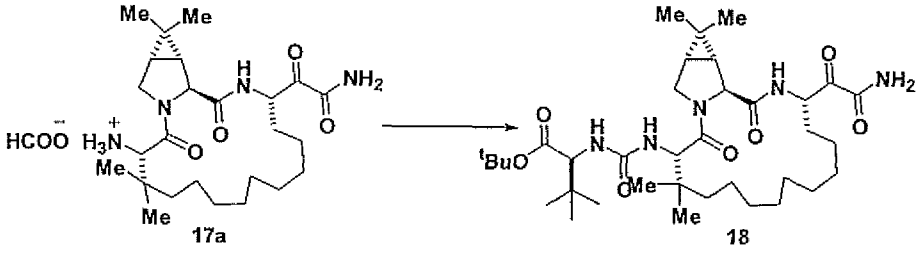
MS (ESI), m/z, relative intensity 584 $[(M+1)^+$, 30], 463 (100).

Preparative Example 18



18

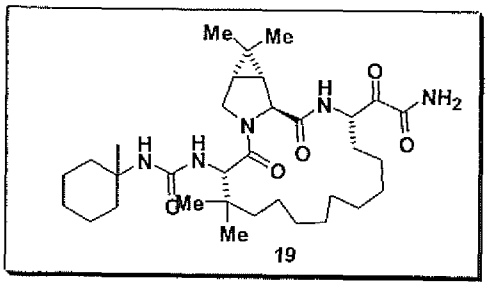
Step A



A solution of **17a** (100 mg) in DMF/CH_2Cl_2 (1:1, 3 mL) was treated with isocyanate of tertbutylester of tert-butylglycine (100 mg, 0.46 mmol) and NMM (52 mg, 0.52 mmol). The reaction mixture was stirred at rt for 16 h and concentrated in *vacuo*. and diluted with CH_2Cl_2 (60 mL) and washed with aq. HCl (1M, 2x30 mL), dried, concentrated in vacuo. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **18** (42 mg) as colorless solid.

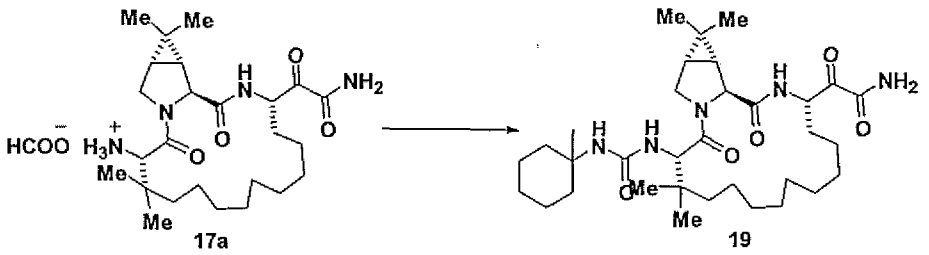
MS (ESI), m/z, relative intensity 698 $[(M+Na)^+$, 40], 676 $[(M+1)^+$, 100], 463 (20).

Preparative Example 19



19

Step A

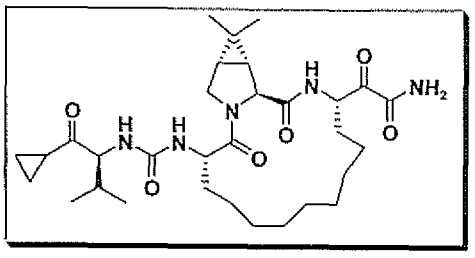


17a 19

A solution of **17a** (100 mg) in DMF/CH_2Cl_2 (1:1, 3 mL) was treated with isocyanate of α-methyl-cyclohexylamine (100 □L) and NMM (52 mg, 0.52 mmol). The reaction mixture was stirred at rt for 16 h and concentrated in *vacuo*. and diluted with CH_2Cl_2 (60 mL) and washed with aq. HCl (1M, 2x30 mL), dried, concentrated in vacuo. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **20** (21 mg) as colorless solid.

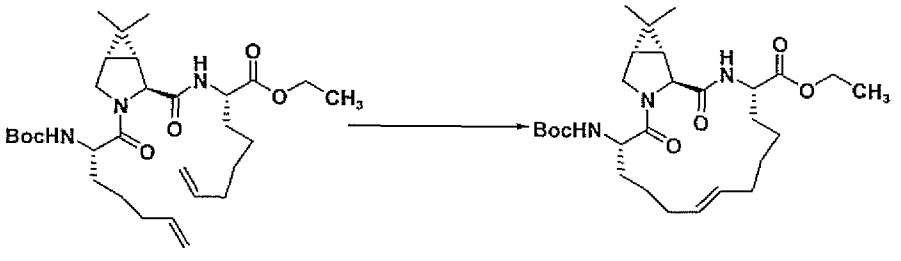
MS (ESI), m/z, relative intensity 624 [$(M+Na)^+$, 30], 602 [$(M+1)^+$, 15], 463 (100), 449 (20), 129 (30).

Preparative Example 20



20

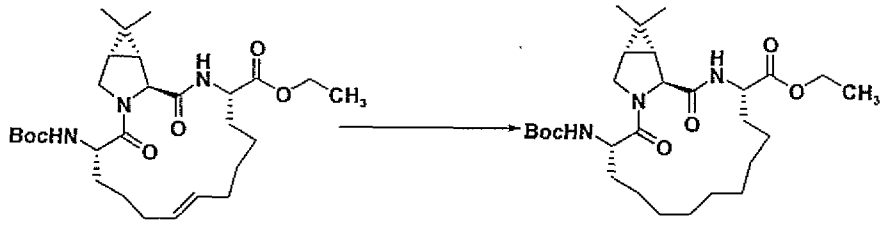
Step A



20a **20b**

A solution of acyclic diene **20a** (6.00 g, 10.954 mmol) in dry toluene (500 mL), degassed with Argon for 0.5 h, was treated with Grubbs catalyst (1.35 g, 1.643 mmol) and heated at 60° C for 12 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/hexanes 1:3) to yield **20b** as a brown foam.

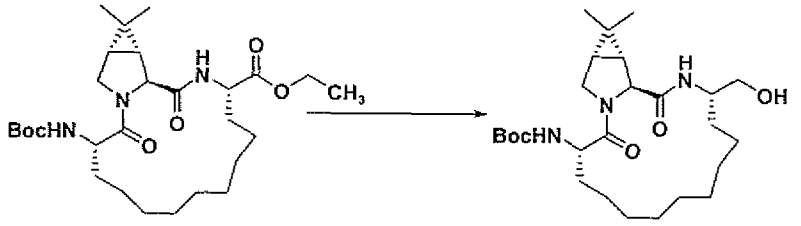
Step B



20b **20c**

A solution of alkene **20b** (5.00g mg, 0.865 mmol) in methanol (100 mL) was treated with Pd/C (1.2g, 5% w/w) and hydrogenated at 50 psi for 3 h. The reaction was filtered through a plug of celite and concentrated in *vacuo*. The residue was purified by chromatography using THF/hexanes gradient from 10-40% to isolated **20c** (3.00 g) as a colorless solid.

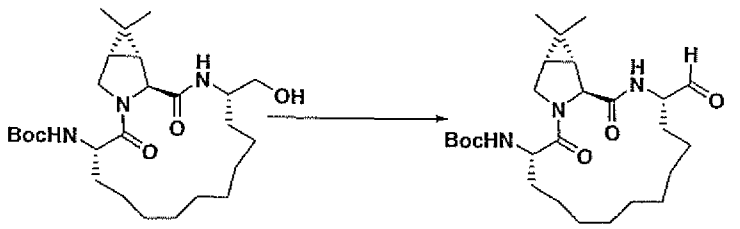
Step C



20c **20d**

A solution of ester **20c** (3.00 g, 5.75 mmol) in dry THF (50 mL) was treated with $LiBH_4$ (2M soln in THF, 3.5 mL, 6.90 mmol) and stirred at rt for 3 h. The reaction was followed by TLC (EtOAc/Hexanes 1:2). The reaction was quenched with methanol (2 mL) and diluted with aq. HCl (1 M, 30 mL) and extracted into CH_2Cl_2 (3x100 mL). The combined organic layers were washed with aq. saturated $NaHCO_3$ (30 mL), brine, dried ($MgSO_4$), filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 1:2) to yield **20d** (2.21 g) as colorless solid. MS (*m/z*, relative intensity) 518 $[(M+K)^+$, 15], 480 $[(M+H)^+$, 75], 380(100).

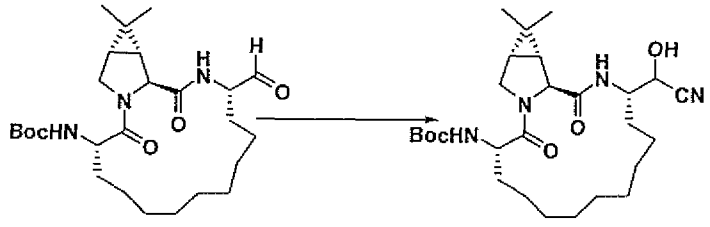
Step D



20d **20e**

A solution of alcohol **20d** (2.2 g, 4.58 mmol) in dry CH_2Cl_2 (50 mL) was treated with Dess-Martin reagent (2.91 g, 6.880 mmol) and stirred at rt for 2 h. The reaction mixture was diluted with aq. $Na_2S_2O_3$ (5%, 50 mL) and aq. saturated $NaHCO_3$ (50 mL) and stirred at rt. for 15 min. The reaction mixture was extracted with CH_2Cl_2 (500 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* to yield crude **20e** (1.9 g) that was used in the next reaction without further purification.

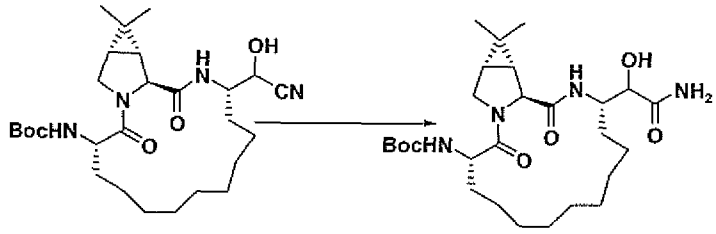
Step E



20e **20f**

A solution of crude **20e** (1.00 g, 2.094 mmol) in CH_2Cl_2 (15 ml) was cooled to 0° C and treated with acetone cyanohydrin (356 mg, 4.187 mmol) and triethylamine (424 mg, 4.187 mmol). The reaction mixture was stirred at 0° C for 12 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, EtOAc/Hexanes 1:5-->1:1) to yield **20f** (500 mg) as a colorless oil.

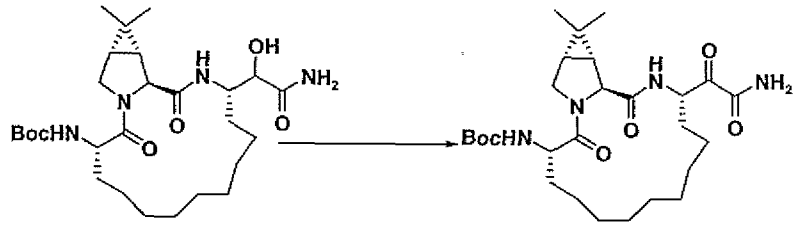
Step F



20f **20g**

A solution of cyanohydrin **20f** (500 mg, ~1.00 mmol) in DMSO (5 mL) was treated with H_2O_2 (5 mL), K_2CO_3 (276 mg, 2.00 mmol) and stirred at rt. for 12 h. The reaction mixture was diluted with aq. $Na_2S_2O_3$ (5%, 100 mL) and extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* to yield **20g** that was used as it is for further oxidation without purification.

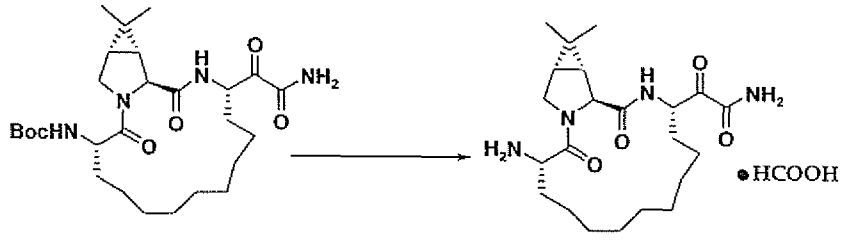
Step G:



20g **20h**

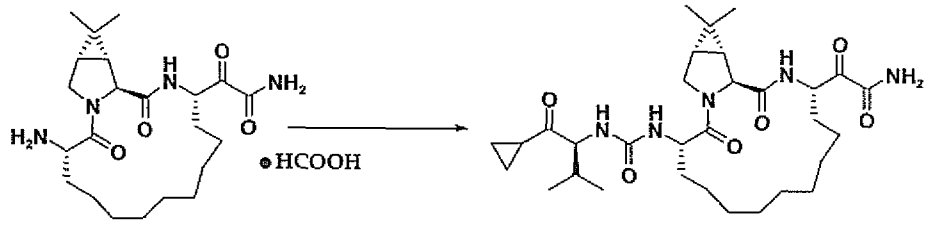
A solution of hydroxylamine **20g** (850 mg, 1.626 mmol) in toluene (5 mL) and DMSO (5 mL) was treated with EDCI (3.117 g, 16.26 mmol), and dichloroacetic acid (1.048 g, 8.13mmol, 698µL) and stirred at rt. for 3 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with aq. saturated $NaHCO_3$ (200 mL), aq. HCl (1 M,200 mL), brine (30 mL), dried ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 1:2) to yield **20h** (300 mg) as a colorless solid.

Step H:



20h **20i**

A solution of Boc protected ketoamide **20h** in formic acid (5 mL) was stirred at rt for 3 h and concentrated in *vacuo* and used as it is in the next step without further purification.

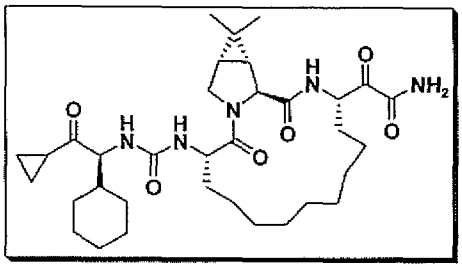


20i **20**

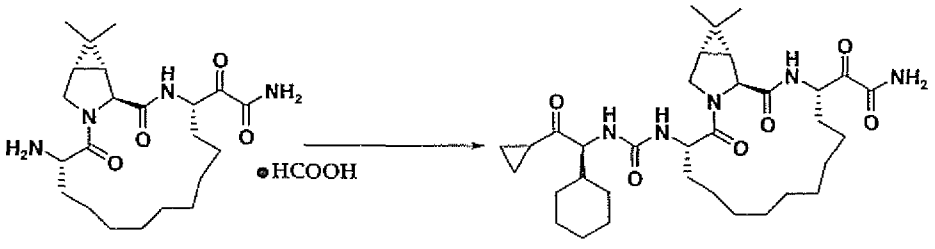
A solution of amine **20i** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M,

30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→50%) to yield ***20*** as a colorless solid. MS (*m/z*, relative intensity) 588 [$(M+H)^+$, 100], 421 (40). HRMS (ESI) Calcd. for $C_{31}H_{50}N_5O_6$: 588.3761 $(M+H)^+$; Found: 588.3751.

Preparative Example 21:



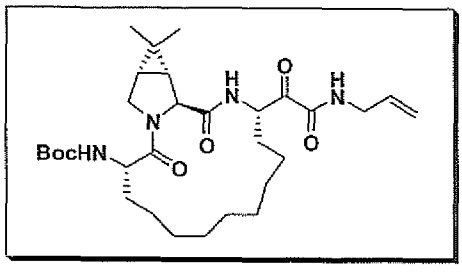
21



20i **21**

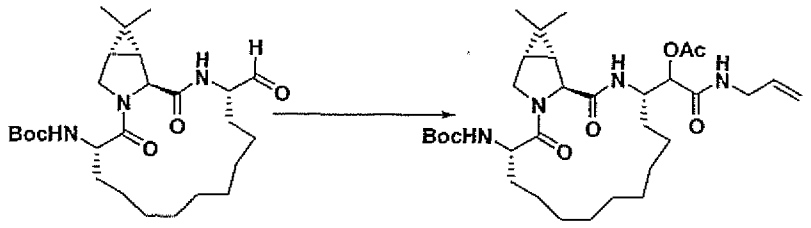
A solution of amine **20i** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of 2-cyclohexyl-1-cyclopropyl-2-isocyanato ethanone (0.15 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20 → 50%) to yield **21** as colorless solid.

Preparative Example 22



22

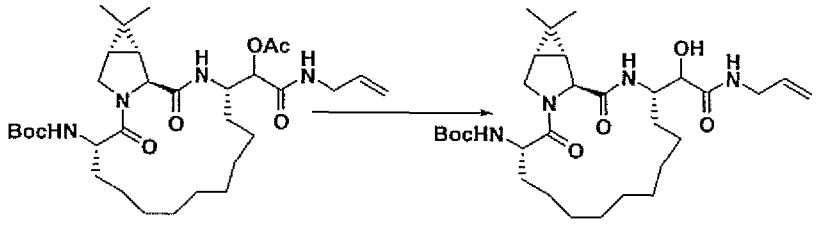
Step A:



20e **22a**

A solution of aldehyde **20e** (100 mg, 0.210 mmol) in methylene chloride (4 mL) was treated with allyl isocyanide (28.01 mg, 0.411 mmol) and acetic acid and stirred at rt. for 12 h. The reaction was concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:4→1:1) to obtain **22a** (75 mg) as colorless solid. MS (*m/z*, relative intensity) 605 [$(M+H)^+$, 100], 505 (98).

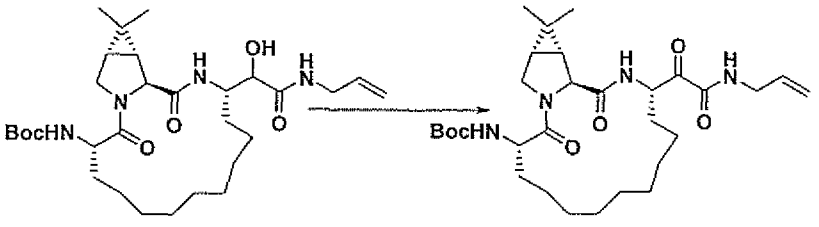
Step B:



22a **22b**

A solution of **22b** (275 mg, 0.454 mmol) in methanol (4 mL), THF(4.0 mL) and water (4.0 mL) was treated with $LiOH \cdot H_2O$ (22 mg, 0.55 mmol) and stirred at rt. for 2 h. The reaction mixture was diluted with aq. HCl (1 M, 30 mL) and extracted in CH_2Cl_2 (2x40 mL). The combined organic layer were dried ($MgSO_4$), filtered, concentrated in *vacuo*, and used as it is in next step without further purification.

Step C:

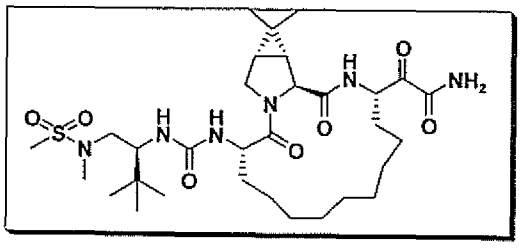


22b **22**

A solution of alcohol **22b** (300 mg, 0.534 mmol) in dry CH_2Cl_2 (15 mL) was treated with Dess-Martin reagent (453 mg, 1.06 mmol) and stirred at rt. for 2 h. The reaction mixture was diluted with aq. $Na_2S_2O_3$ (5%, 30 mL) and aq. saturated $NaHCO_3$ (30 mL) and stirred at rt. for 15 min. The reaction mixture was extracted with CH_2Cl_2

(3x50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 0:1→1:1) to yield **22** as a colorless solid. MS (*m/z*, relative intensity) 561 [$(M+H)^+$, 100], 461 (99). HRMS (ESI) Calcd. for $C_{31}H_{50}N_5O_6$: 588.3761 $(M+H)^+$; Found: 588.3751.

Preparative Example 23



23

Step A:

23a **23b**

A solution of amine **23a** (900 mg, 3.40 mmol) in CH_2Cl_2 at 0 °C was treated with NMM (511 mg, 5.10 mmol) and methanesulfonyl chloride (585 mg, 5.10 mmol) and stirred at 0 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with excess aq. HCl (1M, 500 mL). The organic layer was dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Hex/EtOAc 1:9→1:1) to yield methylsulfonamide **23b** (1.00 g).

Step B:

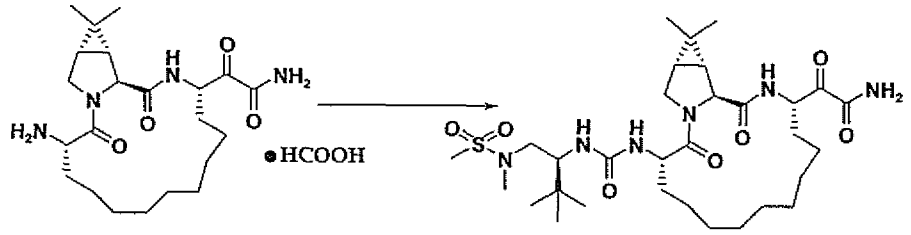
23b **23c**

A solution methanesulfonamide **23b** (1.0 g, 2.9 mmol) in methanol (30 mL) was treated with palladium (200 mg, 10% wt/C) and hydrogenated at 60 psi for 3 h. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated in *vacuo*. The residue was directly used in further reaction without further purification.

A solution of deprotected amine in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0°C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer

was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 10 mL toluene, concentrated the methylene chloride layer and used as a solution of **23c**.

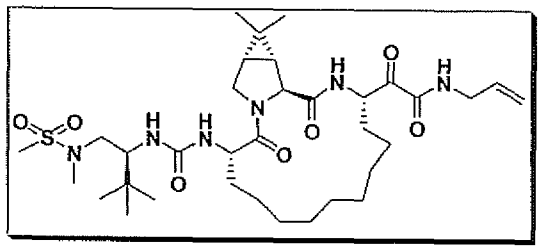
Step C:



20i **23**

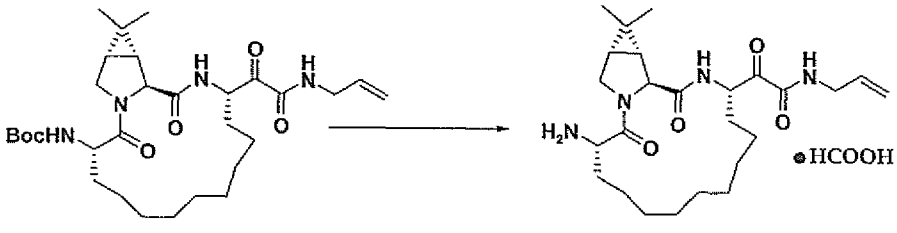
A solution of amine **20i** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate **23** in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→50%) to yield **23**. MS (*m/z*, relative intensity) 693 [$(M+K)^+$, 10], 677 [$(M+Na)^+$, 20], 655 [$(M+H)^+$, 100], 449 (30), 421 (30); HRMS (ESI) Calcd. for $C_{31}H_{54}N_6O_7SNa$ 677.3672 $(M+Na)^+$; Found: 677.3685.

Preparative Example 24



24

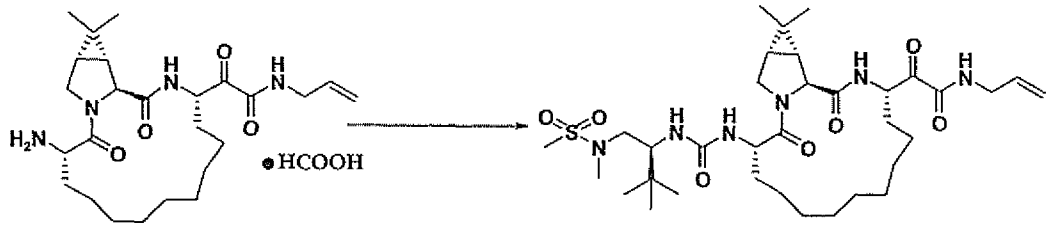
Step A:



22 **24a**

A solution of Boc protected ketoamide **22** (220 mg, 0.39 mmol) in formic acid (5 mL) was stirred at rt. for 3 h and concentrated in *vacuo* and used as it is in the next step without further purification.

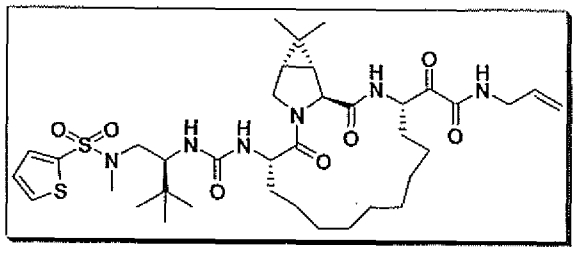
Step B:



24a **24**

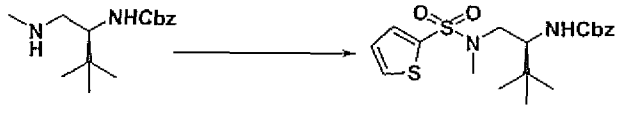
A solution of amine **24a** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→50%) to yield **24** (27 mg) MS (*m/z*, relative intensity) 734 [$(M+K)^+$, 10], 695 [$(M+H)^+$, 100], 461 (20), 443 (20); HRMS (FAB) Calcd. for $C_{34}H_{59}N_6O_7S$ 695.4166 $(M+H)^+$; Found: 695.4161.

Preparative Example 25



25

Step A:



23a 25a

A solution of amine **23a** (900 mg, 3.40 mmol) in CH_2Cl_2 at 0 °C was treated with NMM (511 mg, 5.10 mmol) and thiophene sulfonyl chloride (928 mg, 5.10 mmol) and stirred at 0 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL)

and washed with excess aq. HCl (1M, 500 mL). The organic layer was dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Hex/EtOAc 1:9→1:1) to yield sulfonamide **25a** (1.00 g) of colorless solid.

Step B:

25a 25b

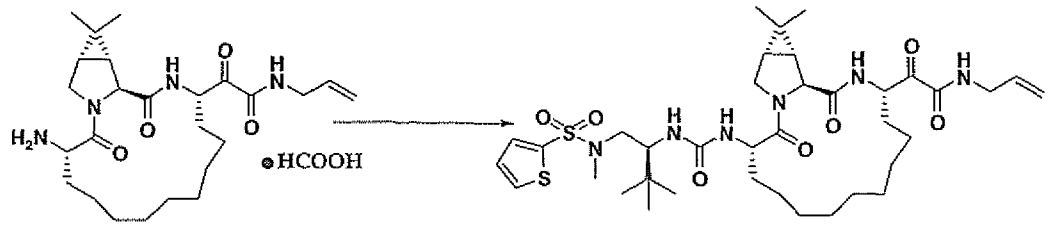
A solution of Cbz-protected compound **25a** (1.00 g, 2.118 mmol) was treated with TFA (30 mL) and dimethylsulfide (7.78 mL) at 0° C and stirred at rt. for 3 h. The reaction mixture was concentrated in *vacuo* and diluted with aq. NaOH (100 mL). The amine was extracted with methylene chloride (2x100 mL) and the combined organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and to yield **25b** (800 mg) that was used in further reaction without purification. MS (*m/z*, relative intensity) 277 [$(M+H)^+$, 100], 190 (50).

Step C:

25b 25c

A solution of deprotected amine **25b** (800 mg, 2.9 mmol) in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 10 mL toluene, concentrated the methylene chloride layer and used as a solution of **25c.**

Step D:

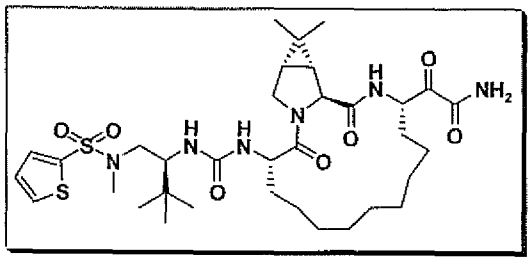


24a **25**

A solution of amine **24a** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in

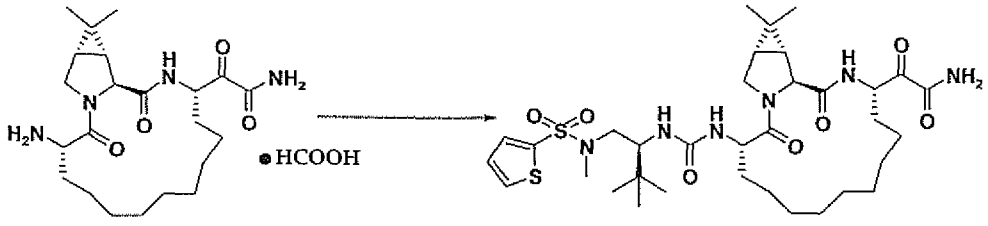
CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 50%) to yield **25** (39 mg) as a colorless solid. MS (*m/z*, relative intensity) 801 [$(M+K)^+$, 10], 763 [$(M+H)^+$, 100], 461 (15), 277 (20); HRMS (ESI) Calcd. for $C_{37}H_{58}N_6O_7S_2Na$ 785.3706 $(M+Na)^+$; Found: 785.3706.

Preparative Example 26



26

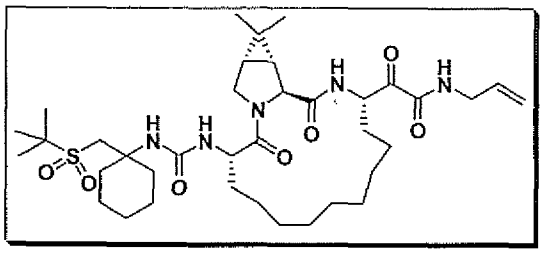
Step A:



20i 26

A solution of amine **20i** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 50%) to yield **26** as colorless solid (31 mg). MS (*m/z*, relative intensity) 761 [$(M+K)^+$, 10], 720 [$(M+H)^+$, 100], 421 (20); HRMS (ESI) Calcd. for $C_{34}H_{54}N_6O_7S_2Na$ 745.3393 $(M+Na)^+$; Found: 745.3396.

Preparative Example 27



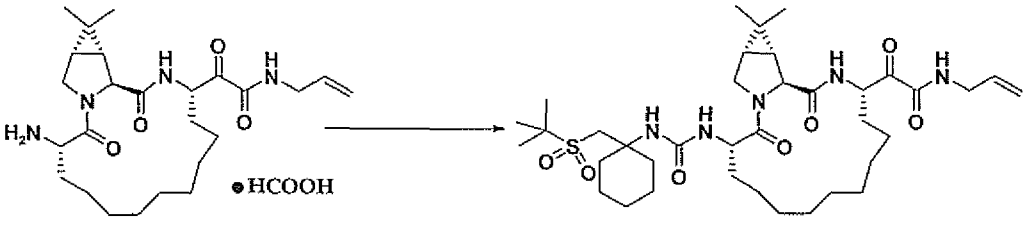
27

Step A:

27a **27b**

A solution of acid **27a** (100 mg, 0.385 mmol) in toluene (5 mL) was treated with DPPA (116.5 mg, 0.425 mmol) and Et_3N (42.5 mg, 0.425 mmol) and stirred at reflux for 1.5 h. The reaction mixture was diluted with saturated $NaHCO_3$ (30 mL) and extracted into CH_2Cl_2 (2x20 mL). The combined organic layers were washed with aq. $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$), filtered, concentrated in *vacuo*, and used as a solution of isocyanate in toluene.

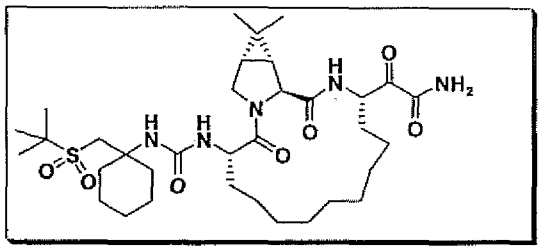
Step B:



24a **27**

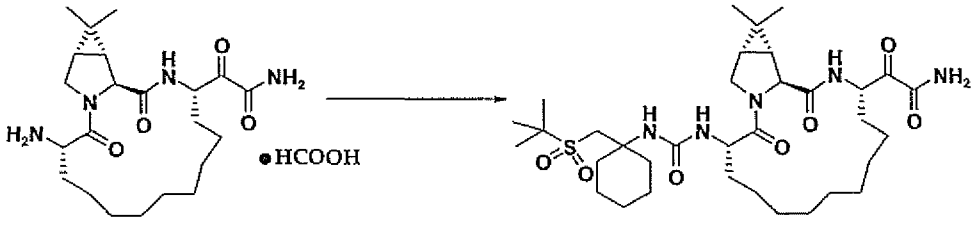
A solution of amine **24a** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (3 equiv) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→50%) to yield 27 as a colorless solid. MS (*m/z*, relative intensity) 720 [$(M+H)^+$, 85], 461(100); HRMS (ESI) Calcd. for $C_{37}H_{61}N_5O_7SNa$ 742.4189 $(M+Na)^+$; Found: 742.4200.

Preparative Example 28



28

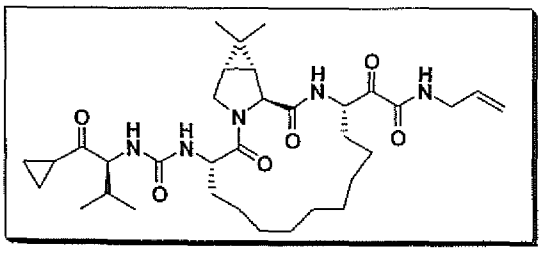
Step A:



20i **28**

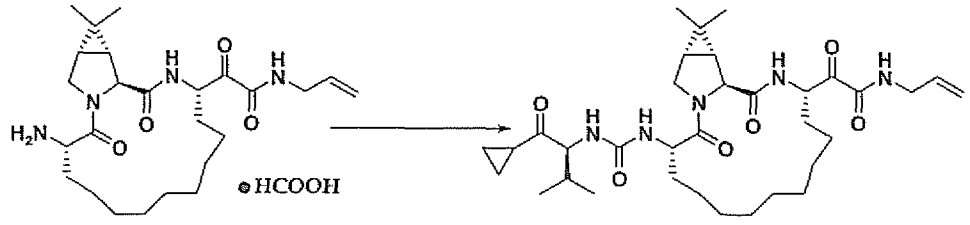
A solution of amine **20i** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (3.00 equiv) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 60%) to yield **28** (29 mg) as a colorless solid. MS (*m/z*, relative intensity) 718 [$(M+K)^+$, 10], 702 [$(M+Na)^+$, 20], 680 [$(M+H)^+$, 80], 421 (100); HRMS (ESI) Calcd. for $C_{34}H_{57}N_5O_7SNa$ 702.3876 $(M+Na)^+$; Found: 702.3889.

Preparative Example 29



29

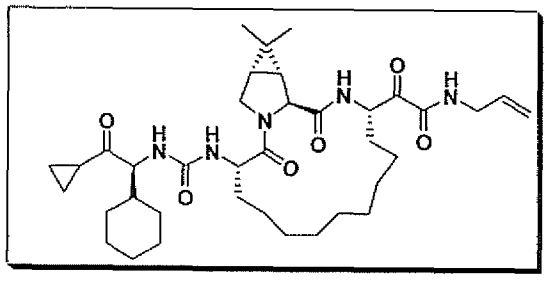
Step A:



24a 29

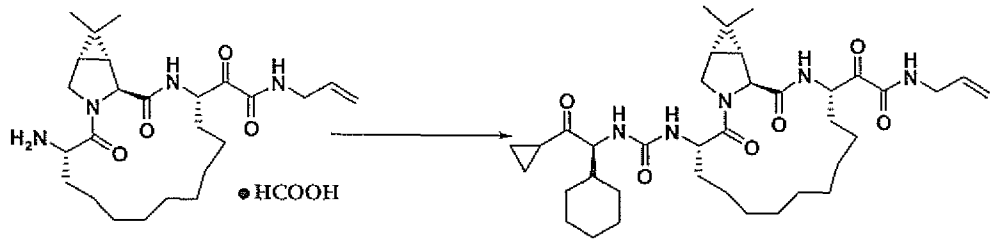
A solution of amine **24a** (50 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20 → 50%) to yield **29** as a colorless solid (41 mg). MS (*m/z*, relative intensity) 628 [$(M+H)^+$, 100], 129 (35).

Preparative Example 30



30

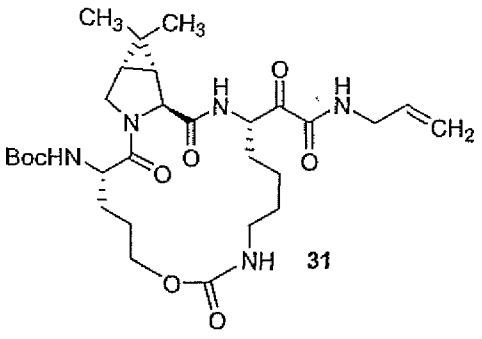
Step A:



24a 30

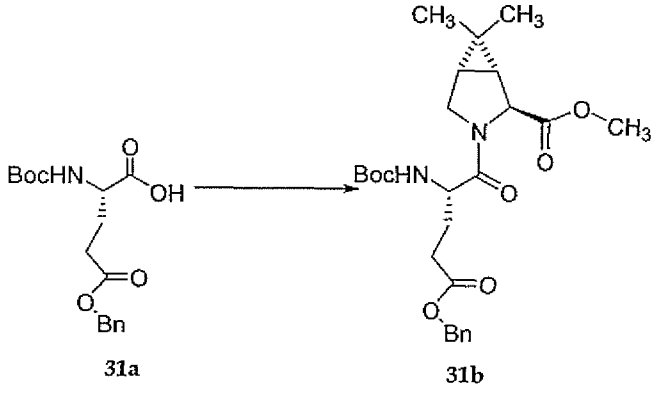
A solution of amine **24a** (50 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate (3.0 equiv.) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 50%) to yield **30** as a colorless solid. MS (*m/z*, relative intensity) 668 [$(M+H)^+$, 100], 169 (50), 128 (80).

Preparative Example 31: Preparation of:



31

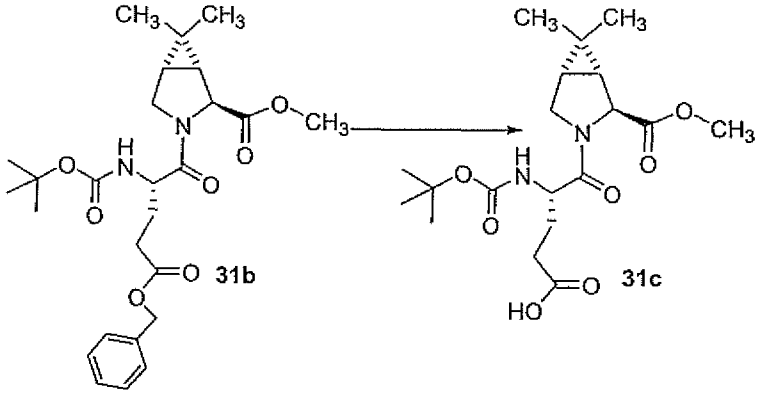
Step A:



31a 31b

A solution of Boc-Glu-OBn **31a** (1.8 g, 5.36 mmol) and amine **1d** (1 g, 4.87 mmol) was reacted as in preparative example 1, step C and purified by silica gel chromatography (10% to 25% EtOAc/hexanes) to give **31b** (1.28 g).

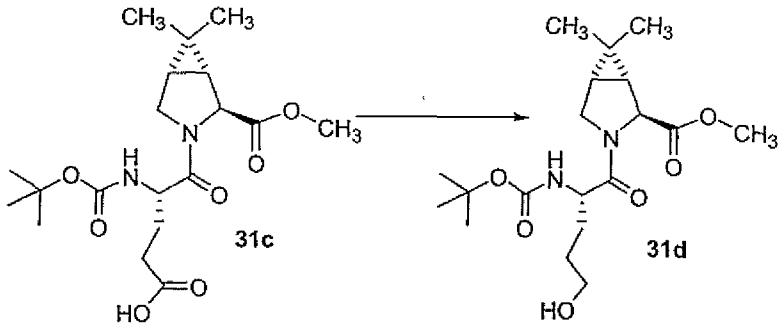
Step B:



31b 31c

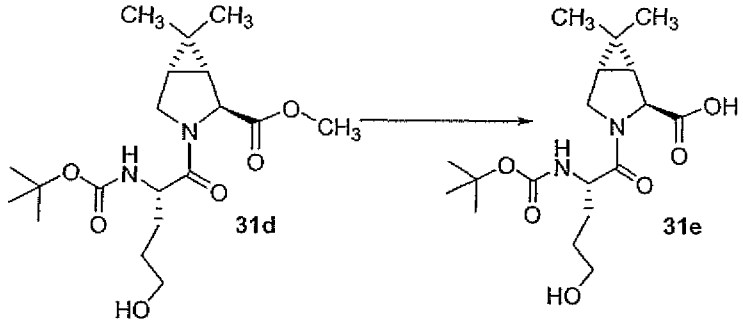
A solution of benzyl ester **31b** (1.25 g, 2.56 mmol) was treated with 10% Pd/C in EtOH and hydrogenated (1 atm., rt.) for 12 hours. The reaction mixture was filtered through a plug of celite and concentrated under vacuum to give **31c** (997 mg) which was used in the next reaction without further purification.

Step C



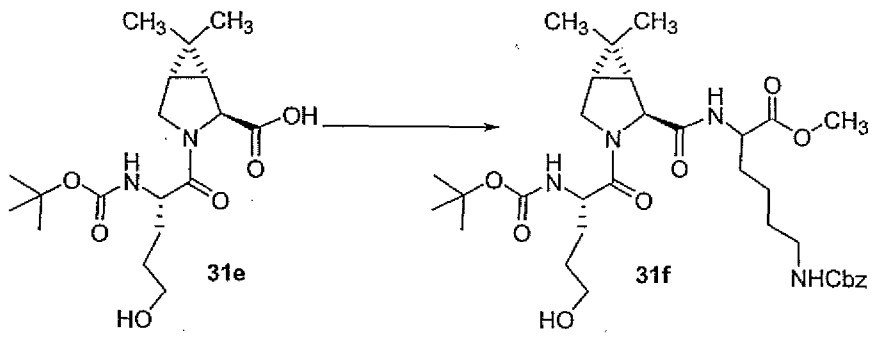
A solution of acid **31c** (20.4 g, 48.7 mmol) in THF (300 ml) was cooled to 0°C and treated with Et_3N (7.47 ml, 53.6 mmol) and ethyl chloroformate (4.89 ml, 51.2 mmol) and stirred for 2 hours. The white precipitate formed was filtered and washed with cold THF. The filtrate was cooled to 0°C and $NaBH_4$ (2.39 g, 63.4 mmol) was added. MeOH (20ml) was added dropwise over 1 hour and stirred for an additional 2.5 hours. Solvent was removed under vacuum, CH_2Cl_2 added and washed with water, brine and dried over Na_2SO_4. Na_2SO_4 was filtered and solvent removed to dryness. The residue was purified by silica gel chromatography (50% to 90% EtOAc/hexanes) to give **31d** (8.15 g).

Step D:



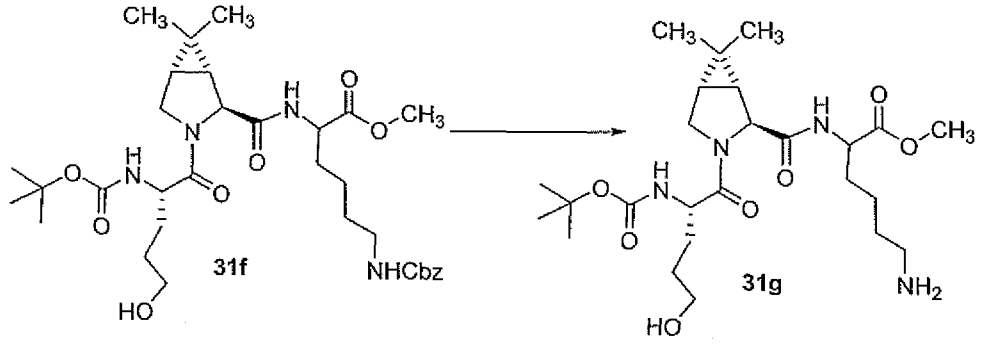
A solution of ester **31d** (8 g, 20.8 mmol) in MeOH (120 ml) and H_2O (24 ml) was treated with $LiOH \cdot H_2O$ (2.62 g, 62.5 mmol) at room temperature for 12 hours. Solvent was removed under vacuum to dryness. CH_2Cl_2 was added and stirred for 5 minutes with 1N. HCl (72.9 mmol). CH_2Cl_2 layer was separated, washed with brine and dried over Na_2SO_4. Na_2SO_4 was filtered and solvent was removed to dryness to give white solid **31e** (7.65 g).

Step E:



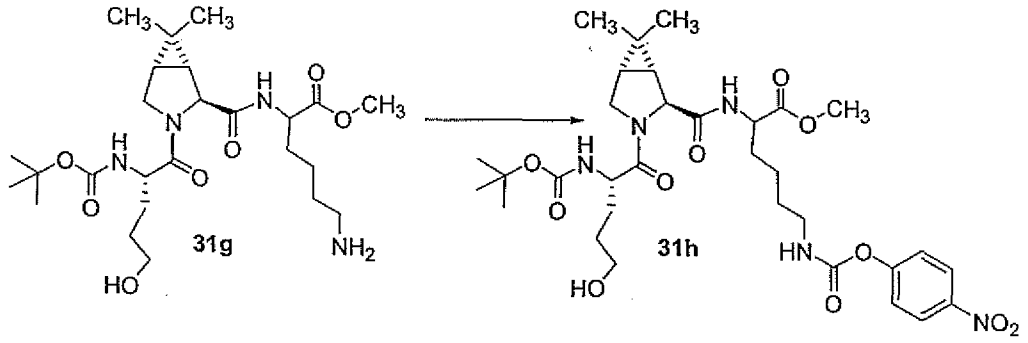
A solution of acid **31e** in anhydrous DMF (75 ml) and anhydrous CH_2Cl_2 (75 ml) was cooled to 0 °C and stirred with HOOBt (3.68 g, 22.5 mmol), NMM (6.77 ml, 61.6 mmol) and EDCI (5.11 g, 26.7 mmol) for 5 minutes. H-Lys(Z)-OMe•HCl (7.13 g, 21.5 mmol) was added and stirred for 3.5 hours at 0 °C. Reaction was held 12 hours at 5 °C after which CH_2Cl_2 was removed, EtOAc added and washed with sat. $NaHCO_3$, 5% H_3PO_4, Brine and filtered through Na_2SO_4. Solvent was removed under vacuum to dryness to give **31f** (12.7g).

Step F



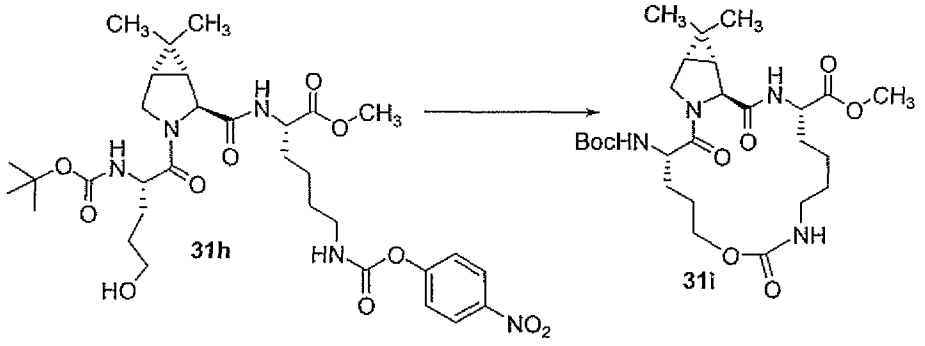
A solution of **31f** (5.5 g, 8.51 mmol) was treated with 10% Pd/C in EtOH (100 ml) and hydrogenated (1atm., rt.) for 12 hours. The reaction mixture was filtered through a plug of celite and concentrated under vacuum to give **31g** (4.25 g).

Step G:



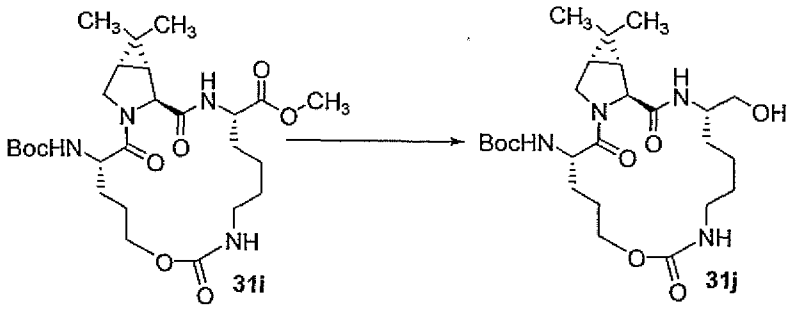
A solution of amine **31g** (4.25 g, 8.3 mmol) in anhydrous CH_2Cl_2 (750 ml) was stirred with triethylamine (1.5 ml, 10.7 mmol) and 4-nitrophenyl chloroformate (2.0 g, 9.96 mmol) at room temperature for 5 hours. Solvent was removed under vacuum to ~200 ml, then washed with sat. $NaHCO_3$, water, 5% H_3PO_4, brine and filtered through Na_2SO_4. Na_2SO_4 was filtered and solvent was removed to give **31h** (5.82 g).

Step H:



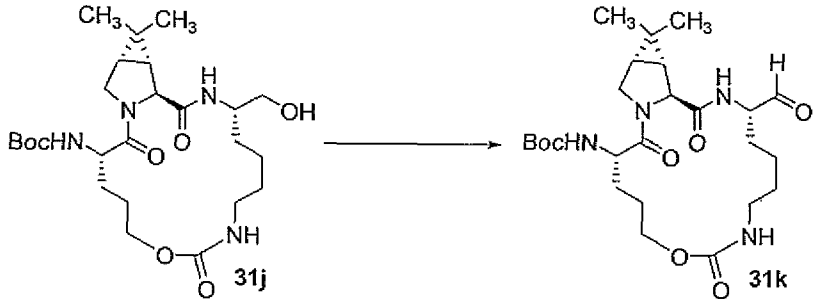
A solution of **31h** (5.8 g, 8.3 mmol) in anhydrous THF (600 ml) was treated with 60% NaH (996 mg, 24.9 mmol) at room temperature for 22 hours. Reaction was quenched by adding H_2O (5 ml) then 1N. HCl (50 ml) over 3 minutes. Solvent was removed under vacuum, CH_2Cl_2 was added and washed with 5% H_3PO_4, Brine and filtered through Na_2SO_4. Na_2SO_4 was filtered, solvent was removed and the residue was chromatographed on silica gel column with 0.25% to 3% MeOH/CH_2Cl_2 to give **31i** (2.86 g, 64 % yield).

Step I:



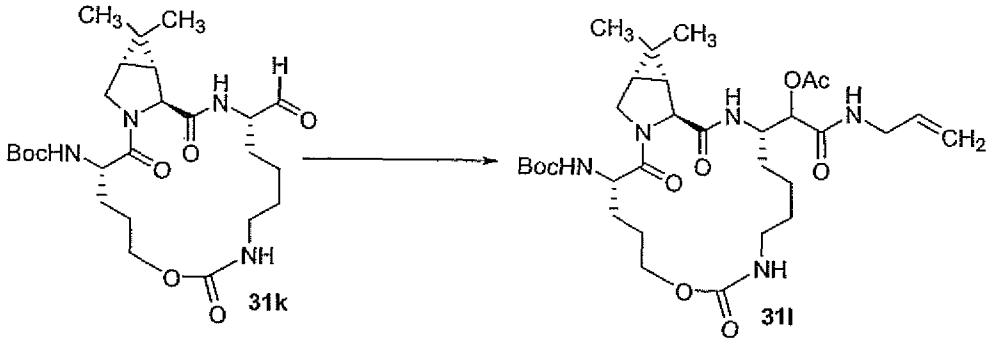
A solution of **31i** (613 mg, 1.13 mmol) was reacted as in preparative example 1, step F and purified by silica gel chromatography (3% to 6% MeOH/CH_2Cl_2) to give alcohol **31j** (500 mg).

Step J:



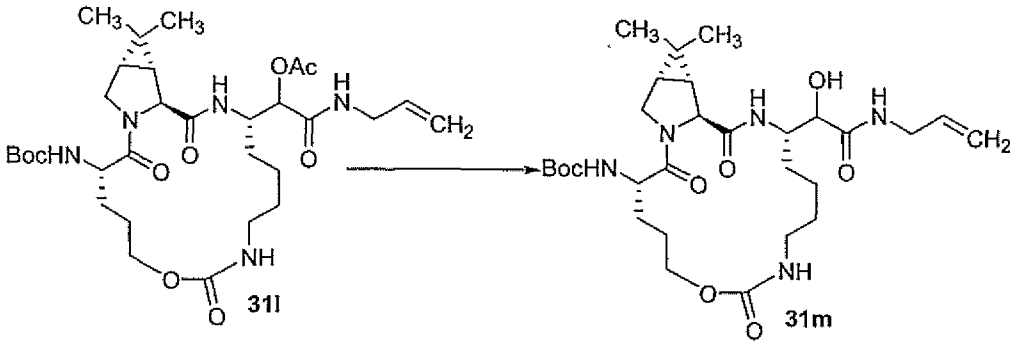
A solution of alcohol **31j** (480 mg, 0.94 mmol) was reacted as in preparative example 1, step H and purified by silica gel chromatography (30% to 60% acetone/hexanes) to give aldehyde **31k** (383 mg).

Step K:



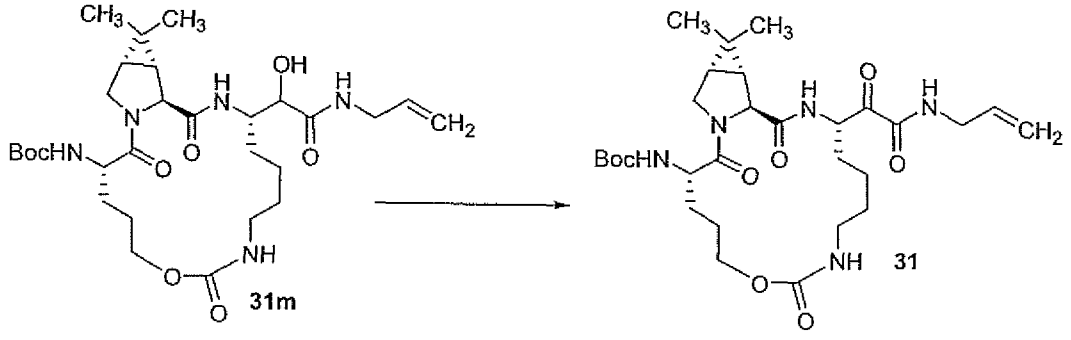
A solution of aldehyde **31j** (365 mg, 0.71 mmol) was reacted as in preparative example 22, step A and purified by silica gel chromatography (30% to 50% acetone/hexanes) to give **31k** (426 mg).

Step L:



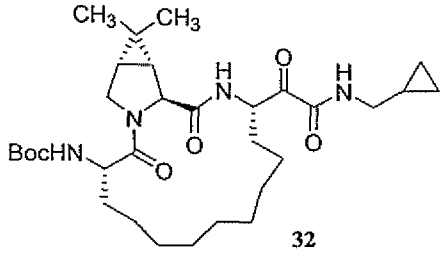
A solution of **31l** (357 mg, 0.56 mmol) was reacted as in preparative example 22, step B to give **31m** (426 mg).

Step M:

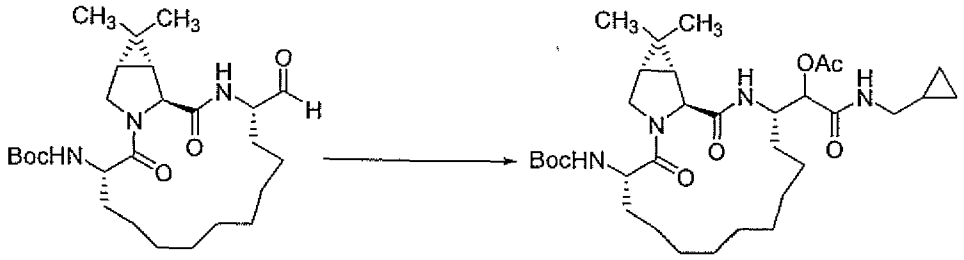


A solution of **31m** (350 mg, 0.59 mmol) was reacted as in preparative example 22, step C and purified by silica gel chromatography (30% to 50% acetone/hexanes) to give **31** (335 mg). MS (ES) *m/z* relative intensity 492 [(M-BOC+1)$^+$, 80]; 592 [(M+1)$^+$, 100]. Calcd. for $C_{29}H_{46}N_5O_8$ [M+1]$^+$: 592.3346; Found 592.3359.

Preparative Example 32: Preparation of:



Step A:

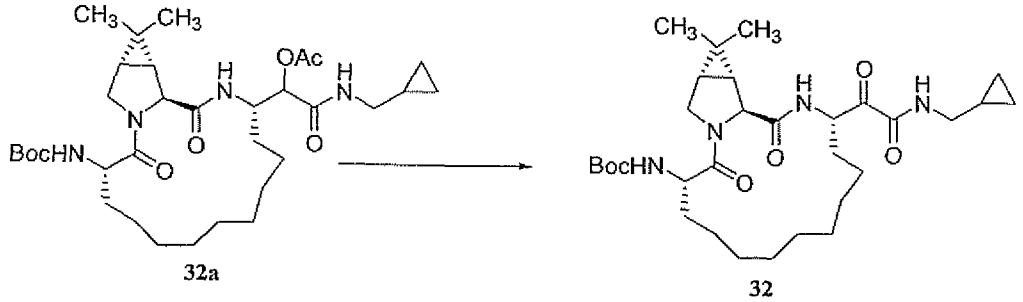


20 e 32a

A solution of aldehyde **20e** (200 mg, 0.42 mmol) in methylene chloride (10 mL) was treated with cyclopropylmethylisocyanide (66.5 mg, 4.11 mmol) and acetic acid (50 mg, 0.82 mmol) and stirred at rt. for 12 h. The reaction was concentrated in *vacuo* and residue was purified by chromatography (SiO_2, acetone/hexanes 1:9◊1:1) to obtain **32a** (230 mg).

MS (ES) *m/z* relative intensity 641 [$(M+Na)^+$, 70]; 619 [$(M+1)^+$, 100], 519 (50).

Step B:



32a 32

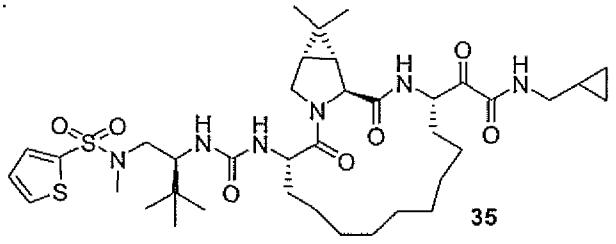
A solution of acetate **32a** (230 mg, 0.371 mmol) in methanol (5.0 mL), THF (5.0 mL) and water (5.0 mL) was treated with $LiOH•H_2O$ (25 mg, 0.55 mmol) and stirred at rt. for 1 h. The reaction mixture was diluted with aq. HCl (1 M, 30 mL) and extracted in CH_2Cl_2 (2 x 50 mL). The combined organic layer were dried ($MgSO_4$), filtered, concentrated in *vacuo*, and used as it is in next step without further purification.

A solution of alcohol in dry CH_2Cl_2 (15 mL) was treated with Dess-Martin reagent (237 mg, 0.558 mmol) and stirred at rt. for 2 h. The reaction mixture was diluted with aq. $Na_2S_2O_3$ (5%, 30 mL) and aq. saturated $NaHCO_3$ (30 mL) and stirred at rt. for 15 min. The reaction mixture was extracted with CH_2Cl_2 (3x50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 0:1→1:1) to yield **32** as a colorless solid (275 mg)

MS (ES) *m/z* relative intensity 629 [$(M+isobutene)^+$, 40], 575 [$(M+1)^+$, 100], 475 (90).

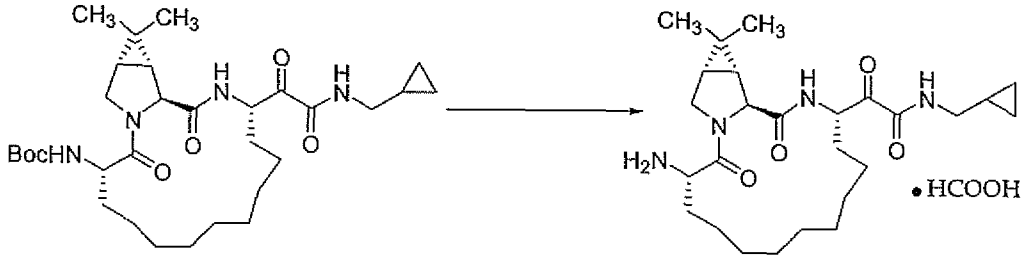
Similar procedures were used to synthesize compounds: ***33*** *and* ***34*** *using cyclopropyl and ethyl isocyanide for Step A: preparative example 32:*

Preparative Example 35: Preparation of:



35

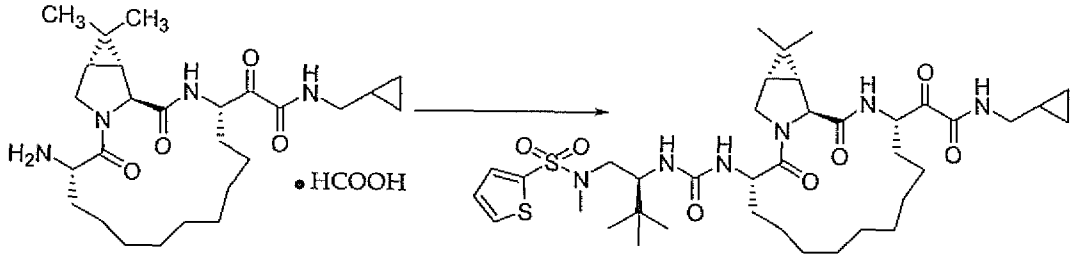
Step A:



32 35a

32 (200 mg, 0.39 mmol) was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield **35a** and used in further reactions without purification.

Step B:

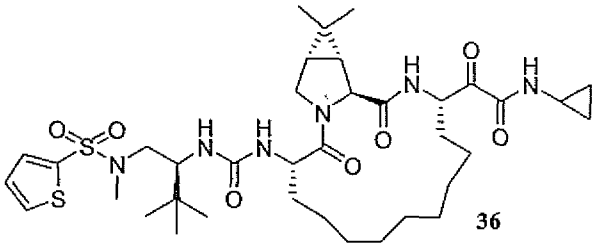


35a 35

A solution of amine **35a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield ***35*** as a colorless solid.

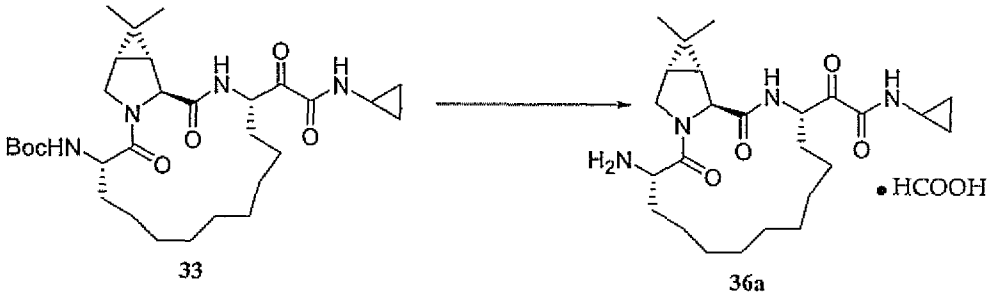
MS (ES) *m/z* relative intensity 799 [$(M+Na)^+$, 60]; 777 [$(M+1)^+$, 100].

Preparative Example 36: Preparation of:



36

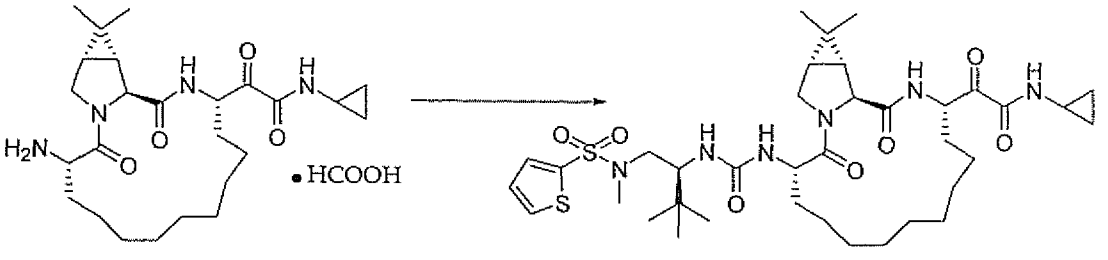
Step A:



33 36a

33 (200 mg, 0.39 mmol) was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield **36a** and used in further reactions without purification.

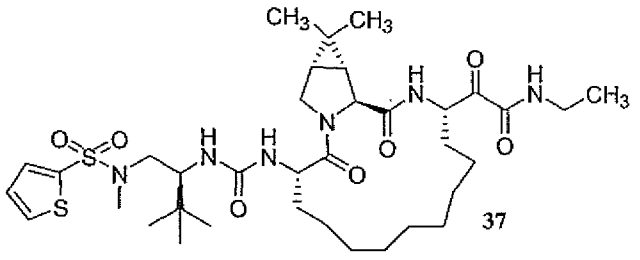
Step B:



36a 36

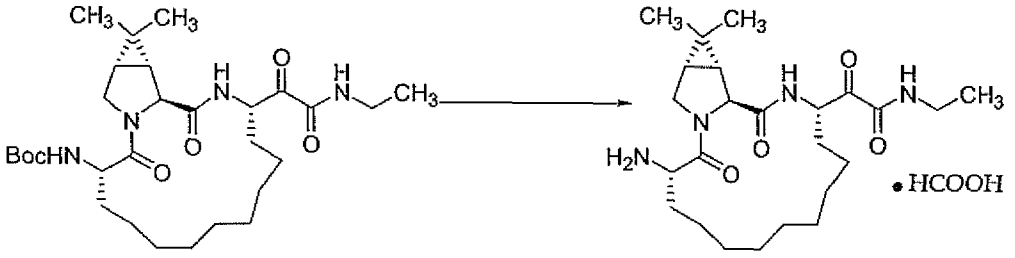
A solution of amine **36a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 0→100%) to yield **36** as a colorless solid. MS (ES) *m/z* relative intensity 785 [$(M+Na)^+$, 50]; 763 [$(M+1)^+$, 100]; 593 (60).

Preparative Example 37: Preparation of:



37

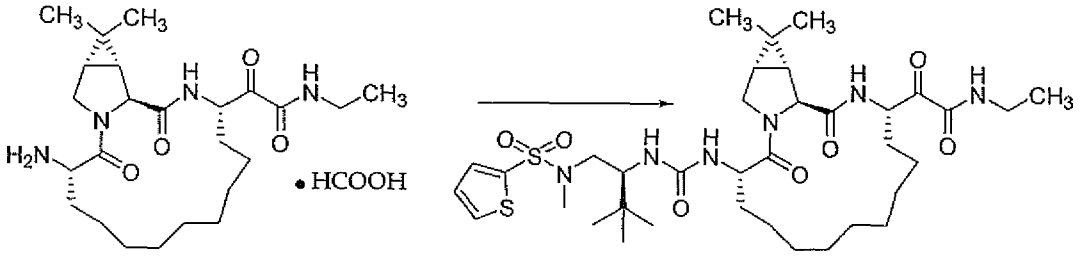
Step A:



34 37a

34 (200 mg, 0.39 mmol) was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield **37a** and used in further reactions without purification.

Step B:

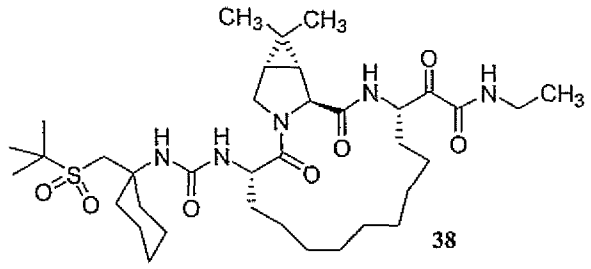


37a 37

A solution of deprotected amine **37a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield **37**.

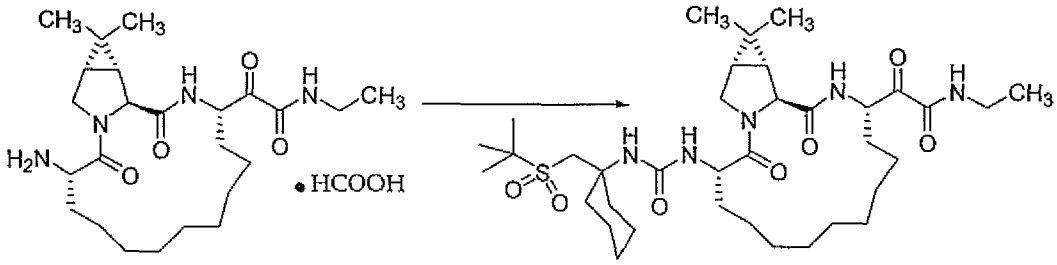
MS (ES) *m/z* relative intensity 773 [$(M+Na)^+$, 100]; 751 [$(M+1)^+$, 70].

Preparative Example 38: Preparation of:



38

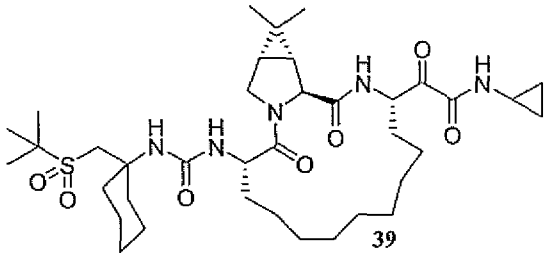
Step A:



37a 38

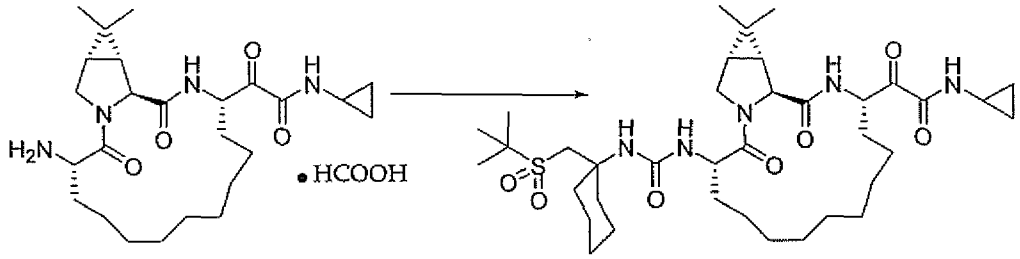
A solution of deprotected amine **37a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (1.5 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50◊ 100%) to yield ***38*** as colorless solid. MS (ES) *m/z* relative intensity 730 [$(M+Na)^+$, 30]; 708 [$(M+1)^+$, 100]; 409 (30).

Preparative Example 39: Preparation of:



39

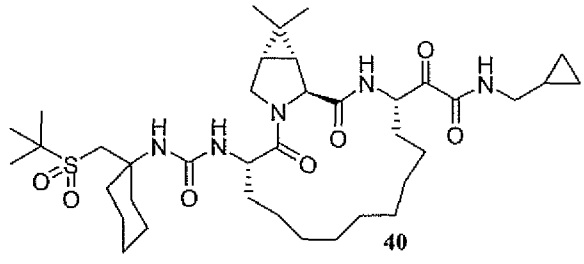
Step A:



36a 39

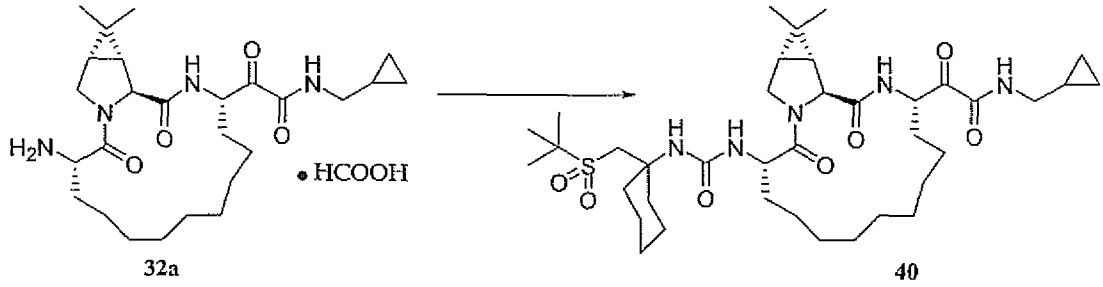
A solution of amine **36a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (1 mL, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield **39**. MS (ES) *m/z* relative intensity 742 [$(M+Na)^+$, 70]; 720 [$(M+1)^+$, 100]; 461 (40). HRMS Calcd. for $C_{37}H_{62}N_5O_7S$ [M+1]$^+$: 720.4370; Found 720.4350.

Preparative Example 40: Preparation of:



40

Step A:



32a 40

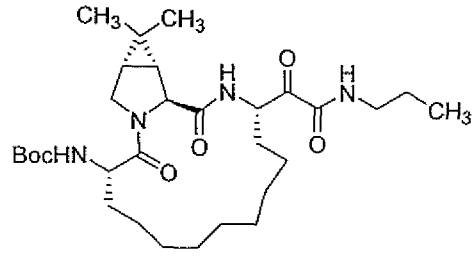
A solution of amine **32a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (1 mL, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered

concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield **40.**

^{1}H NMR(dmso, 500 MHz), δ, 8.80 (t, 1 H, *J*=6.0 Hz), 8.37 (d, 1 H, *J*=9.5 Hz), 6.22 (d, 1 H, *J*=8.8 Hz), 5.88 (s, 1 H), 5.31 (dt, 1 H, *J*=2.8 & 9.5 Hz), 4.35 (s, 1 H), 4.28-4.22 (m, 1 H), 3.85 (d, 1 H, *J*=10 Hz), 3.76 (q, 1 H, *J*=5.4 Hz), 3.59 (t, 1 H, *J*=13.5 Hz), 3.41 (d, 1 H, *J*=13.9 Hz), 3.07-2.95 (m, 2 H), 2.22-2.15 (m, 2 H), 1.69-1.00 (b, 23 H), 1.25 (s, 9 H), 0.99 (s, 3 H), 0.99-0.70 (m, 1 H), 0.88 (s, 3 H), 0.42-0.38 (m, 2 H), 0.21-0.18 (m, 2 H).

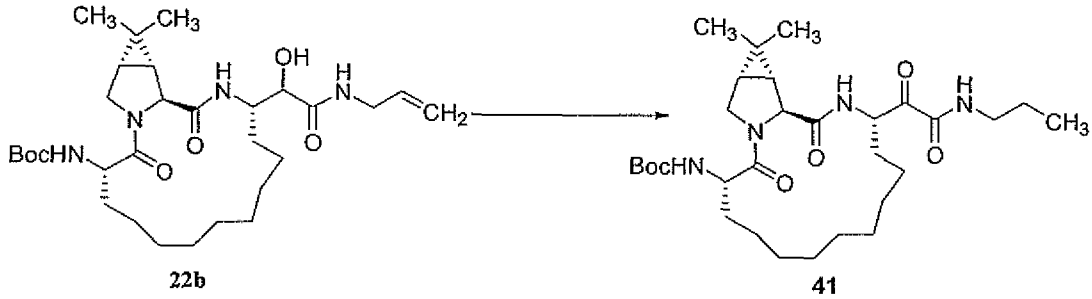
^{13}C NMR (dmso, 125 MHz) δ, 198.5, 172.1, 171.3, 162.0, 157.3, 60.5, 60.1, 54.4, 52.8, 51.5, 47.6, 43.8, 35.4, 35.1, 34.8, 32.3, 31.6, 31.4, 28.3, 28.0, 27.9, 27.3, 26.9, 26.6, 25.8, 25.6, 24.6, 23.4, 22.4, 21.5, 19.5, 13.7, 11.5. MS (ES) *m/z* relative intensity 756 [(M+Na)$^+$, 45]; 734 [(M+1)$^+$, 100]; 475 (20). HRMS cacld. for $C_{38}H_{64}N_5O_7S$ [M+1]$^+$: 734.4526; Found 734.4535.

Preparative Example 41: Preparation of:



41

Step A:



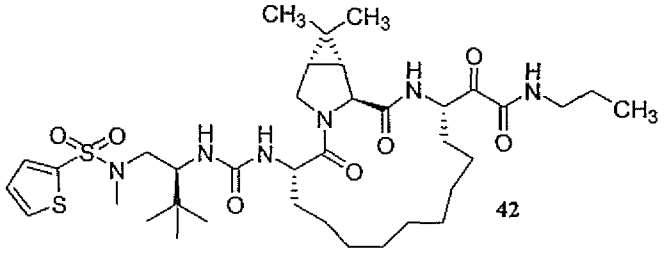
22b 41

A solution of intermediate **22b** (300 mg, 0.54 mmol) was taken in methanol (25 mL) and treated with 10% Pearlman's catalyst and hydrogenated at 50 psi for 4 h. The reaction mixture was filtered through a plug of celite® and concentrated in vacuo to yield reduced product that was used in further reaction without purification.

A solution of reduced alcohol in dry CH_2Cl_2 (5 mL) was treated with Dess-Martin reagent (350 mg, 0.82 mmol) and stirred at rt. for 2 h. The reaction mixture was

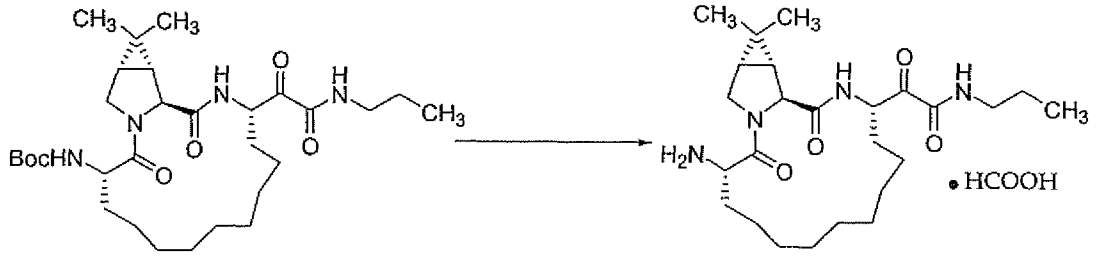
diluted with aq. $Na_2S_2O_3$ (5%, 30 mL) and aq. saturated $NaHCO_3$ (30 mL) and stirred at rt. for 15 min. The reaction mixture was extracted with CH_2Cl_2 (3x75 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 0:1 →1:1) to yield **41** (270 mg) as a colorless solid.

Preparative Example 42: Preparation of:



42

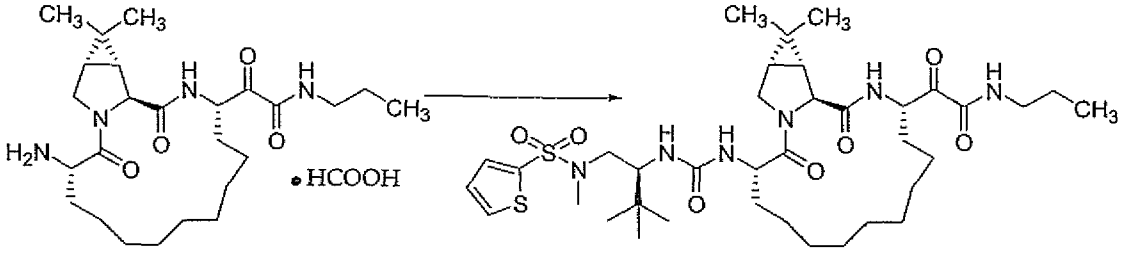
Step A:



41 **42a**

41 was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield **42a** and used in further reactions without purification.

Step B:

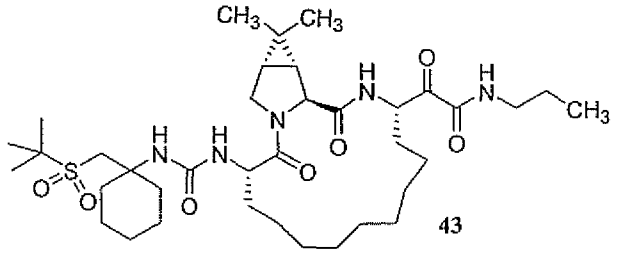


42a **42**

A solution of amine **42a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1.5 mL, 0.25 mmol, 0.38 mmol) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with

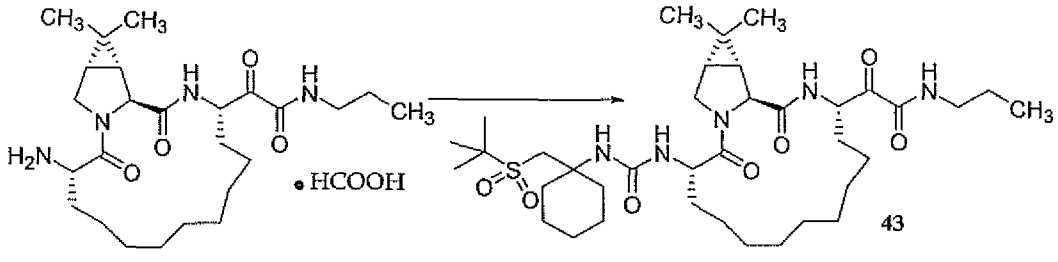
($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, Ethyl acetate/hexanes 1:1□ 1:0) yield **42** (65 mg) as a colorless solid. ^{1}H NMR (dmso, 500 MHz), δ, 8.71 (t, 1 H, *J*=6.3 Hz), 8.36 (d, 1 H, *J*=9 Hz), 8.00 (dd, 1 H, *J*=1.3 & 5.0 Hz), 7.65 (dd, 1 H, *J*=1.3 & 2.5 Hz), 7.25 (dd, 1 H, *J*= 3.8 &1.3 Hz), 6.15 (d, 1 H, *J*=9.0 Hz), 5.88 (d, 1 H, *J*=10 Hz), 5.31 (m, 1 H), 4.34 (s, 1 H), 4.30 (m, 1 H), 3.93 (d, 1 H, *J*=10.5 Hz), 3.79-3.75 (q, 1 H, *J*=5.0 Hz), 3.67-3.62 (dt, 1 H, *J*= 4.1 & 5.6 Hz), 3.12-3.05 (m, 2 H), 2.95-2.91 (m, 2 H), 2.67 (s, 3 H), 1.70-1.61 (m, 2 H) 1.40-1.00 (b, 20 H), 0.99 (s, 3 H), 0.85 (s, 3 H), 0.83 (s, 9 H), 0.83 (t, 3 H).^{13}C NMR (dmso, 125 MHz) □, 198.5, 172.0, 171.7, 162.2, 158.3, 137.7, 133.9, 133.1, 129.0, 60.5, 55.8, 55.7, 52.7, 51.6, 51.5, 47.6, 36.0, 35.0, 32.2, 31.6, 31.3, 28.5, 27.9, 27.4, 27.1, 26.9, 26.7, 26.3, 24.4, 22.8, 22.3, 19.5, 13.7, 12.1. MS (ES) *m/z* relative intensity 788 [$(M+Na)^+$, 50]; 765 [$(M+1)^+$, 100].

Preparative Example 43: Preparation of:



43

Step A:

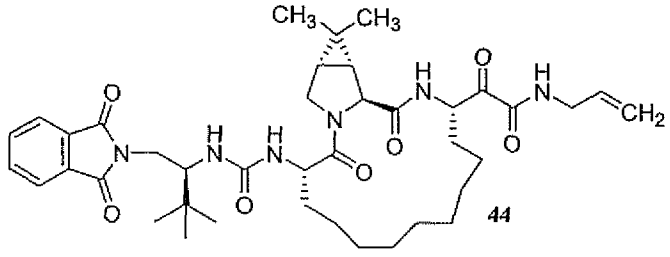


42a

A solution of amine **42a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (3 mL, 0.1 M soln., 0.3 mmol) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hexanes 1:1→ 1:0) yield **43** (42 mg) as a colorless solid.^{1}H NMR (dmso, 500 MHz) δ, 8.71 (t, 1 H, *J*=6.0 Hz), 8.36 (d, 1 H, *J*=9.0 Hz), 6.22 (d, 1 H, *J*=8.5 Hz), 5.88 (s, 1 H), 5.29 (dt, 1

H, *J*=9.5 & 2.5 Hz), 4.34 (s, 1 H), 4.23 (t, 1 H, *J*=9.0 Hz), 3.86 (d, 1 H, *J*=10.5 Hz), 3.76 (dd, 1 H, *J*=5.0 & 5.5 Hz), 3.60 (d, 1 H, *J*=13.5 Hz), 3.41 (d, 1 H, *J*=13.5 Hz), 3.13-3.04 (m, 2 H), 2.23-2.15 (m, 2 H), 1.67-0.9 (bm, 30 H), 1.25 (s, 9 H), 0.99 (s, 3 H), 0.88 (s, 3 H), 0.83 (t, 3 H, *J*=7.0 Hz). ^{13}C NMR (dmso, 125 MHz) δ, 198.5, 172.1, 171.3, 162.1, 157.3, 60.5, 60.1, 55.8, 54.3, 52.8, 51.0, 47.6, 35.4, 35.1, 32.3, 31.7, 31.3, 28.3, 28.0, 27.9, 27.3, 26.9, 26.6, 26.2, 25.8, 24.6, 23.3, 22.8, 21.5, 19.5, 13.7, 12.2. MS (ES) *m/z* relative intensity 744 [$(M+Na)^+$, 40]; 722 [$(M+1)^+$, 100].

Preparative Example 44: Preparation of:



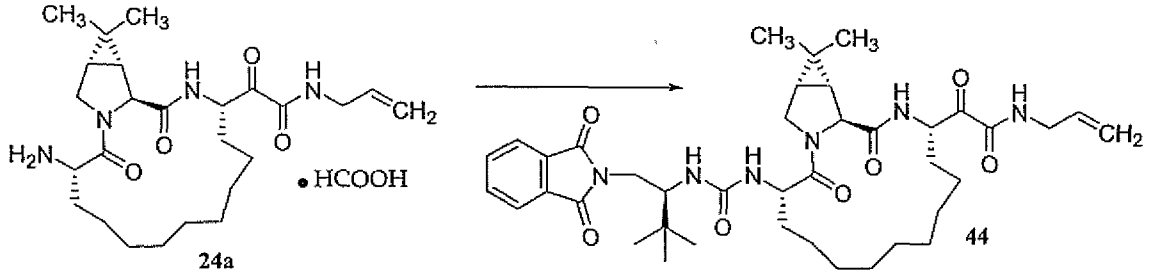
44

Step A:

44a 44b

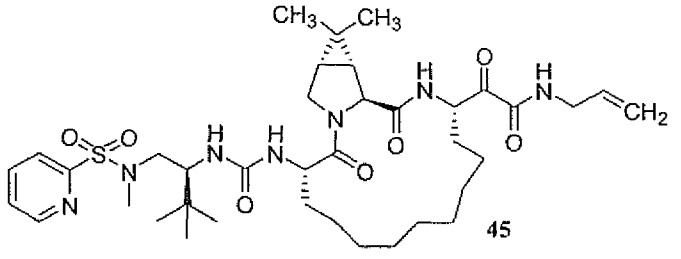
A solution of deprotected amine **44a** (**B**usacca, C. A.; Grossbach, D.; Spinelli, E. *Tetrahedron: Asymmetry*; **2000**, *9*, 1907) in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 10 mL toluene, concentrated the methylene chloride layer and used as a solution

Step B:

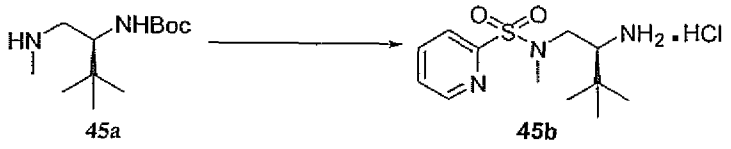


A solution of amine **24a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **44b** (2.5 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1□ 1:0) yield **44** (31 mg) as a colorless solid. MS (ES) *m/z* relative intensity 755 [$(M+Na)^+$, 40]; 733 [$(M+1)^+$, 100].

Preparative Example 45: Preparation of:



Step A:

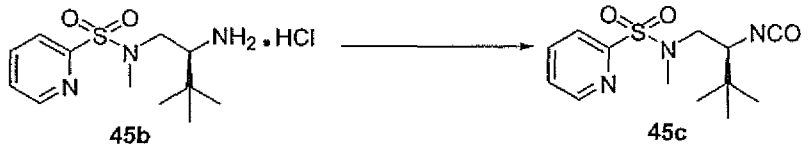


A solution of amine **45a*** (2.00 g, 9.20 mmol) in CH_2Cl_2 at 0 °C was treated with $(C_2H_5)_3N$ (3.7 g, 37 mmol) and 2-pyridinesulfonyl chloride (2.4 g, 11.2 and stirred at rt. for 12 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with excess aq. $NaHCO_3$ (1M, 500 mL). The organic layer was dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 0:1→1:1) to yield sulfonamide (2.3 g). A solution of Boc-protected amine was deprotected by dissolving (2.1 g, 5.7 mmol) in 4M soln. of HCl in dioxane and stirred

at rt. for 2 h. The reaction mixture was concentrated in *vacuo* and used as it is in next step without further purification.

* obtained by the protection of *tert*-leucine-N-methylamide (TCI-Jpn) with ditertbutyldicarbonate and subsequent reduction with BH_3•DMS in THF (reflux, 2 h).

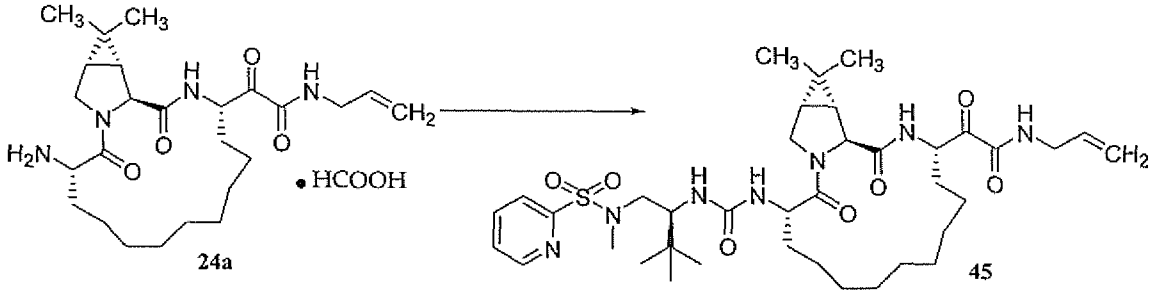
Step B:



45b 45c

A solution of amine **45b** (300 mg, 1 mmol) in CH_2Cl_2 (3 mL) aq. saturated $NaHCO_3$ (3 mL) at 0°C was treated with phosgene (2.5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 3 mL toluene, concentrated the methylene chloride layer and used as a solution.

Step C.

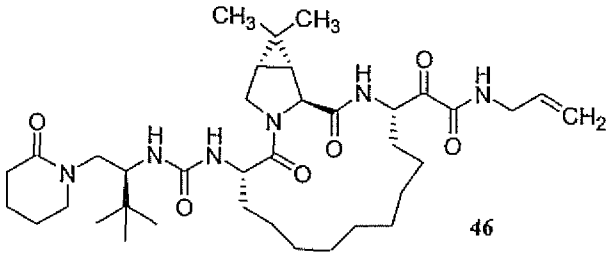


24a 45

A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **45c** (2.5 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1→ 1:0) yield product **45** as a colorless solid. The crude mixture was further purified using HPLC to yield pure product **45** (27 mg). ^{1}H NMR (dmso, 500 MHz) δ 8.89 (t, 1 H, *J*=7.0 Hz), 8.72 (d, 1 H, *J*=6.0 Hz), 8.37 (d, 1 H, *J*=10.5 Hz), 8.07 (t, 1 H, *J*=9.0 Hz), 7.88 (d, 1 H, *J*=9.0 Hz), 7.66 (dd, 1 H, *J*=6.5 &3.5 Hz), 6.12 (d, 1 H, *J*=11 Hz), 5.84-5.75 (m, 2 H), 4.27 (s, 1 H), 4.22 (bt, 1 H, *J*=11.5 Hz), 3.92 (d, 1 H, *J*=13 Hz), 3.77-3.60 (m, 4 H), 3.33 (bd, 1 H), 3.06 (bt, 1 H, *J*=12.5 Hz), 2.75 (s, 3 H),

1.68-1.59 (m, 2 H), 1.44-1.12 (m, 18 H), 0.98 (s, 3 H), 0.83 (s, 3 H), 0.78 (s, 9 H). ^{13}C NMR (dmso, 125 MHz) δ, 198.3, 172.1, 171.7, 162.1, 158.3, 157.1, 151.0, 139.6, 135.0, 127.9, 123.3, 116.4, 60.5, 55.8, 52.8, 52.2, 51.5, 36.4, 35.0, 28.0, 27.1, 26.9, 26.3, 19.5, 13.7.MS (ES) *m/z* relative intensity 780 [$(M+Na)^+$, 50]; 758 [$(M+1)^+$, 100].

Preparative Example 46: Preparation of:



46

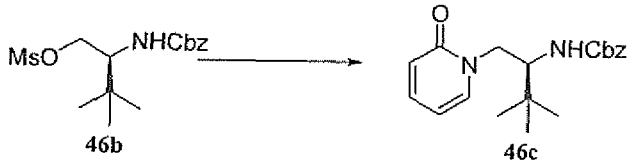
Step A:

46a **46b**

A solution of (S) –*tert*-leucinol (5.0 g, 42.7 mmol, Aldrich) **46a** at 0 °C in CH_2Cl_2 (100.0 mL) was treated with benzyl chloroformate (6.7 mL, 47.0 mmol), followed by Hunig's base (9.3 mL, 53.3 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (500 mL), washed with 10 % KH_2PO_4, followed by saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated to yield protected leucinol (10.7 g, 100%) that was used in further reaction without any purification.

To a solution of protected leucinol (crude) (10.7 g, 42.7 mmol) in CH_2Cl_2 (100.0 mL) at 0 °C was added pyridine (20.0 mL) and methanesulfonyl chloride (3.63 mL, 47.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight, concentrated, redissolved in ethyl acetate (500 mL), washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated and purified by flash chromatography over SiO_2 using ethyl acetate/hexane (1:4) to yield **46b** (14.0 g, 100 %).

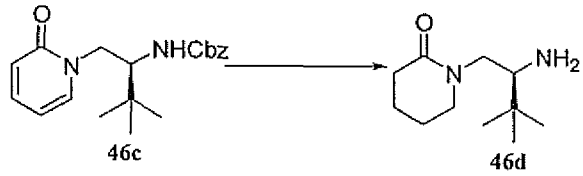
Step B:



46b **46c**

A solution of **46b** (3.1g, 9.9 mmol) in toluene (72 mL) containing water (400 μL) was treated with $(C_4H_9)_4NBr$ (582 mg, 1.8 mmol), K_2CO_3(2.72 g, 1.97 mmol) and 2-hydroxypyridine (937 mg, 9.85 mmol). The reaction mixture was refluxed overnight with stirring, filtered and the filtrate was concentrated in *vacuo*. The residue was purified by flash chromatography over SiO_2 using ethyl acetate/CH_2Cl_2 (1:9 to 1:1) to yield **46c** (1.15 g, 35 %) as a colorless oil.

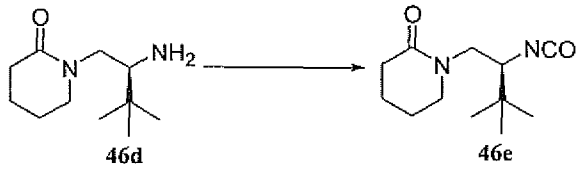
Step C:



46c 46d

A solution of pyridone **46c** (1.15 g) in MeOH (50 mL) was treated with Pd/C (10% w/w, 450 mg) and placed in a Parr® shaker and hydrogenated at 40 psi for 4 h. The reaction mixture was filtered through a plug of celite® and concentrated in *vacuo* to yield **46d** that was used in the next step without further purification.

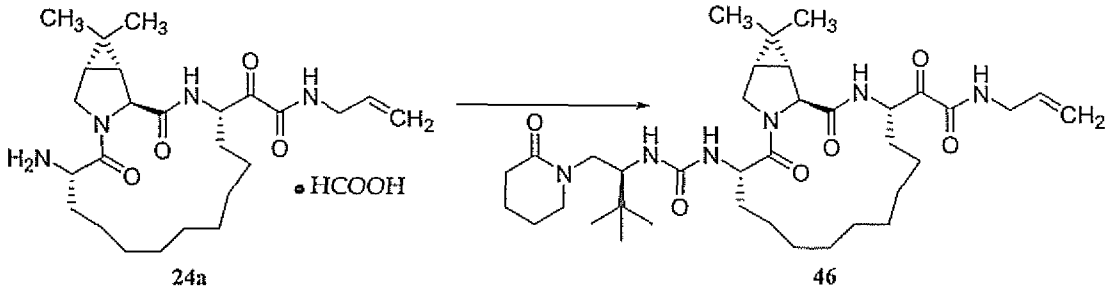
Step D:



46d 46e

A solution of amine **46d** (600 mg, 3.03 mmol) in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0° C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 3 mL toluene, concentrated the methylene chloride layer and used as a solution in toluene.

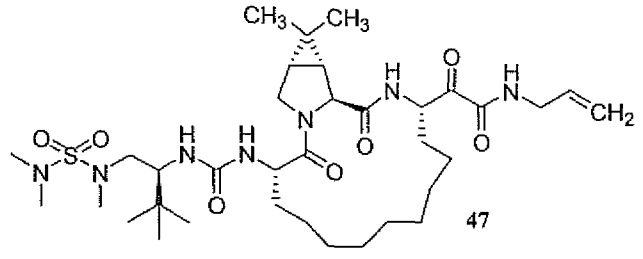
Step E:



24a 46

A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **46e** (1.5 mL, 0.25 mmol) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and
5 washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1◊ 1:0) and 100% ethyl acetate to yield **46** (30 mg) as a colorless solid. ^1H NMR (dmso, 500 MHz) δ, 8.92 (t, 1 H, *J*=6.5 Hz), 8.39 (d, 1 H, *J*=9.0 Hz), 6.17 (d, 1 H, *J*=9.0 Hz), 5.81 (m, 1 H), 5.69 (d, 1 H, *J*=10.5 Hz), 5.29 (bt, 1 H, *J*=10.0
10 Hz), 5.13-5.10 (m, 2 H), 4.33 (s, 1H), 4.30-4.26 (m, 1 H), 3.86-3.65 (m, 6 H), 3.50 (bt, 1 H, *J*=12 Hz), 3.15-3.08 (m, 2 H), 2.21-2.05 (m, 2 H), 1.74-1.54 (bm, 6 H), 1.46-1.11 (bm, 18 H), 0.99 (s, 3 H), 0.84 (s, 3 H), 0.82 (s, 9 H). ^{13}C NMR (dmso, 125 MHz) δ, 198.2, 172.1, 171.3, 169.3, 162.1, 158.2, 135.0, 116.4, 60.5, 55.8, 55.1, 52.8, 51.5, 48.3, 47.6, 47.0, 41.7. 34.6, 33.0, 32.4, 31.5, 28.3, 28.0, 27.8, 27.2, 26.9, 26.2, 24.5,
15 23.7, 22.4, 21.9, 19.5, 13.7.

Preparative Example 47: Preparation of:



47

Step A:

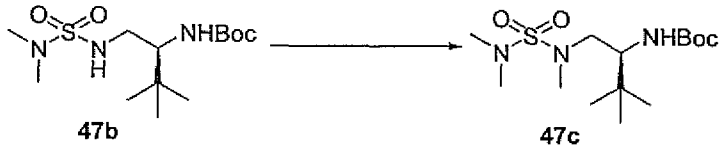
47a 47b

20 The amine, **47a**, (C. A. Busacca *et al, Tetrahedron: Asymmetry*; (**2000**) 9 1907) (1.5 g, 6.9 mmol, 1 equiv.) was dissolved in dry dichloromethane (20 ml) and cooled to -78 °C. Added 3 ml (3 equiv.) of Et_3N followed by the slow addition of dimethylsulfamyl chloride (1.5 eq., Sigma-Aldrich) dissolved in DCM. The temperature was kept at -78 °C until the addition is complete and then stirred overnight allowing it to rise to room
25 temperature. Diluted with methylene chloride and washed with water, aq. 1N HCl and finally brine. The organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. Crude product isolated was purified via flash column

(10→30 % EtOAc-Hexane) to afford 1.27g (58%) of **47b**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ, 4.6 (d, 1 H), 3.45 (m, 1 H,), 3.25 (d, 1 H), 2.89 (s, 6 H), 1.89 (bs, NH), 1.22 (s, 9H), 0.98 (s, 9 H).

MS (ESI), m/z, relative intensity 324 [(M+1) 85], 268 (100), 224 (50).

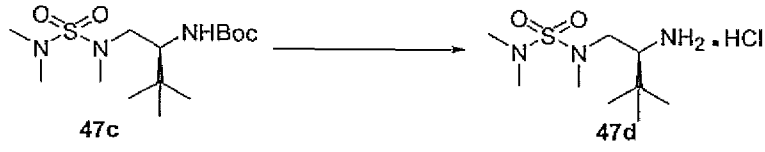
Step B:



47b 47c

To the Boc protected sulfonyl urea **47b** (440 mg, 1.25 mmol, 1 equiv.) in DMF (10 mL) at 0° C was added Cs_2CO_3 (613 mg, 1.5 equiv, 1.88 mmol) and MeI (6.36 mmol, 5 equiv., 0.601 mL) under inert atmosphere. The reaction mixture was stirred at room temperature for 90 min and quenched with water. The aqueous layers were extracted with EtOAc, washed 4 times with water and brine. The organic layers were dried over anhydrous sodium sulfate, filtered and evaporated off the solvent to afford 420 mg (91%) of **47c** that was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) □ 4.59 (d, 1 H), 3.62-3.58 (m, 1 H,), 3.29-3.22 (m, 1 H), 2.80 (s, 3 H), 2.79 (s, 6H), 1.89 (bs, NH), 1.22 (s, 9 H), 0.98 (s, 9 H). MS (ESI), m/z, relative intensity 338 [(M+1) 60], 282 (100), 238 (90).

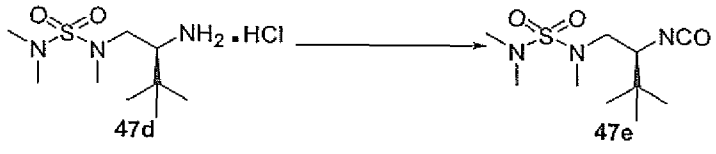
Step C:



47c 47d

To the Boc-protected sulfonyl urea **47c** (890 mg, 1 equiv.) was added 4 M solution of HCl in dioxane (25 mL) at room temperature and stirred for 1 hr. After the disappearance of starting material (TLC), the reaction mixture was concentrated and azeotroped with hexanes and ether. The residue was triturated with ether and the solid separating out was filtered and dried in vacuum to afford a pale yellow solid (720 mg, ~100%). It was used in further reaction without purification.

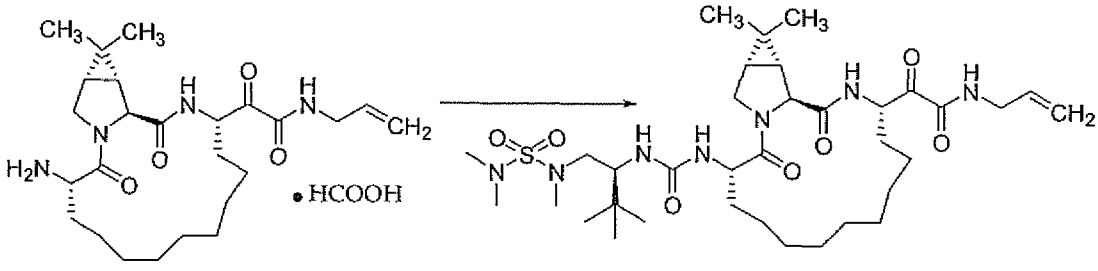
Step D:



47d 47e

To the amine hydrochloride salt **47d** (720 mg, 2.63 mmol) in dichloromethane (1 5 ml) was added 15 ml of aq. saturated $NaHCO_3$ and stirred vigorously at 0 °C for 5 min. A solution of phosgene (2 equiv. 20% in toluene) was syringed out to the lower layer and restored the vigorous stirring immediately. Checked the TLC at times and after 2 hrs, it showed complete consumption of starting material. The methylene chloride layer was separated and the aqueous layer was extracted with dichloromethane (30 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated using rotary evaporator under reduced pressure at rt. to half the volume and then flushed N_2 for 15 minutes. Diluted the solution to 130 mL with dichloromethane and used as 0.02 M solution in further reactions.

Step E:



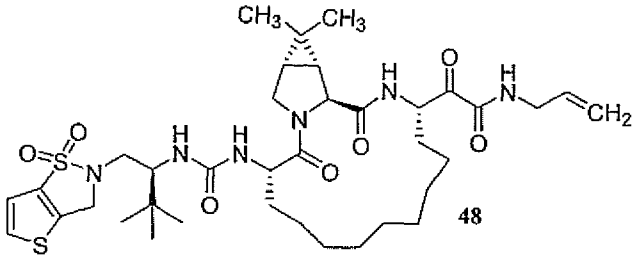
24a 47

A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **47e** (1.5 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1◊ 1:0) and 100% ethyl acetate to yield **47** (49 mg) as a colorless solid.

^{1}H NMR (dmso, 500 MHz) δ, 8.89 (t, 1 H, *J*=6 Hz), 8.37 (d, 1 H, *J*=9.0 Hz), 6.15 (d, 1 H, *J*=9.0 Hz) 5.83-5.76 (m, 2 H), 5.31-5.27 (m, 2 H), 4.33 (s, 1 H), 4.30-4.28 (m, 1 H), 3.91 (d, 1 H, *J*=10.5 Hz), 3.80-3.70 (m, 4 H), 3.63-3.59 (m, 1 H), 2.93 (dd, 1 H), 2.7 (s, 3 H), 2.69 (s, 6 H), 1.73-1.65 (m, 2 H), 1.51-1.02 (m, 18 H), 0.99 (s, 3 H), 0.84 (s, 3 H), 0.81 (m, 9 H) ^{13}C NMR (dmso, 125 MHz) δ, 198.3, 172.1, 171.7, 162.1, 158.2, 135.0, 116.5, 60.5, 55.8, 52.8, 51.7, 1.3, 47.6, 41.1, 38.5, 36.0, 34.9, 32.3, 31.6, 31.3,

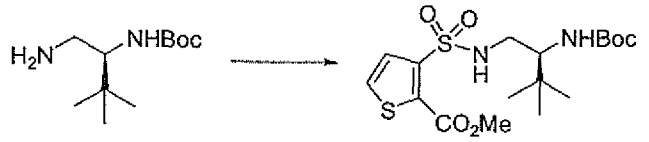
28.5, 28.4, 27.9, 27.4, 27.4, 27.1.MS (ES) *m/z* relative intensity 746 [(M+Na)$^+$, 40]; 724 [(M+1)$^+$, 100].

Preparative Example 48: Preparation of:



48

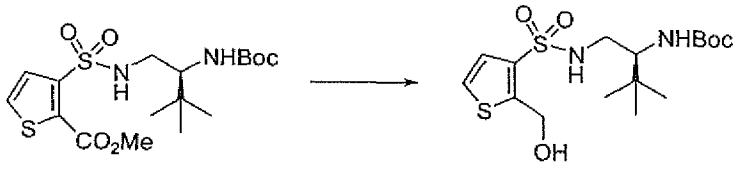
Step A:



48a 48b

Compound **48b** was prepared from **48a** and 2-carbomethoxy-3-thiophenesulfonyl chloride according to the procedures described for the preparation of compound **45b**.

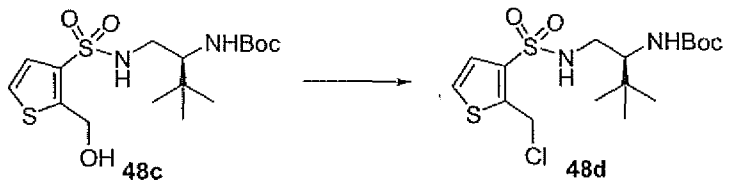
Step B:



48b 48c

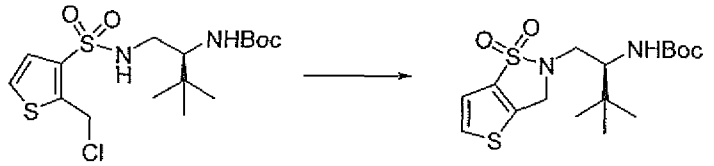
To the solution of ester **48b** (4.65 g, 11.1 mmol) in anhydrous toluene (40 mL) at -78 °C was added a solution of DIBAL-H in toluene (23.0 mL, 34.5 mmol). The mixture was stirred at -78 °C for 20 min and at rt. for 2 h. Methanol (20 mL) was added followed by 10% aqueous citric acid solution (100 mL). After stirred for 5 min, EtOAc (200 mL) was added and layers were separated. The aqueous solution was extracted with EtOAc (2 x100mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 10-50% acetone/hexanes to give 4.6 g (quant.) of **48c**.

Step C:



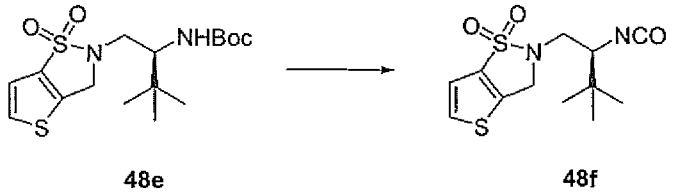
To a solution of **48c** (1.04 g, 2.65 mmol) in CH_2Cl_2 I (50 mL) at 0 °C was added methanesulfonyl chloride (0.23 mL, 2.97 mmol) and triethylamine (0.80 mL, 5.74 mmol). The mixture was warmed to rt along with ice bath and stirred for 18 h. EtOAc (200 mL) and 5% H_3PO_4 solution (100 mL) was added and the layers were separated. The organic solutions were washed with 1 N sodium carbonate solution (100 mL) before it was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 10-50% acetone/hexanes to give 0.80 g (73%) of **48d**.

Step D:



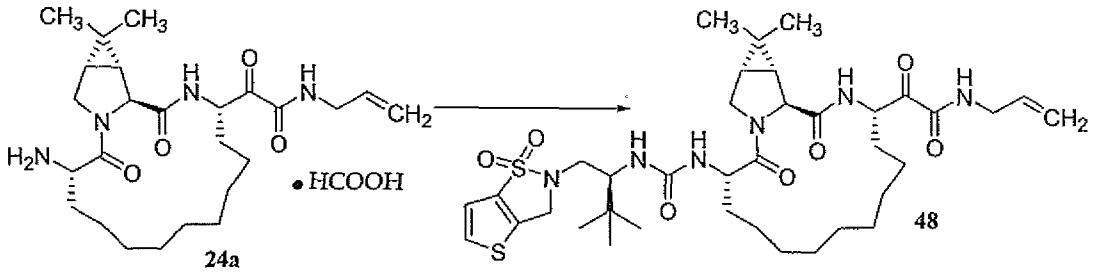
A suspension of **48d** (1.17 g, 2.85 mmol) and cesium carbonate (1.40 g, 4.30 mmol) in anhydrous DMF (100 mL) was stirred at rt. for 18 h. Water (50 mL), brine (50 mL) and EtOAc (300 mL) were added and the layers were separated. The organic solution was washed water (3 x 150 mL) before it was dried, filtered and concentrated to give 0.99 g of the desired product **48e** (93%).

Step E:



Compound **48f** was prepared from **48e** according to the procedures described for the preparation of compounds **45b** and **45c**.

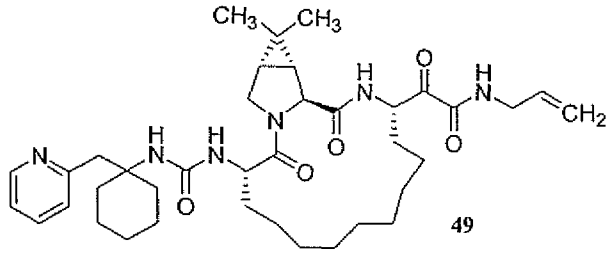
Step F:



24a 48

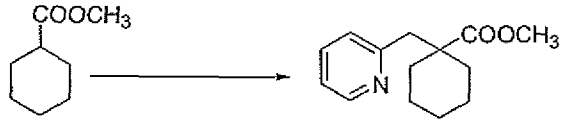
A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **48f** (2 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1→1:0) and 100% ethyl acetate to yield **48** as a colorless solid.

Preparative Example 49: Preparation of:



49

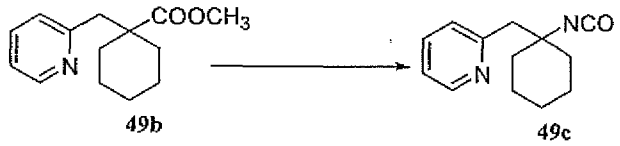
Step A:



49a 49b

A solution of 2 M LDA / THF-heptane (Acros Chemical Co.) in 50 mL of THF was cooled to -70° C, methyl cyclohexanecarboxylate **49a** was added drop wise at < -60° C. After an additional 0.5 hr stirring at –70 °C, 2-picolyl chloride in 40 mL ether was added drop wise at < -60° C. The temperature was then allowed to rise slowly to room temperature over 2 hr, and stirred an additional 2 hr. The reaction was quenched in a cold mixture of 200 mL 20% aqueous KH_2PO_4 and 5 mL of 12 N HCl, the mixture was extracted with EtOAc, the extract was washed with brine, and then dried with $MgSO_4$. The mixture was filtered, the filtrate was evaporated, the residue was evaporated twice from xylene, and the final residue was chromatographed on silica gel (1:3 Et_2O-CH_2Cl_2 to 1:1 acetone-CH_2Cl_2) to obtain **49b.**

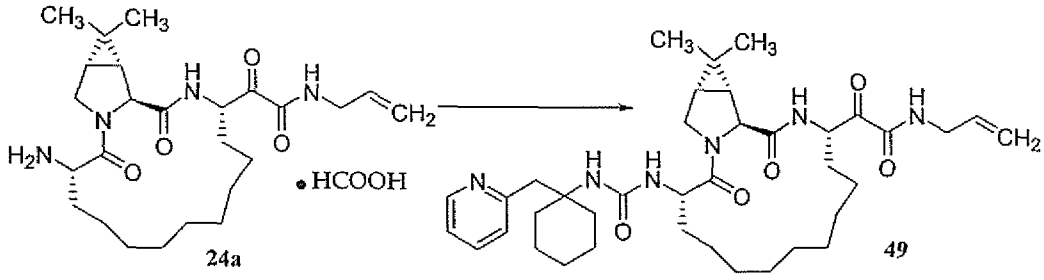
Step B:



49b 49c

A solution of ester **49b** in 20 mL of dioxane was treated with 30 mL of 1 N aqueous LiOH, and the mixture was stirred at 100° C for 6 hr. The mixture was quenched in ice-water, extracted with ether, and the cold aqueous was slowly acidified to pH ~4 with 3 N HCl. The precipitate was filtered, washed with water, and dried to leave product acid that was used in the following step without further purification. The conversion of the acid to the isocyanate **49c** was identical to the synthesis of **27b** in preparative example **27.**

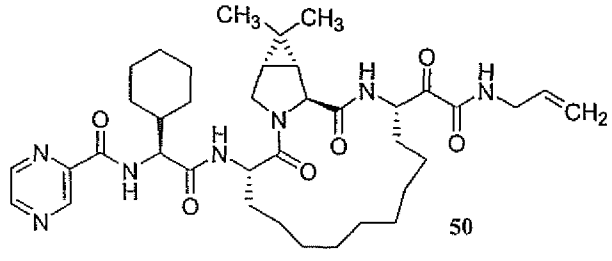
Step C:



24a 49

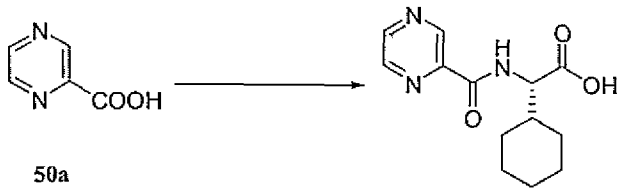
A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **49c** (2.9 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1◊ 1:0) and 100% ethyl acetate to yield **49** as a colorless solid.

Preparative Example 50: Preparation of:



50

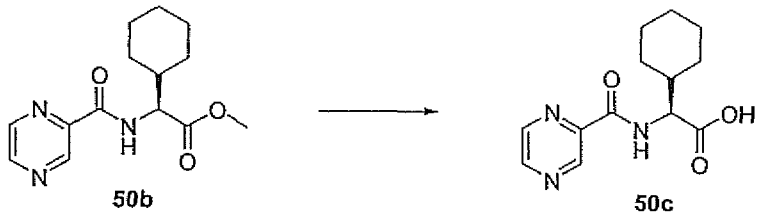
Step A:



50a 50b

A solution of pyrazinecarboxylic acid **50a** (Aldrich, 3 g) in 150 mL of dry dichloromethane and 150 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 6.03 g). L-cyclohexylglycine-methyl ester hydrochloride (1.2 eq, 6.03 g) was added in small portions. Then, N-methylmorpholine (4 eq, 10 mL, d 0.920) was added dropwise. The reaction mixture was gradually warmed to room temperature and stirred for 20 h. All the volatiles were removed under vacuum and the residue was dissolved in 500 mL of ethyl acetate. The organic layer was washed with water (100 mL), aq. 1N HCl (100 mL), aq. saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 3:7) to afford the product **50b** (6.5 g, 95%) as a white solid.

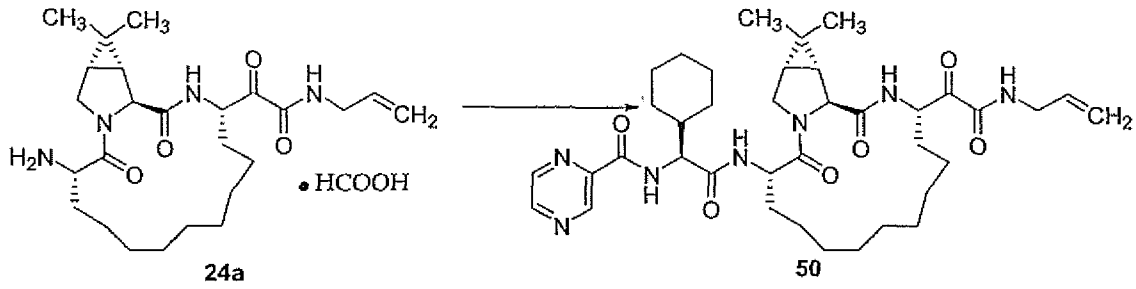
Step B:



50b 50c

A solution of methyl ester **50b** (6.5 g) in 270 mL of a 1:1:1 mixture of THF/MeOH/H_2O was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 2.45 g). The mixture was stirred and monitored by TLC (acetone/hexanes; 2:8). When all the starting material had been consumed, the reaction mixture was treated with 100 mL of aq 1N HCl and the mixture was concentrated in *vacuo.* Dichloromethane (250 mL) was added and layers separated. The aqueous layer was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford acid **50c.**

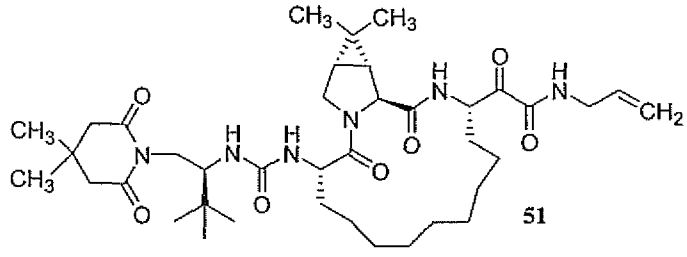
Step C:



24a 50

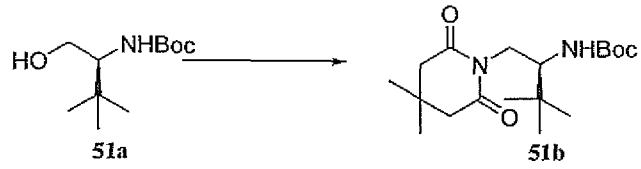
A solution of acid **24a** (100 mg, 0.197 mmol) in dry CH_2Cl_2 (2 mL) and DMF (2 mL) was cooled to 0° C and treated with acid **50c** (51.8 mg, 0.197 mmol), HATU (94 mg, 0.25 mmol) and NMM (45 mg, 0.45 mmol). The reaction was stirred at 0° C for 12 h and concentrated in *vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with aq. HCl (1 M, 2x 30 mL), aq. saturated $NaHCO_3$ (2x30mL), brine (30 mL), dried ($MgSO_4$), filtered, concentrated in *vacuo*. The crude dipeptide was purified by chromatography (SiO_2, acetone/Hexanes 0:1→1:1) to yield **50**. ^1H NMR (dmso, 400 MHz) δ, 9.16 (δ, 1 H, *J*=12 Hz), 8.89 (d, 1 H, *J*=2.4 Hz), 8.74 (s, 1 H), 8.59 (d, 1 H, *J*=7.4 Hz), 8.43-8.38 (m, 2 H), 5.81-5.75 (m, 1 H), 5.28 (t, 1 H, *J*=10.8 Hz), 5.11-5.03 (m, 2 H), 4.45-4.31 (m, 3 H), 3.88-3.70 (m, 5 H), 1.65-1.22 (m, 31 H), 0.97 (s, 3 H), 0.83 (s, 3 H).MS (ES) *m/z* relative intensity 728 [$(M+Na)^+$, 4]; 706 [$(M+1)^+$, 80].

Preparative Example 51: Preparation of:



51

Step A:

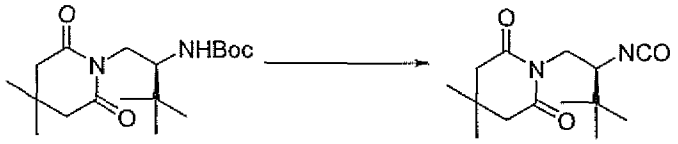


51a 51b

A solution of the alcohol **51a** (1.00 g, 4.6 mmol) in anhydrous CH_2Cl_2 (30 mL) in an inert atmosphere was treated with triphenylphosphine (1.52 g, 5.75 mmol) and dimethylglutarimide (780 mg, 5.52 mmol). The reaction mixture was cooled to 0 °C and treated with DIAD (930 mg, 4.60 mmol, in 4 mL CH_2Cl_2) dropwise and warmed to rt. It was stirred at rt. for 5 h and concentrated in *vacuo*. The residue was purified by

chromatography (SiO_2, Hexanes/acetone 1:0→1:1) to obtained **51b** (600 mg) as a colorless solid.

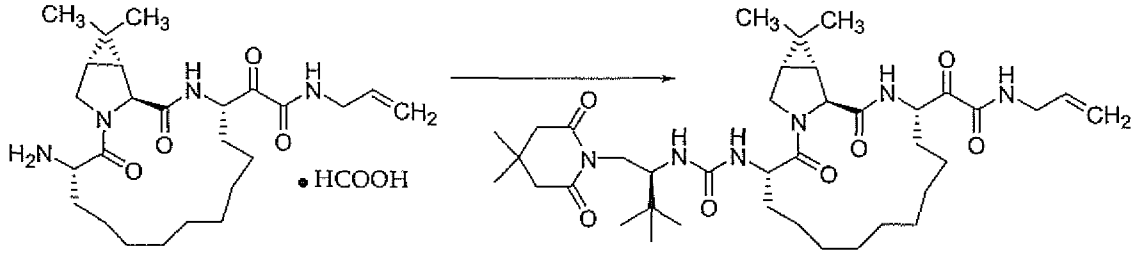
Step B:



51b **51c**

A solution of **51b** (500 mg, 1.5 mmol) in HCl (15 mL, 4M soln. in dioxane) was stirred at rt. for 1 h and concentrated in *vacuo.* The residue was used in further reaction without purification. A solution of the deprotected amine in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0° C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 3 mL toluene, concentrated the methylene chloride layer and used as a solution.

Step C:

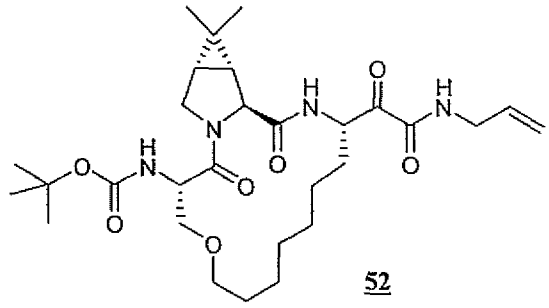


24a **51**

A solution of amine **24a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0° C. A solution of isocyanate **51c** (2 mL, 0.5 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2 Acetone/hexanes 0:1→1:1) yield **51** as a colorless solid. ^{1}H NMR (dmso, 500 MHz) δ, 8.91 (d, 1H), 6.19 (d, 1 H, *J*=8.5 Hz), 5.84-5.57 (m, 1 H), 5.58 (d, 1 H, *J*=10.5 Hz), 5.28 (t, 1 H, *J*=7.0 Hz), 5.10-5.05 (m, 2 H), 4.31 (s, 1 H), 4.18 (t, 1 H, *J*=8.5 Hz), 3.83-3.57 (m, 7 H), 2.44-2.38 (AB, 4 H), 1.66-1.62 (m, 2 H), 1.44-1.03 (m, 18 H), 0.98 & 0.96 (2s, 9 H), 0.84 & 0.81 (2s, 12 H). ^{13}C NMR (dmso, 125 MHz) δ,198.2, 172.7, 172.1, 171.3, 162.1, 158.1, 135.0, 116.4, 60.5, 55.5, 52.9, 51.3, 47.5, 46.4, 41.7, 39.6, 35.0, 32.4, 31.5,

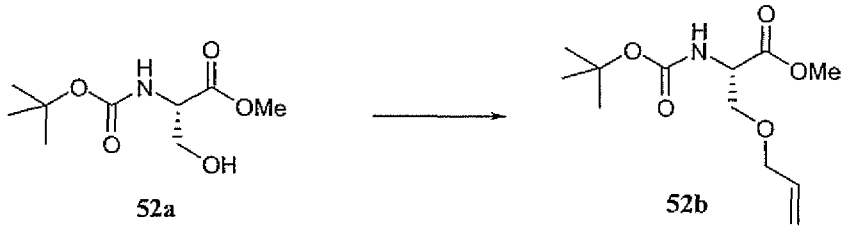
31.3, 29.3, 28.3, 27.9, 27.0, 26.9, 26.6, 26.1, 24.5, 22.4, 19.5, 13.7.MS (ES) *m/z* relative intensity 749 [$(M+Na)^+$, 20]; 727 [$(M+1)^+$, 100].

Preparative Example 52: Preparation of:



52

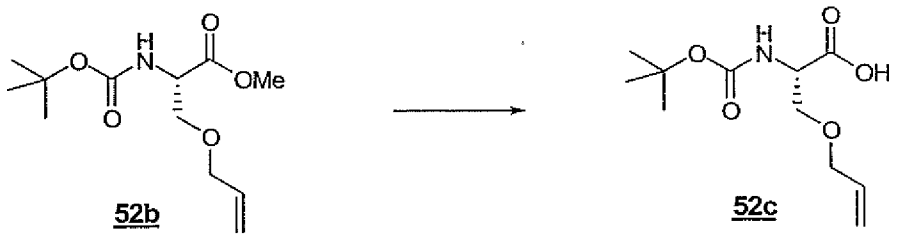
Step A:



52a 52b

A solution of N-Boc-L-Ser-OMe (3.6 g, Aldrich) in 150 mL of dry THF was degassed (vacuum/N2-flush) and treated with allylmethyl carbonate (1.4 eq, 2.6 mL, d 1.022). A catalytic amount of tetrakis(triphenylphosphine)palladium (0.02 mol%, 379 mg) was added. The slightly yellow mixture was degassed again and heated at 60 °C for about 3 h until TLC analysis (acetone/hexanes; 2:8) showed no more starting material left (reaction mixture became brown). The THF was removed under reduced pressure and the residue was diluted with 300 mL of ethyl acetate and washed with 80 mL of aqueous saturated sodium bicarbonate solution and 80 mL of brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 2:8) to afford the product **52b** as a clear oil (2.7 g, 64%).

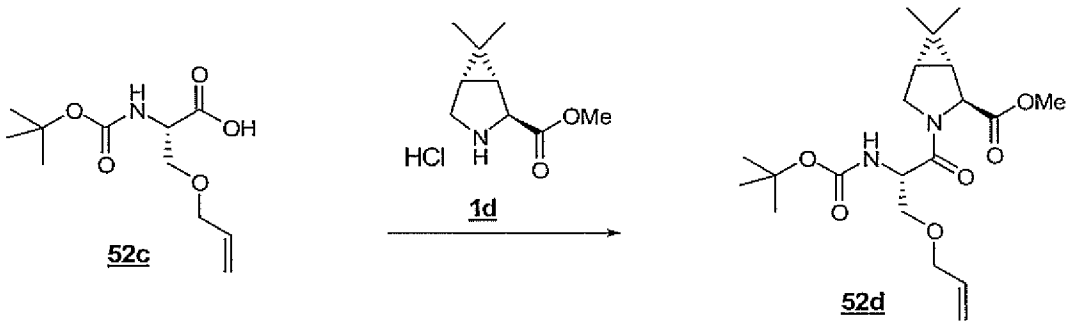
Step B:



52b 52c

A solution of methyl ester **52b** (1.5 g) in 90 mL of a mixture of THF/MeOH/H_2O (1:1:1) was treated with lithium hydroxide monohydrate (2.5 eq, 630 mg). Reaction was stirred at room temperature and monitored by TLC (acetone/hexanes; 1:9). After 45 min, all the volatiles were removed under reduced pressure. The residue was partitioned between 80 mL of aqueous 1N HCl and 200 mL of dichloromethane. The aqueous layer was back extracted with dichloromethane (2 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **52c** as a clear oil (1.4 g, 95%).

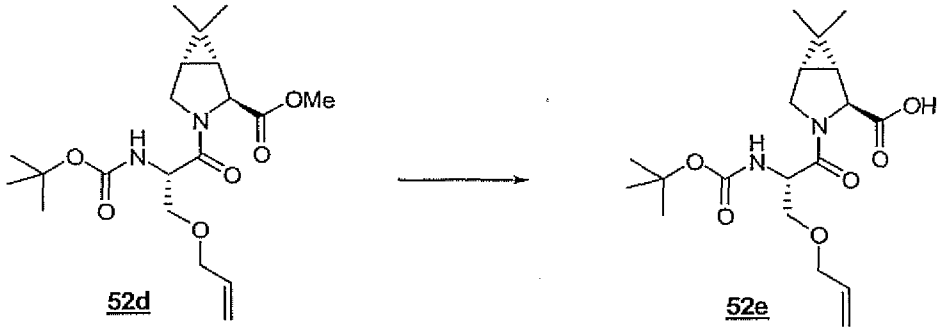
Step C:



52c 1d 52d

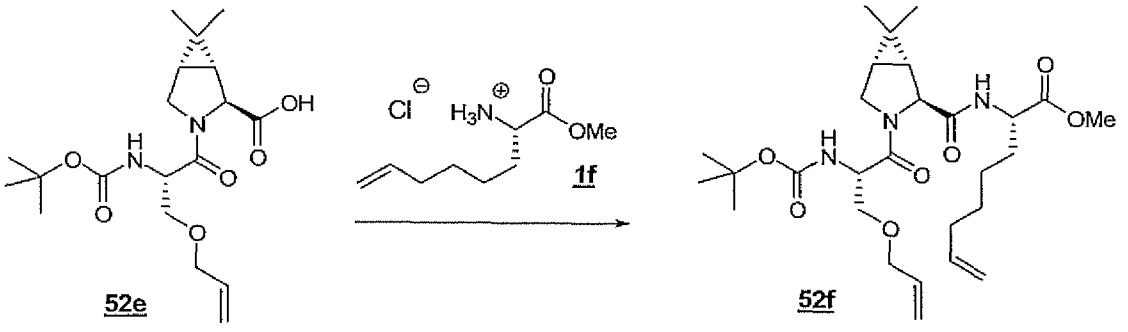
A solution of acid **52c** (6 mmol) in 40 mL of dry dichloromethane and 40 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 3.2 g). The amine hydrochloride **1d** (1.3 eq, 1.6 g) and N-methylmorpholine (4 eq, 2.6 mL, d 0.920) were successively added. The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 300 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (50 mL), aqueous saturated sodium bicarbonate (50 mL), and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 2:8) to afford the desired product **52d** (2.23 g, 93%) as a clear oil.

Step D:



A solution of methyl ester **52d** (2.23 g) in 45 mL of a mixture of THF/MeOH/H_2O (1:1:1) was treated with lithium hydroxide monohydrate (2.5 eq, 300 mg) at 0 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature and monitored by TLC (acetone/hexanes; 2:8). After 1 h, 10 mL of aq 1N HCl were added and all the volatiles were removed under reduced pressure. The residue was partitioned between 30 mL of aqueous 1N HCl and 100 mL of dichloromethane. The aqueous layer was back extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **52e** (1.88 g, 88%) as a clear oil.

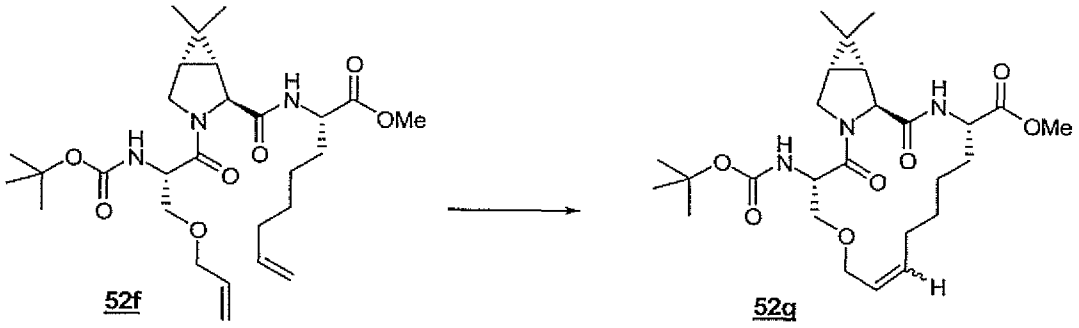
Step E:



A solution of acid **52e** (830 mg) in 20 mL of dry dichloromethane and 20 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 1.15 g). The amine hydrochloride **1f** (1.1 eq, 227 mg) was added in 10 mL of dichloromethane followed by N-methylmorpholine (4 eq, 0.95 mL, d 0.920). The reaction mixture was kept in the freezer (-20 °C) for 48 h. All the volatiles were removed under vacuum and the residue was dissolved in 200 mL of ethyl acetate. The organic layer was washed with water (50 mL), aqueous 1N HCl (50 mL), aqueous saturated sodium bicarbonate solution (50 mL), and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 3:7) to afford the product **52f** (680

mg) as a white solid along with a minor diastereomeric product (130 mg) for a combined yield of 70%.

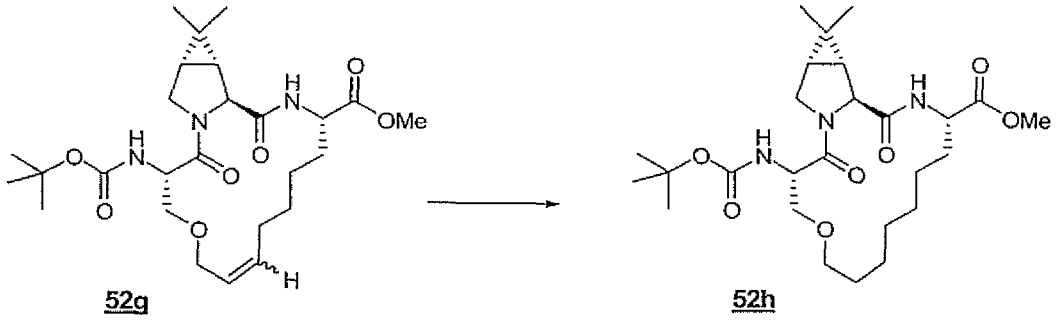
Step F:



52f 52g

A 0.01M solution of diene **52f** (670 mg) in toluene was degassed for 30 min (argon bubbling) and treated with Grubb's catalyst (0.2 eq, 205 mg). The pink solution was heated to 60 °C for 16 h (the solution became dark after heating 10 min). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 2:8 to 1:1) to afford the alkene product **52g** (570 mg, 90%) as a mixture of E- and Z-isomers (approx 4:1).

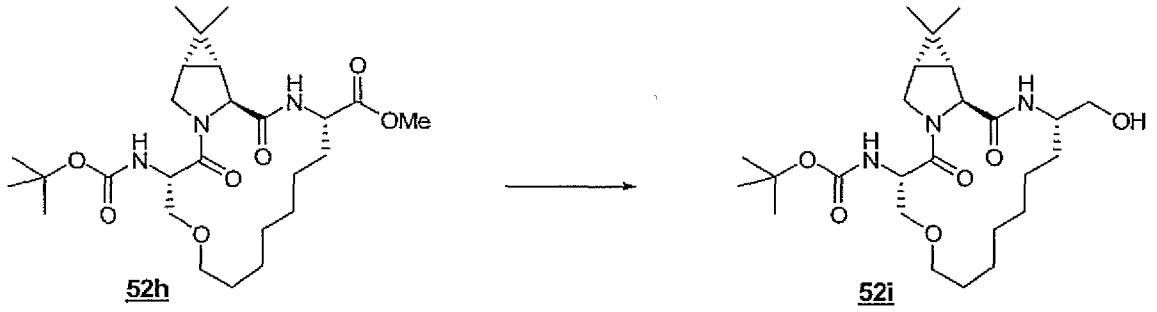
Step G:



52g 52h

A solution of alkene **52g** (570 mg) in 20 mL of methanol was treated with palladium dihydroxide on carbon (0.1 mol%, 78 mg of 20% Pd(OH)2/C). The mixture was hydrogenated at 50 psi until all the starting material had been consumed. The reaction mixture was diluted with 100 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated and the residue was chromatographed on silica gel to afford the product **52h** (590 mg, 70%) as a clear oil.

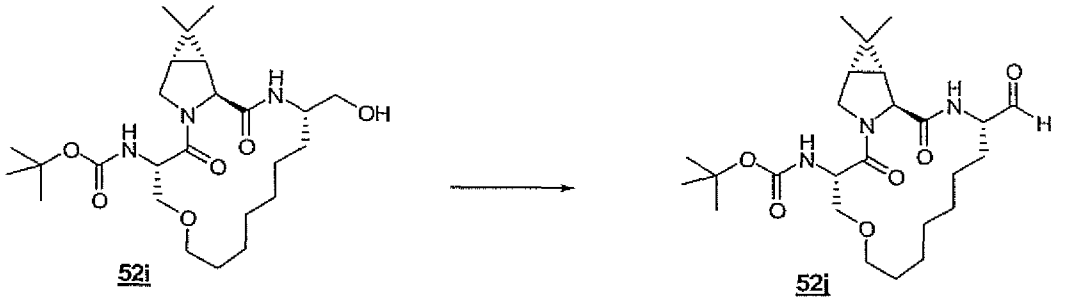
Step H:



52h 52i

A solution of methyl ester **52h** (580 mg) in 20 mL of dry THF was treated with lithium borohydride (2.1 eq, 1.2 mL of a 2M soln in THF). The reaction mixture was stirred at room temperature and monitored by TLC (acetone/hexanes; 3:7) for disappearance of the starting material. After 5 h, the excess lithium borohydride was quenched by addition of aqueous saturated ammonium chloride solution (3 mL). The mixture was partitioned between ethyl acetate (100 mL) and aqueous saturated sodium bicarbonate solution (50 mL). The aqueous layer was back extracted with ethyl acetate (2 x 30 mL) and dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 5:5) to afford the product **52i** (360 mg, 68%) as a white solid.

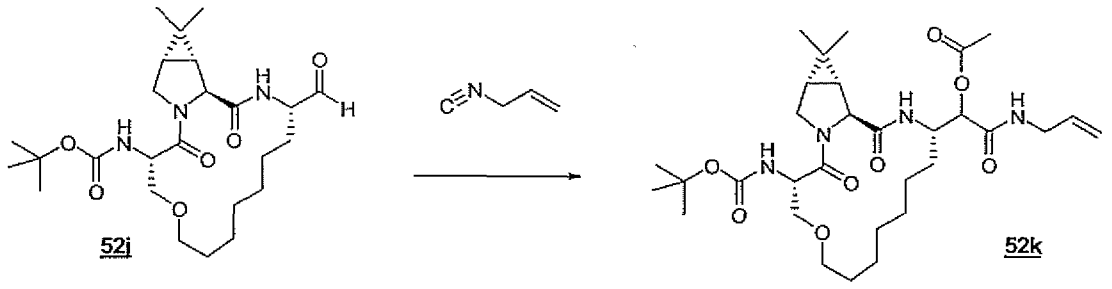
Step I:



52i 52j

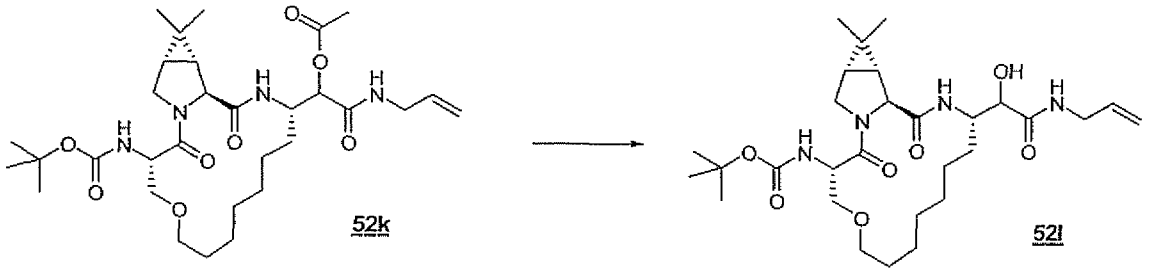
A solution of alcohol **52i** (350 mg) in 20 mL of dry dichloromethane was treated with Dess-Martin periodinane (3 eq, 925 mg). The reaction mixture was stirred at room temperature for 45 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (15 mL) and aqueous saturated sodium bicarbonate solution (15 mL) and stirred for 15 min. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **52j** (285 mg, 83%) as a colorless solid.

Step J:



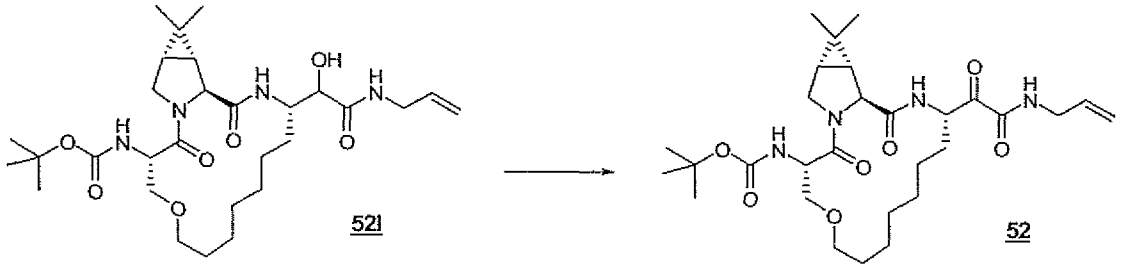
A solution of aldehyde **52j** (270 mg) in 10 mL of dry dichloromethane was treated with allylisocyanide (2 eq, 77 mg) and acetic acid (2 eq, 0.064 mL, d 1.049). The mixture was stirred for about 5 h. All the volatiles were removed under vacuum and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **52k** (303 mg, 90%) as a white solid.

Step K:



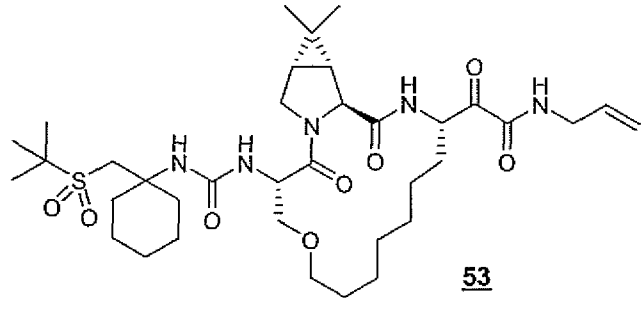
The acetate **52k** (300 mg) was dissolved in 15 mL of a 1:1:1 mixture of THF/MeOH/H_2O and treated with lithium hydroxide monohydrate (2.5 eq, 51 mg). The flow of the reaction was followed by TLC (acetone/hexanes; 4:6). After 15 min the reaction mixture was concentrated in the rotavap and the residue was partitioned between dichloromethane (80 mL) and aqueous saturated sodium bicarbonate solution (20 mL). The aqueous layer was back extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product **52l** (276 mg, 98%) was used without further purification.

Step L:



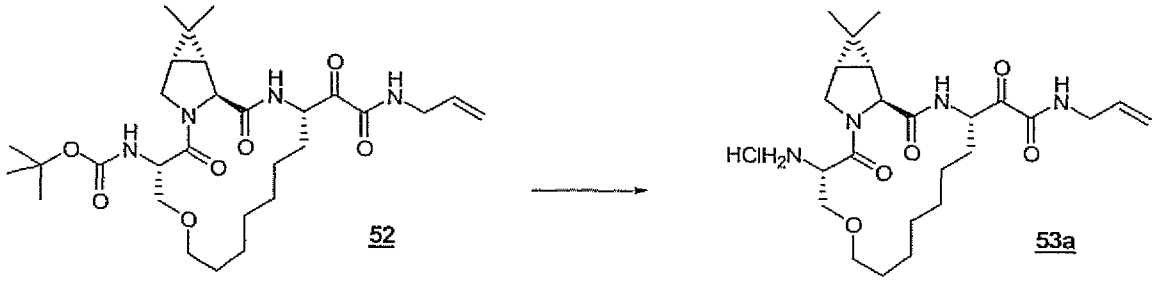
A solution of hydroxyamide **52l** (276 mg) in 20 mL of dry dichloromethane was treated with Dess-Martin periodinane (3 eq, 424 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (20 mL) and aqueous saturated sodium bicarbonate solution (10 mL) and stirred for 10 min. The mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **52** (236 mg, 86%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.47 (d, 1H, J = 7.56 Hz), 7.03 (dd, 1H, J = 5.68, 5.99 Hz), 5.88 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.50 (d, 1H, J = 8.83 Hz), 5.46 (m, 1H), 5.28 (dd, 1H, J = 0.9, 17.0 Hz), 5.25 (dd, 1H, J = 0.9, 10.0 Hz), 4.61 (m, 1H), 4.51 (s, 1H), 3.99 (dt, 2H, J = 1.2, 5.6 Hz), 3.88 (dd, 1H, J = 5.0, 10.8 Hz), 3.83 (d, 1H, J = 11.0 Hz), 3.66 (m, 2H), 3.48 (dd, 2H, J = 4.7, 5.6 Hz), 1.95 (m, 1H), 1.81 (d, 1H, J = 7.56 Hz), 1.47 (s, 9H), 1.27-1.63 (m, 12H), 1.09 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.7, 170.9, 170.7, 159.3, 155.6, 133.2, 117.9, 80.4, 71.0, 70.8, 61.2, 54.5, 52.9, 48.2, 42.1, 31.4, 29.3, 28.7, 27.8, 26.8, 26.6, 26.4, 23.6, 23.4, 19.2, 13.2 ppm; HRMS calcd for $C_{29}H_{47}N_4O_7$ $[M+H]^+$: 563.3445, found 563.3457.

Preparative Example 53: Preparation of:



53

Step A:

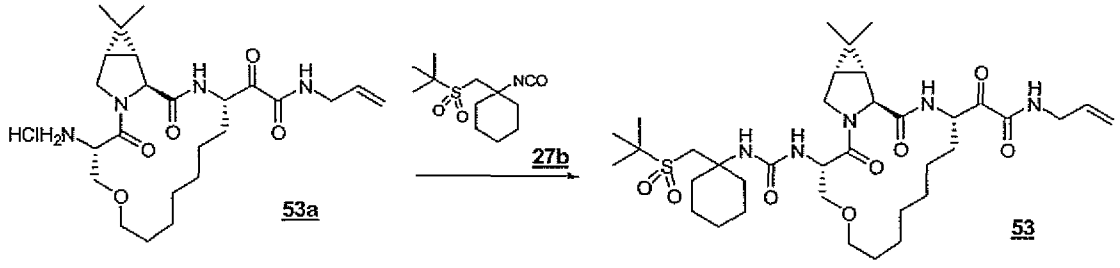


52 53a

The N-Boc protected amine **52** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes and stirred at room temperature for 1 h. All the volatiles were

removed under reduced pressure and the product was placed under high vacuum for 3 h. No further purification was done for the product **53a** (99%).

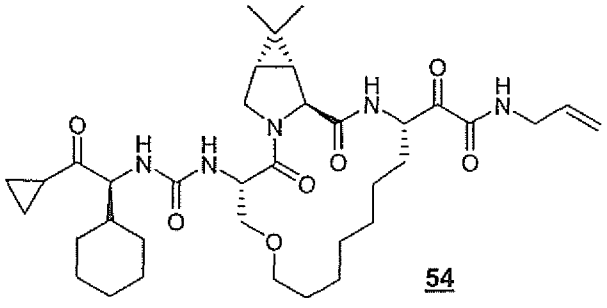
Step B:



53a 53

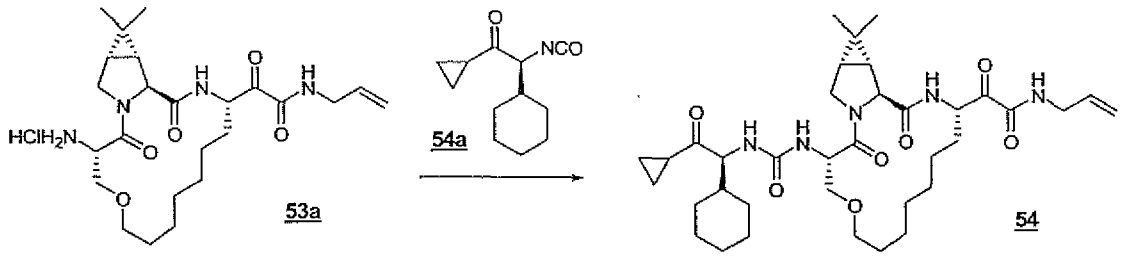
The amine salt **53a** (31 mg) was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a solution of the isocyanate **27b** (2.5 eq, 0.8 mL of a 0.2M solution in toluene) was added and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to yield the product **53** (25 mg, 58%) as a white solid. ^{1}H NMR (500 MHz, CDCl3): δ, 7.90 (d, 1H, J = 8.5 Hz), 7.38 (br s, 1H), 5.9 (ddt, 1H, J = 5.6, 10.4, 17.0 Hz), 5.61 (ddd, 1H, J = 1.6, 8.8, 10.4 Hz), 5.27 (dd, 1H, J = 1.26, 17.3 Hz), 5.24 (dd, 1H, J = 1.26, 10.0 Hz), 4.9 (dd, 1H, J = 3.4, 8.8 Hz), 4.53 (s, 1H), 3.94-4.08 (m, 4H), 3.62 (dd, 1H, J = 8.5, 8.8 Hz), 3.56 (m, 1H), 3.47 (dd, 1H, J = 4.0, 7.9 Hz), 3.37 (ddd, 1H, J = 2.2, 7.2, 9.4), 3.15 (d, 1H, J = 13.5 Hz), 2.4 (m, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.27-1.70 (m, 20H), 1.4 (s, 9H), 1.2 (m, 1H), 1.07 (s, 3H), 0.94 (s, 3H), 0.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.0, 172.1, 171.0, 159.5, 157.0, 133.3, 117.7, 70.8, 70.5, 61.0, 60.8, 54.9, 53.8, 51.0, 48.4, 42.2, 36.2, 32.0, 30.5, 28.7, 27.9, 27.2, 27.0, 26.8, 25.9, 24.1, 23.9,23.5, 21.9, 21.8, 19.3, 13.4 ppm; HRMS calcd for $C_{36}H_{60}N_5O_8S$ $[M+H]^+$: 722.4163, found 722.4193.

Preparative Example 54: Preparation of:



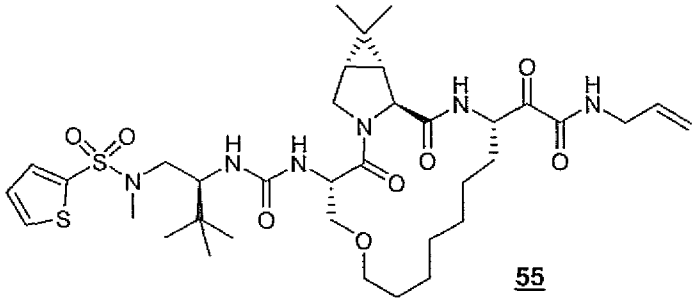
54

Step A:

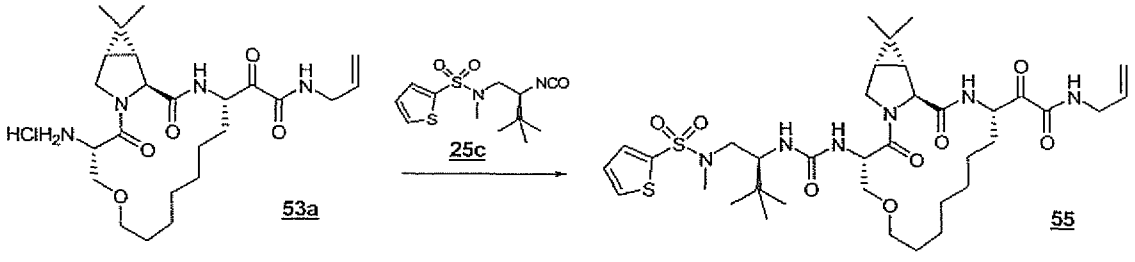


A solution of amine salt **53a** (17 mg) in 2 mL of dry dichloromethane was treated with solid sodium bicarbonate (3 eq, 8 mg) followed by the addition of isocyanate **54a** (2.5 eq, 0.26 mL of a 0.307M solution in toluene). The resulting heterogeneous mixture was stirred at room temperature for approximately 3 h. The mixture was diluted with 50 mL of ethyl acetate and washed with aqueous 1M HCl (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to yield the product **54** (8 mg, 34%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.91 (br s, 1H), 7.40 (m, 1H), 6.37 (br s, 1H), 5.91 (ddt, 1H, J = 5.6, 10.4, 17.3 Hz), 5.88 (br s, 1H), 5.62 (dt, 1H, J = 1.26, 9.45 Hz), 5.28 (dd, 1H, J = 1.26, 17.3 Hz), 5.23 (dd, 1H, J = 1.26, 10.4 Hz), 4.92 (ddd, 1H, J = 3.46, 8.5, 8.5 Hz), 4.77 (dd, 1H, J = 4.7, 8.8 Hz), 4.55 (s, 1H), 3.94-4.06 (m, 4H), 3.63 (t, 1H, J = 8.2 Hz), 3.54 (ddd, 1H, J = 3.4, 6.6, 9.7 Hz), 3.47 (m, 1H), 3.38 (m, 1H), 2.09 (ddd, 1H, J = 4.4, 7.8, 12.3 Hz), 1.91 (m, 2H), 0.91-1.83 (m, 27H), 1.07 (s, 3H), 0.94 (s, 3H); HRMS calcd for $C_{36}H_{56}N_5O_7$ $[M+H]^+$: 670.4180, found 670.4177.

Preparative Example 55: Preparation of:

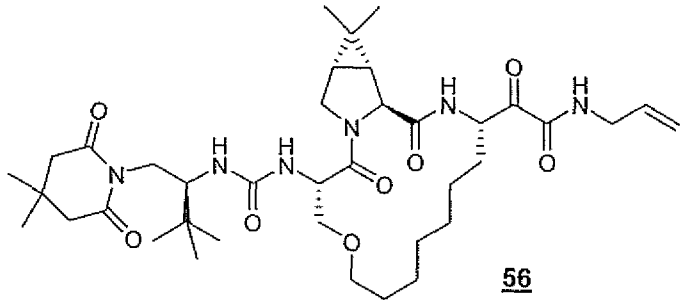


Step A:



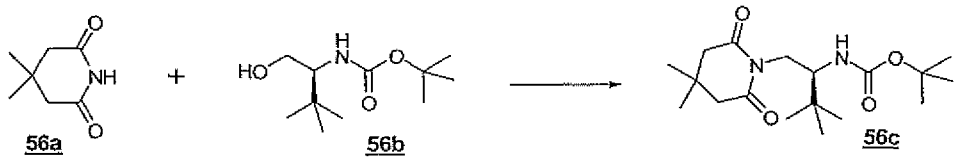
A solution of amine salt **53a** (17 mg) in 2 mL of dry dichloromethane was treated with solid sodium bicarbonate (3 eq, 8 mg) followed by the addition of isocyanate **25c** (2.5 eq, 0.45 mL of a 0.18M solution in toluene). The resulting heterogeneous mixture was stirred at room temperature for approximately 3 h. The mixture was diluted with 50 mL of ethyl acetate and washed with aq 1M HCl (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to yield the product **55** (8 mg, 30%) as a white solid. HRMS calcd for $C_{36}H_{57}N_6O_8S_2$ $[M+H]^+$: 765.3679, found 765.3687.

Preparative Example 56: Preparation of:



56

Step A:

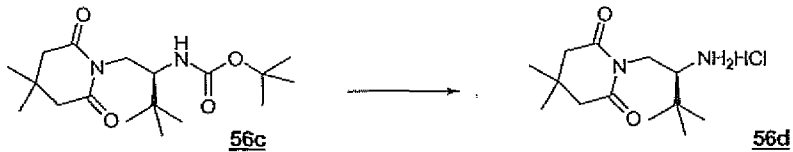


56a **56b** **56c**

A solution of 4,4-dimethylglutarimide **56a** (Aldrich, 1.5 eq, 4.86 g) in 200 mL of dry THF was cooled to 0 °C and treated with triphenylphosphine (3 eq, 18.07 g) and S-Boc-tert-butylglycinol **56b** (Aldrich, 5 g).

Diisopropylazodicarboxylate (2.5 eq, 11.3 mL, d 1.027) was added dropwise and the resulting solution was stirred at 0 °C. After 10 min, the mixture became a slurry and stirring was continued overnight (0 to 25 °C). The mixture was concentrated under reduced pressure and the residue was dissolved in 80 mL of ether. Hexanes (100 mL) was added and the precipitated solids were filtered off. The filtrate was concentrated to half its volume and hexanes (100 mL) was added again. The solids were filtered off. The filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 2:8) to afford the product **56c** (4.0 g, 51%) as a white solid.

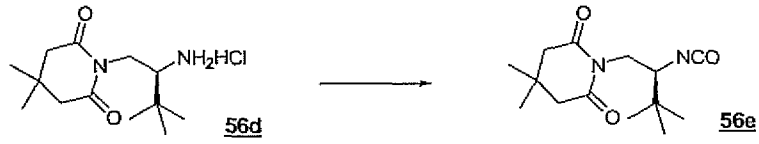
Step B:



56c 56d

The N-Boc protected amine **56c** (4.0 g) was dissolved in 200 mL of 4M HCl solution in dioxanes. The mixture was stirred at room temperature and a white solid precipitated after 10 min. The mixture was further stirred for 2 h. All the volatiles were removed under reduced pressure to afford the product **56d** (3.24 g, 98%) as a white solid.

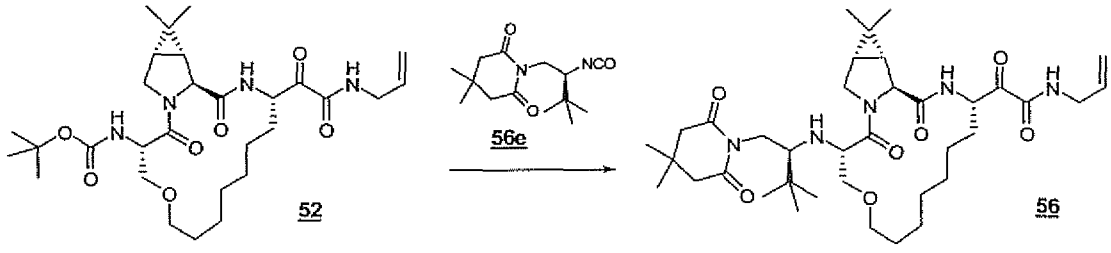
Step C:



56d 56e

A solution of amine hydrochloride **56d** (1.5 g) in 60 mL of dichloromethane was treated with 50 mL of aqueous saturated sodium bicarbonate solution and stirred vigorously for 10 min at 0 °C. Stirring was stopped and layers were allowed to separate. Phosgene (15 mL of 20% soln in toluene) was added through a needle to the organic layer (lower layer) in one portion. The mixture was vigorously stirred immediately after addition for 10 min at 0 °C and further stirred at room temp for 2.5 h. The mixture was diluted with 100 mL of dichloromethane and layers were separated. The organic layer was washed with 40 mL of cold aqueous saturated sodium bicarbonate solution and dried over magnesium sulfate. The organic layer was filtered and diluted with 50 mL of toluene. The product **56e** (1.44 g, 98%) was kept as a 0.216M solution in toluene.

Step C:

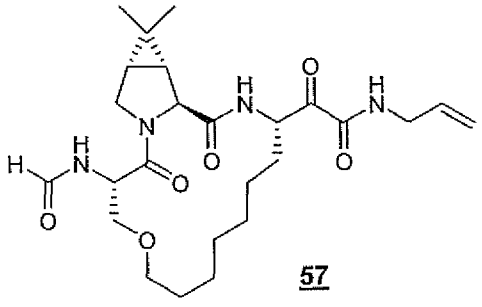


52 56e 56

The N-Boc amine **52** (200 mg) was dissolved in 20 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry

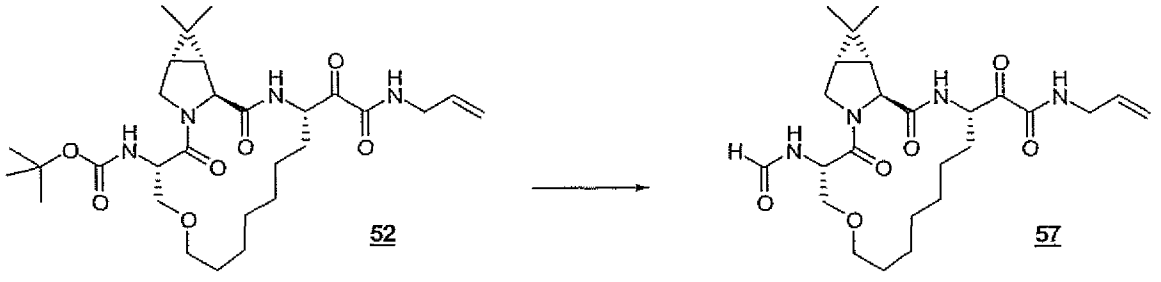
dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a solution of the isocyanate **56e** was added dropwise (1.2 eq, 1.97 mL of a 0.216M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 55:45) to afford the product **56** (172 mg, 66%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.95 (d, 1H, J = 8.8 Hz), 7.59 (br s, 1H), 5.91 (br s, 1H), 5.84 (ddt, 1H, J = 5.8, 10.2, 16.8 Hz), 5.61 (ddd, 1H, J = 1.5, 8.7, 10.2 Hz), 5.21 (dd, 1H, J = 1.4, 17.5 Hz), 5.17 (dd, 1H, J = 1.4, 10.2 Hz), 5.13 (br s, 1H), 4.86 (br s, 1H), 4.52 (s, 1H), 4.05 (d, 1H, J = 10.2 Hz), 3.80-3.99 (m, 6H), 3.50 (m, 2H), 3.27 (m, 2H), 2.51 (d, 2H, J = 16.8 Hz), 2.43 (d, 2H, J = 16.8 Hz), 1.88 (m, 1H), 1.77 (m, 1H), 0.84-1.58 (m, 12H), 1.05 (s, 6H), 0.97 (s, 3H), 0.92 (s, 9H), 0.81 (s, 3H); ^{13}C NMR (CDCl3, 125 MHz): δ 198.6, 172.8, 172.0, 171.2, 159.3, 157.8, 133.4, 117.7, 71.4, 70.8, 60.7, 57.0, 53.5, 48.5, 46.8, 42.2, 40.0, 34.9, 32.1, 30.9, 29.4, 28.7, 28.1, 27.7, 27.4, 26.9, 24.3, 19.3, 13.5 ppm; HRMS calcd for $C_{38}H_{61}N_6O_8$ $[M+H]^+$: 729.4551, found 729.4529.

Preparative Example 57: Preparation of:



57

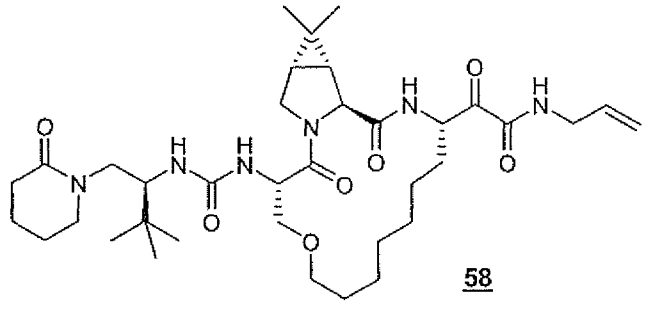
Step A:



52 57

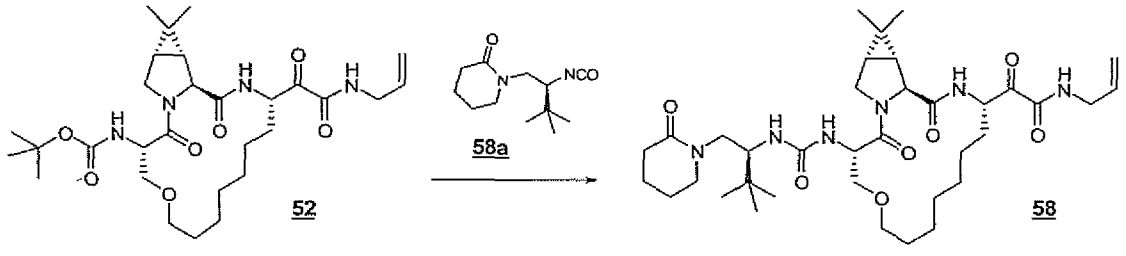
The N-Boc protected amine **52** (101 mg) was dissolved in 10 mL of formic acid and stirred at room temperature for 1 h. All the volatiles were removed in rotovap and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to give the formylated product **57** (35 mg, 40%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ, 8.24 (s, 1H), 7.35 (d, 1H, J = 7.8 Hz), 7.07 (br s, 1H), 6.83 (d, 1H, J = 6.9 Hz), 5.89 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.47 (m, 1H), 5.28 (dd, 1H, J = 1.2, 17.3 Hz), 5.25 (dd, 1H, J = 1.2, 10.4 Hz), 4.95 (ddd, 1H, J = 3.1, 5.9, 8.5 Hz), 4.51 (s, 1H), 3.99 (m, 2H), 3.92 (dd, 1H, J = 5.3, 11.0 Hz), 3.75 (d, 1H, J = 11.0 Hz), 3.74 (m, 1H), 3.70 (dd, 1H, J = 5.6, 9.1 Hz), 3.48 (m, 2H), 1.96 (m, 1H), 1.77 (d, 1H, J = 7.8 Hz), 1.76 (m, 1H), 1.27-1.63 (m, 11H), 1.10 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.8, 170.5, 169.4, 160.8, 159.3, 133.1, 117.9, 71.3, 70.0, 61.5, 54.4, 50.8, 48.2, 42.1, 32.0, 31.5, 29.4, 28.6, 27.8, 26.7, 26.6, 23.6, 23.5, 19.3, 14.5, 13.2 ppm; HRMS calcd for $C_{25}H_{39}N_4O_6$ $[M+H]^+$: 491.2870, found 491.2882.

Preparative Example 58: Preparation of:



58

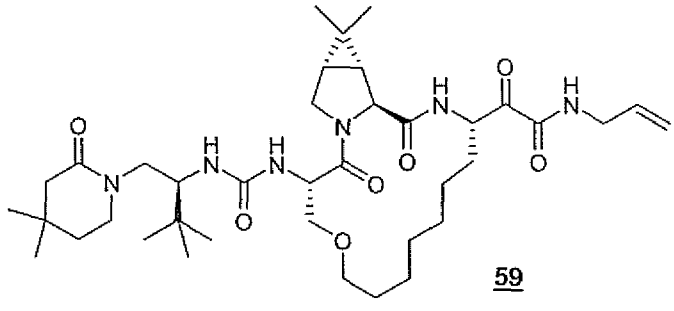
Step A:



The N-Boc protected amine **52** (80 mg) was dissolved in 5 mL of 4M HCl soln in dioxanes and stirred at room temperature for 45 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 3 mL of dry dichloromethane and treated with N-methylmorpholine (3 eq, 0.05 mL, d 0.920). The isocyanate **58a** was added in solution (2 eq, 3.8 mL of a 0.075M solution in toluene). The reaction mixture was stirred at room temperature for about 3 h. The mixture was diluted with ethyl acetate (50 mL)

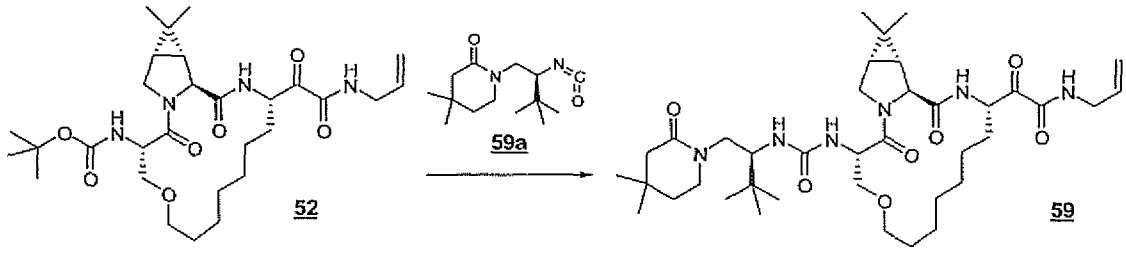
and washed with aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 3:7 to 7:3) to afford the product **58** (16 mg, 16%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ, 8.19-8.39 (br s, 1H), 8.05 (d, 1H, J = 8.5 Hz), 6.22 (br s, 1H), 5.91 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.71 (dd, 1H, J = 9.4, 10.0 Hz), 5.33 (d, 1H, J = 9.4 Hz), 5.28 (m, 1H), 5.26 (dd, 1H, J = 1.2, 17.0 Hz), 5.20 (dd, 1H, J = 1.2, 10.4 Hz), 4.96 (ddd, 1H, J = 4.0, 9.4, 9.4 Hz), 4.60 (s, 1H), 4.32 (t, 1H, J = 12.6 Hz), 4.12 (d, 1H, J = 10.7 Hz), 3.86-4.07 (m, 4H), 3.49-3.63 (m, 3H), 3.38 (dd, 1H, J = 4.1, 7.9 Hz), 3.31 (m, 1H), 3.16 (m, 1H), 2.66 (dd, 1H, J = 2.8, 13.8 Hz), 2.39 (dt, 1H, J = 5.6, 17.3 Hz), 2.27 (dt, 1H, J = 6.6, 17.3 Hz), 1.89-2.04 (m, 2H), 1.71-1.87 (m, 4H), 0.88-1.64 (m, 11H), 1.03 (s, 3H), 0.93 (s, 9H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.2, 171.8, 171.3, 159.5, 158.2, 133.7, 117.3, 71.4, 70.8, 60.6, 55.7, 53.5, 51.0, 48.3, 48.1, 46.5, 42.2, 34.3, 32.7, 31.8, 31.0, 28.7, 27.8, 27.6, 27.0, 26.9, 24.6, 24.4, 23.5, 21.7, 19.2, 13.5 ppm; HRMS calcd for $C_{36}H_{59}N_6O_7$ $[M+H]^+$: 687.4445, found 687.4434.

Preparative Example 59: Preparation of:



59

Step A:

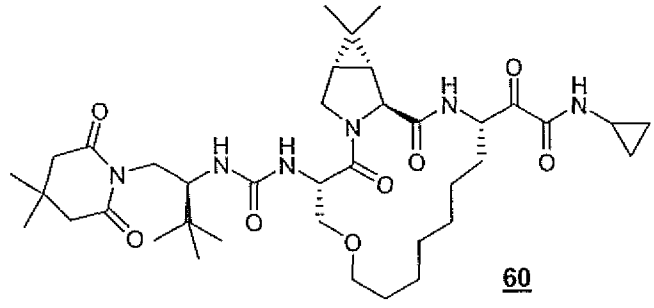


52 **59a** **59**

The N-Boc amine **52** (56 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry

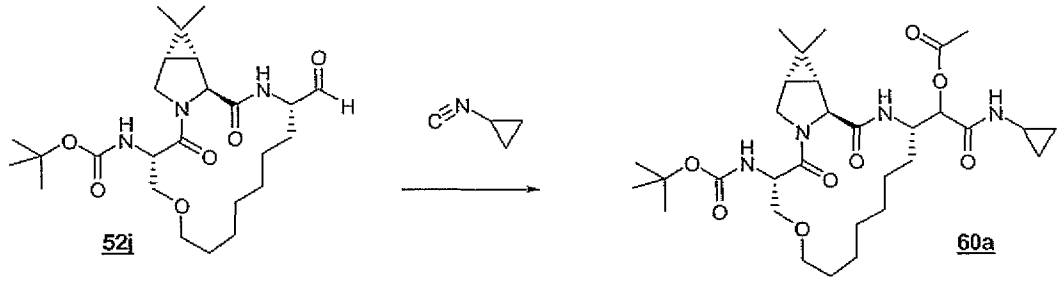
dichloromethane and cooled to 0 °C. Then, 15 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **59a** was added dropwise (1.0 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aqueous 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **59** (35 mg, 50%) as a white solid. HRMS calcd for $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715.4758, found 715.4739.

Preparative Example 60: Preparation of:



60

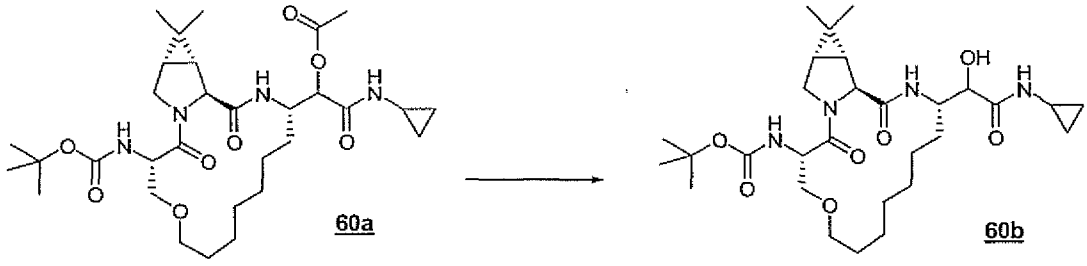
Step A:



52j **60a**

A solution of aldehyde **52j** (405 mg) in 15 mL of dry dichloromethane was treated with cyclopropylisocyanide (Oakwood Prod., 2 eq, 117 mg) and acetic acid (2 eq, 0.1 mL, d 1.049). The mixture was stirred at room temperature overnight. All the volatiles were removed under reduced pressure and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **60a** (500 mg, 98%) as a white solid.

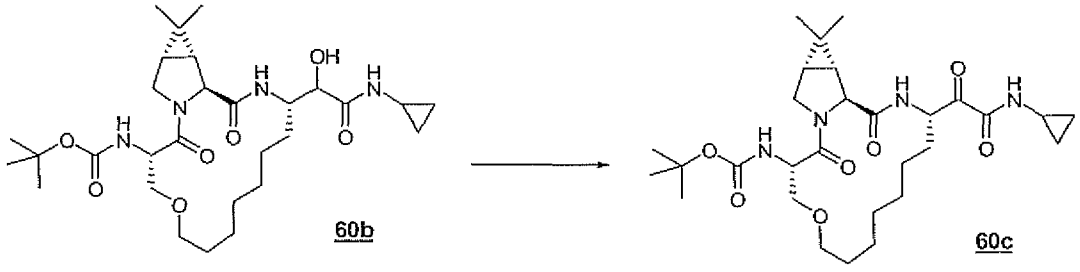
Step B:



60a 60b

A solution of acetate **60a** (500 mg) in 15 mL of a 1:1:1 mixture of THF/MeOH/water was treated with lithium hydroxide monohydrate (2.5 eq, 86 mg) and stirred for approx. 30 min until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 6:4). The reaction mixture was diluted with 30 mL of aqueous saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the crude product **60b** (464 mg, 98%) as a colorless semi-solid which was used without further purification.

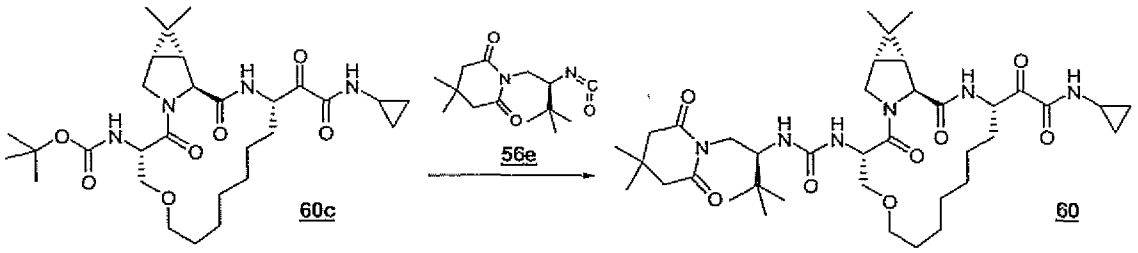
Step C:



60b 60c

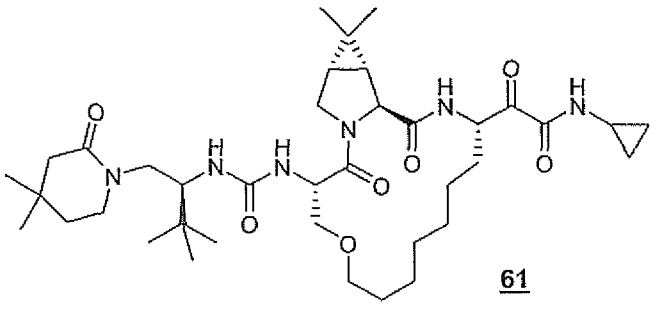
A solution of hydroxyamide **60b** (0.824 mmol) in 20 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 698 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (15 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (20 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 35:65) to afford the product **60c** (333 mg, 72%) as white solid.

Step D:

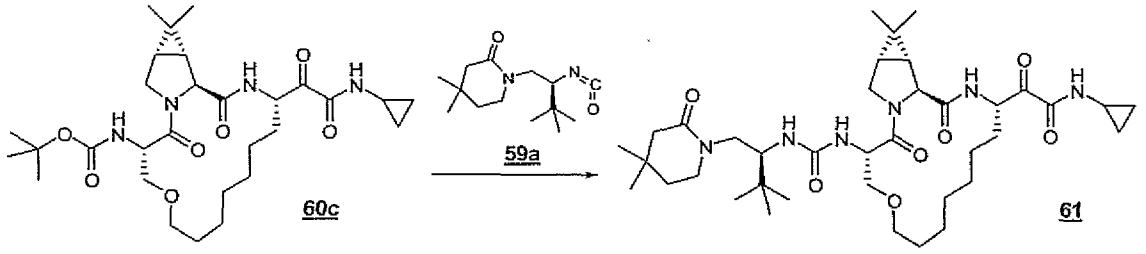


The N-Boc amine **60c** (70 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **56e** (1.3 eq, 0.7 mL of a 0.241M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (50 mL) and washed with aqueous saturated sodium bicarbonate solution (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 55:45) to afford the product **60** (70 mg, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.56 (br s, 1H), 5.86 (br s, 1H), 5.65 (t, 1H, J = 8.8 Hz), 5.09 (br s, 1H), 4.91 (br s, 1H), 4.56 (s, 1H), 4.07 (d, 1H, J = 10.4 Hz), 3.98 (dd, 1H, J = 5.0, 10.7 Hz), 3.91 (m, 3H), 3.54 (m, 2H), 3.34 (m, 2H), 2.88 (ddd, 1H, J = 3.7, 7.5, 15.1 Hz), 2.56 (d, 2H, J = 16.7 Hz), 2.50 (d, 2H, J = 16.7 Hz), 1.94 (m, 1H), 0.87-1.76 (m, 15H), 1.11 (s, 6H), 1.03 (s, 3H), 0.97 (s, 9H), 0.86 (s, 3H), 0.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.0, 172.9, 172.0, 171.2, 160.8, 157.7, 71.5, 70.8, 60.7, 56.9, 53.4, 51.1, 48.4, 46.8, 39.9, 34.9, 32.1, 30.8, 29.4, 28.7, 28.1, 27.7, 27.5, 26.9, 26.8, 24.4, 23.0, 19.2, 13.5, 6.8, 6.7 ppm. HRMS calcd for $C_{38}H_{61}N_6O_8$ $[M+H]^+$: 729.4551, found 729.4558.

Preparative Example 61: Preparation of:

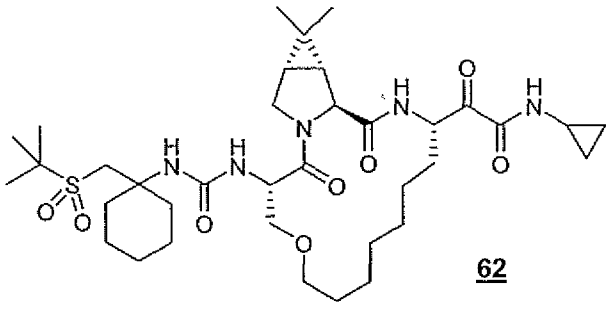


Step A:



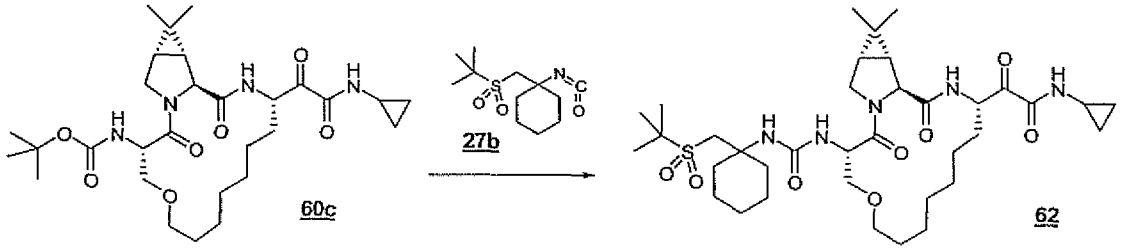
The N-Boc amine **60c** (56 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln of the isocyanate **59a** in toluene (1.3 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **61** (52 mg, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30-8.53 (br s, 1H), 8.15 (d, 1H, J = 8.8 Hz), 6.13 (br s, 1H), 5.74 (dd, 1H, J = 8.8, 9.7 Hz), 5.38 (d, 1H, J = 9.1 Hz), 4.96 (br s, 1H), 4.59 (s, 1H), 4.35 (dd, 1H, J = 12.9, 12.9 Hz), 4.10 (d, 1H, J = 10.4 Hz), 4.01 (dd, 1H, J = 5.0, 10.4 Hz), 3.94 (m, 1H), 3.56 (m, 2H), 3.50 (dd, 1H, J = 8.5, 8.8 Hz), 3.31 (m, 2H), 3.17 (ddd, 1H, J = 5.6, 6.0, 12.3 Hz), 2.91 (ddd, 1H, J = 4.0, 7.8, 15.4 Hz), 2.67 (dd, 1H, J = 3.4, 13.5 Hz), 2.17 (d, 1H, J = 17.0 Hz), 2.10 (d, 1H, J = 17.0 Hz), 1.94 (m, 3H), 1.24-1.70 (m, 12H), 1.14 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.89 (s, 3H), 0.84 (m, 2H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 171.9, 171.3, 171.0, 160.9, 158.0, 71.4, 70.9, 60.4, 55.4, 53.2, 48.2, 46.3, 45.0, 35.8, 34.6, 31.7, 30.3, 28.8, 28.7, 27.8, 27.7, 27.6, 27.1, 26.9, 26.8, 24.8, 24.7, 23.2, 19.1, 13.4, 6.4 ppm. HRMS calcd for $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715.4758, found 715.4768.

Preparative Example 62: Preparation of:



62

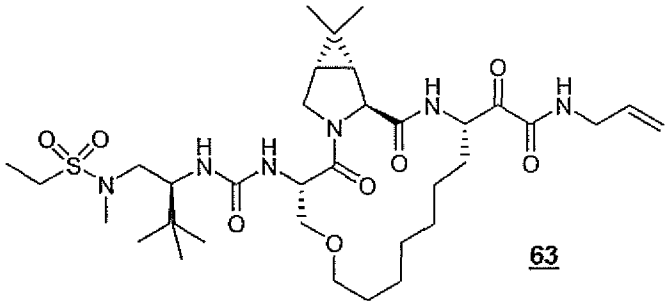
Step A:



The N-Boc amine **60c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln of the isocyanate **27b** in toluene (1.2 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **62** (65 mg, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, 1H, *J* = 8.2 Hz), 7.28 (br s, 1H), 5.73-6.02 (br s, 1H), 5.57 (ddd, 1H, *J* = 1.9, 8.2, 8.5 Hz), 5.22 (br s, 1H), 4.88 (dd, 1H, *J* = 3.4, 8.5 Hz), 4.51 (s, 1H), 4.01 (m, 3H), 3.62 (dd, 1H, *J* = 8.5, 8.5 Hz), 3.55 (ddd, 1H, *J* = 3.7, 6.3, 9.7 Hz), 3.48 (dd, 1H, *J* = 4.0, 8.1 Hz), 3.38 (m, 1H), 3.18 (d, 1H, *J* = 13.5 Hz), 2.86 (ddd, 1H, *J* = 3.8, 7.2, 14.8 Hz), 2.41 (d, 1H, *J* = 11.6 Hz), 2.24 (d, 1H, *J* = 11.6 Hz), 1.93 (m, 1H), 1.72-1.89 (m, 4H), 1.40 (s, 9H), 1.28-1.70 (m, 16H), 1.21 (m, 1H), 1.06 (s, 3H), 0.93 (s, 3H), 0.91 (m, 2H), 0.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 197.9, 172.0, 171.0, 160.9, 157.0, 70.8, 70.6, 61.0, 60.8, 54.9, 53.7, 51.1,

48.4, 36.2, 32.0, 30.5, 28.7, 27.9, 27.2, 26.9, 26.8, 25.9, 24.1, 23.8, 23.5, 23.0, 21.9, 21.8, 19.3, 13.4, 6.9, 6.8 ppm.

Preparative Example 63: Preparation of:



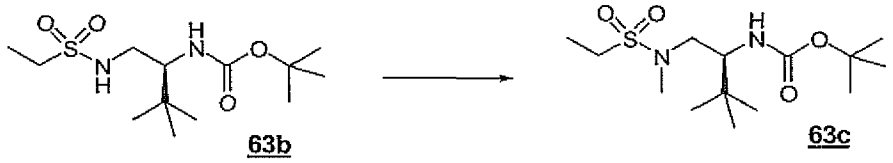
63

Step A:

63a 63b

A solution of amine **63a** (2.0 g) in 100 mL of dry dichloromethane was cooled to 0 °C and treated with pyridine (3.0 eq, 2.24 mL, d 0.978) and ethanesulfonyl chloride (1.2 eq, 1.05 mL, d 1.357). The resulting yellow homogeneous solution was stirred overnight (temp 0 to 25 °C). The mixture was diluted with 200 mL of ether and washed with aqueous 1M HCl (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (gradient: dichloromethane to ethyl acetate/dichloromethane 3:7) to afford the product 63b (850 mg, 30%) as a white solid.

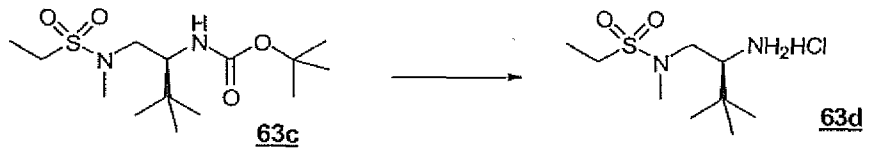
Step B:



63b 63c

A solution of ethylsulfonamide **63b** (850 mg) in dry DMF (30 mL) was treated with cesium carbonate (3.0 eq, 2.74 g) and iodomethane (3.0 eq, 0.51 mL, d 2.280). The reaction mixture was stirred for approximately 4 h. TLC analysis (acetone/hexanes; 2:8) showed that all the starting material had been consumed. The mixture was diluted with ethyl acetate (300 mL) and washed with water (3 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **63c** (860 mg, 97%) as a white solid. No further purification was carried out for the product.

Step C:



63c 63d

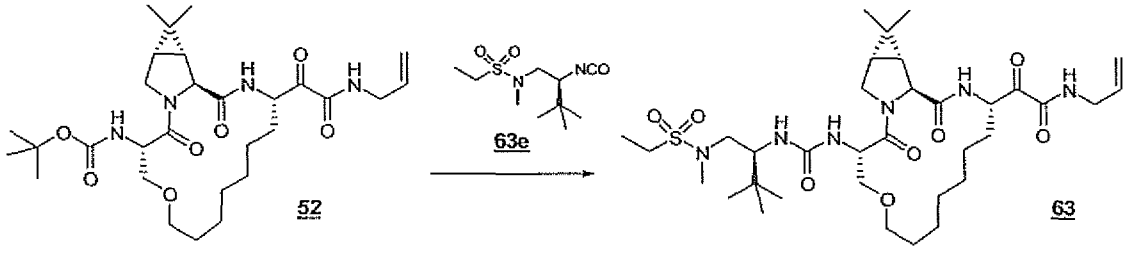
The N-Boc protected amine **63c** (850 mg) was dissolved in 100 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature until all the starting material had been consumed as determined by TLC (acetone/hexanes; 2:8). All the volatiles were removed under reduced pressure and the residue was placed under high vacuum to afford the product **63d** (680 mg, 98%).

Step D:

63d 63e

A solution of amine hydrochloride **63d** (2.636 mmol) in 40 mL of dichloromethane was treated with 40 mL of aqueous saturated sodium bicarbonate solution and stirred vigorously for 10 min at 0 °C. Stirring was stopped and layers were allowed to separate. Phosgene (10 mL of 20% soln in toluene) was added through a needle to the organic layer (lower layer) in one portion. The mixture was vigorously stirred immediately after addition for 10 min at 0 °C and further stirred at room temp for 2.5 h. The mixture was diluted with 100 mL of dichloromethane and layers were separated. The organic layer was washed with 30 mL of cold aqueous saturated sodium bicarbonate solution and dried over magnesium sulfate. The organic layer was filtered and the filtrate was diluted with 50 mL of toluene. The product **63e** (654 mg, 98%) was concentrated and kept as a 0.131M solution in toluene (the solution contains about 2 mL of dichloromethane).

Step E:

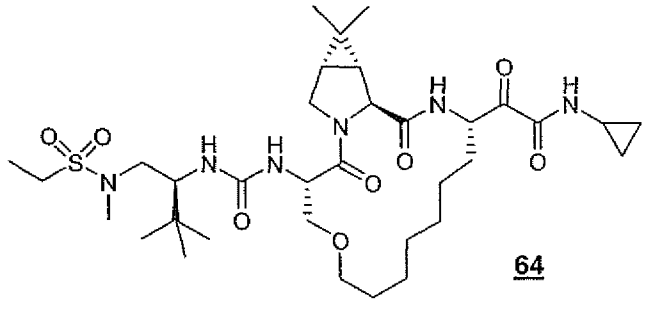


52 63e 63

The N-Boc amine **52** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the

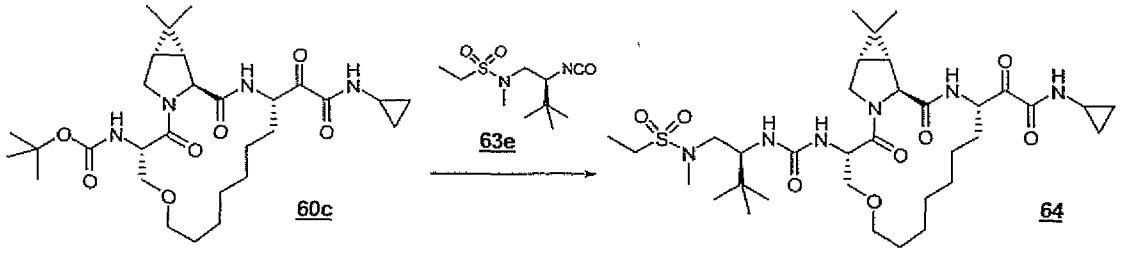
volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **63e** was added dropwise (1.2 eq, 0.97 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **63** (49 mg, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 1H, J = 8.5 Hz), 7.52 (br s, 1H), 6.04 (br s, 1H), 5.89 (ddt, 1H, J = 5.6, 10.4, 17.0 Hz), 5.65 (dd, 1H, J = 8.8, 10.4 Hz), 5.26 (dd, 1H, J = 1.2, 17.0 Hz), 5.22 (dd, 1H, J = 1.2, 10.0 Hz), 5.17 (d, 1H, J = 10.0 Hz), 4.99 (br s, 1H), 4.61 (s, 1H), 4.19 (d, 1H, J = 10.7 Hz), 4.02 (m, 2H), 3.95 (m, 2H), 3.60 (dd, 1H, J = 8.1, 9.1 Hz), 3.54 (m, 1H), 3.49 (d, 1H, 1.9 Hz), 3.44 (m, 1H), 3.32 (m, 1H), 3.07 (m, 3H), 2.94 (s, 3H), 1.93 (m, 1H), 1.35 (t, 3H, J = 7.5 Hz), 1.27-1.62 (m, 15H), 1.16 (m, 1H), 1.03 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ, 198.6, 172.3, 171.3, 159.4, 158.0, 133.4, 117.6, 71.1, 70.6, 60.7, 54.7, 53.5, 51.0, 50.6, 48.4, 45.8, 42.2, 34.8, 34.5, 32.0, 30.9, 28.7, 27.8, 27.3, 27.0, 26.9, 24.3, 24.2, 19.2, 13.5, 8.6 ppm; HRMS calcd for $C_{34}H_{59}N_6O_8S$ $[M+H]^+$: 711.4115, found 711.4133.

Preparative Example 64: Preparation of:



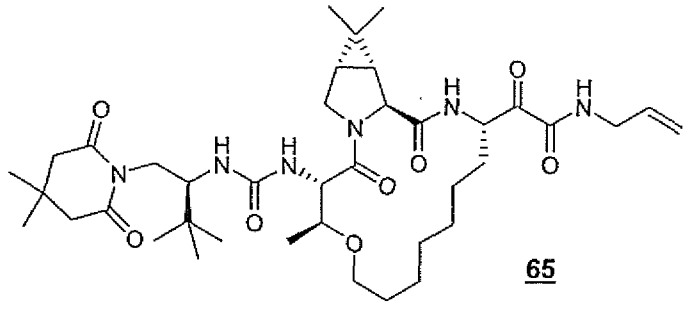
64

Step A:



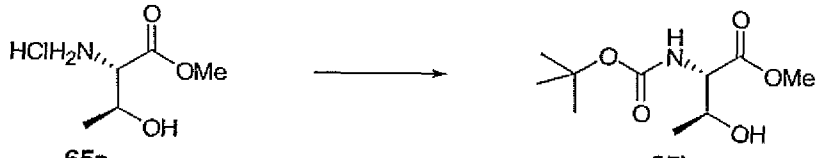
The N-Boc amine **60c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **63e** was added dropwise (1.2 eq, 0.97 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **64** (62 mg, 82%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (br s, 1H), 7.47 (br s, 1H), 5.94-6.19 (br s, 1H), 5.65 (dd, 1H, J = 8.8, 10.7 Hz), 5.21 (d, 1H, J = 7.8 Hz), 5.00 (dd, 1H, J = 3.7, 9.4 Hz), 4.59 (s, 1H), 4.21 (d, 1H, J = 10.7 Hz), 4.02 (dd, 1H, J = 5.0, 10.7 Hz), 3.93 (dd, 1H, J = 9.1, 9.7 Hz), 3.55 (m, 2H), 3.48 (d, 1H, J = 12.6 Hz), 3.40 (m, 1H), 3.29 (m, 1H), 3.07 (q, 2H, J = 7.2 Hz), 3.06 (m, 1H), 2.93 (s, 3H), 2.85 (dddd, 1H, J = 1.8, 4.0, 7.5, 15.1 Hz), 1.91 (m, 1H), 1.34 (t, 3H, J = 7.2 Hz), 1.25-1.61 (m, 12H), 1.13 (m, 1H), 1.01 (s, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.87 (m, 2H), 0.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.9, 172.3, 171.4, 160.9, 158.0, 71.0, 70.6, 60.6, 53.2, 50.9, 50.6, 48.4, 45.9, 34.8, 34.5, 32.1, 31.1, 28.7, 27.8, 27.5, 27.0, 26.9, 24.4, 23.0, 19.2, 13.6, 8.6, 6.7 ppm; HRMS calcd for $C_{34}H_{59}N_6O_8S$ $[M+1]^+$: 711.4115, found 711.4133.

Preparative Example 65: Preparation of:



65

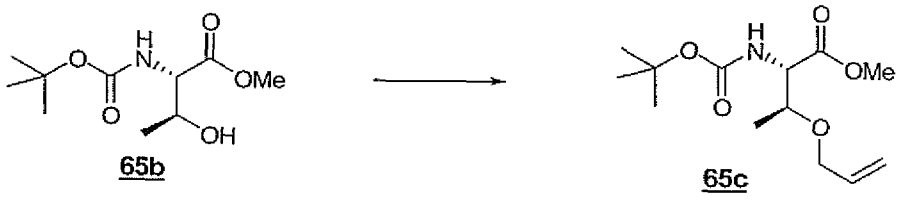
Step A:



65a 65b

A solution of (S)-allo-threonine-OMe hydrochloride **65a** (Chem-Impex, 5 g) in dry dichloromethane (150 mL) was cooled to 0 °C and treated with di-tert-butyldicarbonate (1.1 eq, 7.0 g) in 50 mL of dry dichloromethane. N-methylmorpholine (2.5 eq, 8.1 mL, d 0.920) was added dropwise and the mixture was stirred for 30 min. The cooling bath was removed and the mixture was stirred for further 3 h. The mixture was concentrated to one third of its volume and then diluted with ethyl acetate (300 mL) and washed with aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate (80 mL) and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the product **65b** (6.78 g, 98%) as a colorless oil.

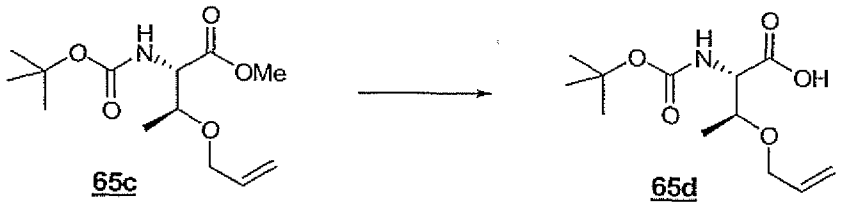
Step B:



65b 65c

A solution of Boc-L-allo-Thr-OMe **65b** (6.8 g) in 250 mL of dry THF was degassed (vacuum/N2-flush) and treated with allylmethyl carbonate (1.3 eq, 4.3 mL, d 1.022). A catalytic amount of tetrakis(triphenylphosphine)palladium (0.02 mol%, 673 mg) was added. The slightly yellow mixture was degassed again and heated at 60 °C for about 3 h until TLC analysis (acetone/hexanes; 2:8) showed no more starting material left (reaction mixture became brown). The mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate/hexanes; 1:9) to afford the product **65c** (5.72 g, 72%) as a colorless oil.

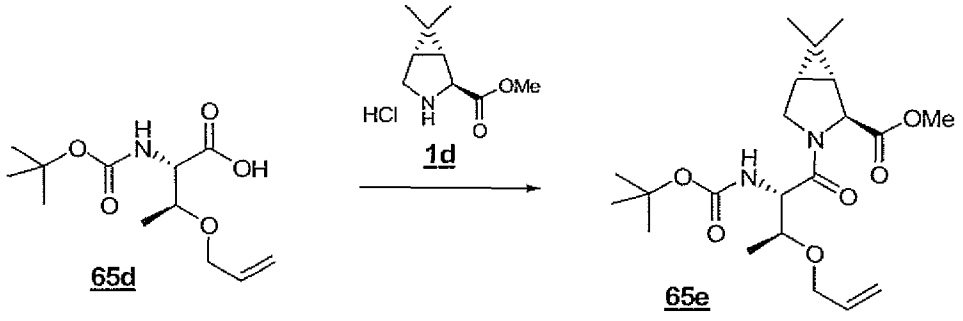
Step C:



65c 65d

A solution of methyl ester **65c** (1.45 g) in 250 mL of a 4:2:1 mixture of THF/water/MeOH was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 2.19 mg). The cooling bath was removed after 30 min and the mixture was stirred at room temp for further 4 h until all the starting material had been consumed as determined by TLC analysis (acetone/hexanes; 15:85). The reaction mixture was treated with 200 mL of aqueous 1M HCl (pH of mixture = 1) and the product was taken into dichloromethane (4 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the product. No further purification was carried out for the product **65d** (5.42 g, 98%).

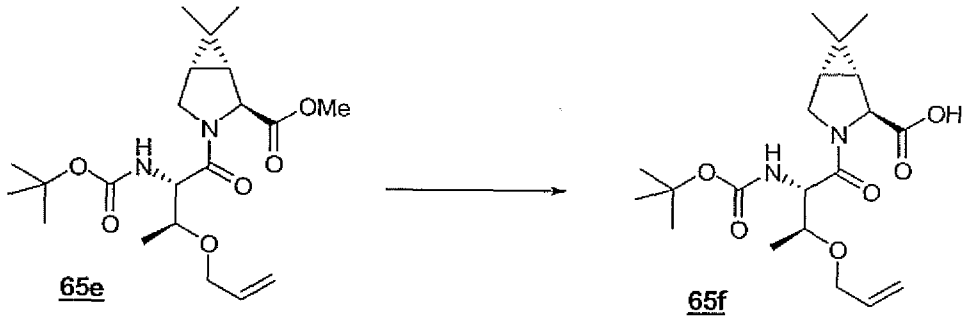
Step D:



65d 1d 65e

A solution of acid **65d** (20.92 mmol) in 200 mL of dry dichloromethane and 100 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 11.16 g). The amine salt **1d** (1.2 eq, 5.16 g) was added followed by N-methylmorpholine (4 eq, 9.19 mL, d 0.920). The reaction mixture was stirred overnight. All the volatiles were removed under vacuum and the residue was dissolved in 500 mL of ethyl acetate. The organic layer was washed with water (200 mL), aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 2:8) to give the product **65e** (7.6 g, 88%) as a colorless oil along with a small amount of its corresponding diastereomeric product.

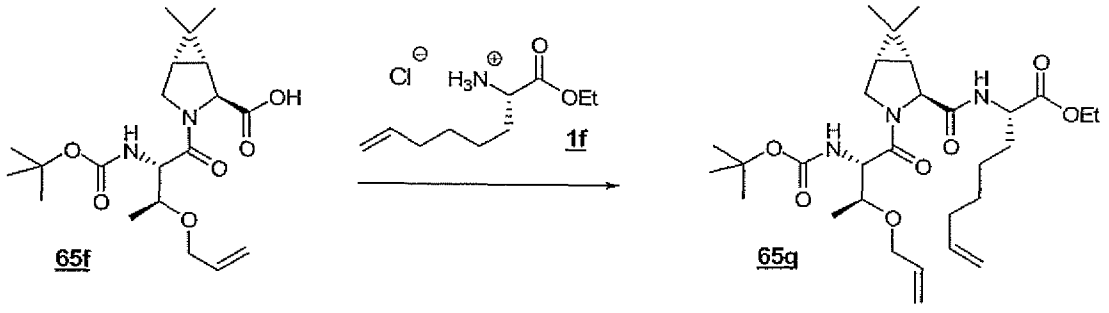
Step E:



65e 65f

A solution of methylester **65e** (7.6 g) in 300 mL of a 2:1 mixture of THF/water was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 1.93 mg). The cooling bath was removed after 30 min and the mixture was stirred at room temp for further 4 h until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 25:75). The reaction mixture was treated with 200 mL of aqueous 1M HCl (pH of mixture = 1) and the product was taken into dichloromethane (4 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the product **65f** (6.86 g, 93%) as a colorless solid.

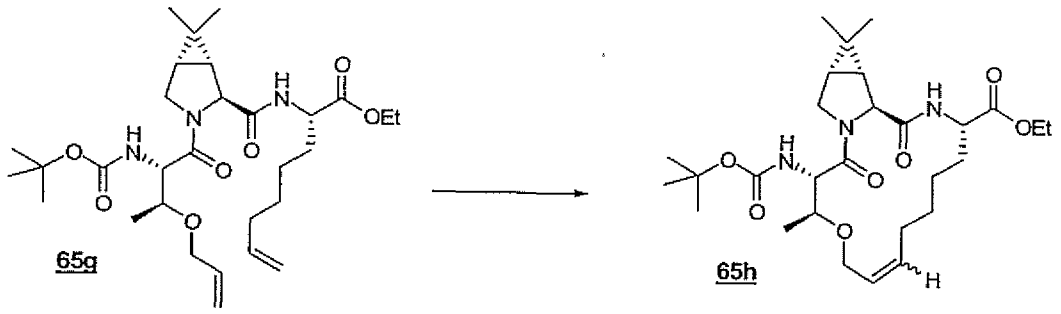
Step F:



65f 1f 65g

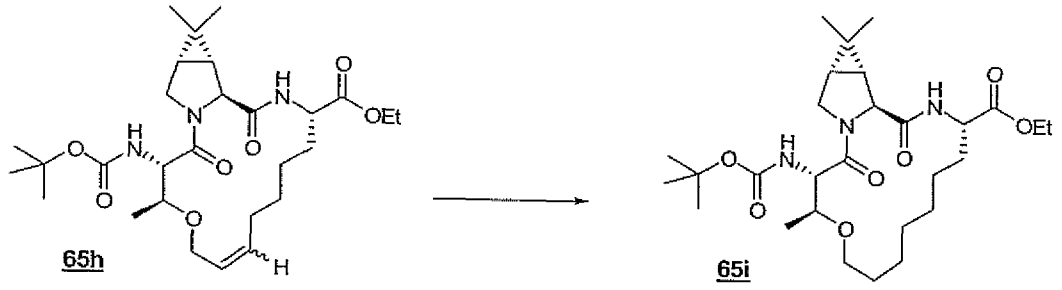
A solution of acid **65f** (6.86 g) in 100 mL of dry dichloromethane and 100 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 9.23 g). The amine salt **1f** (1.1 eq, 4.21 g) was added in 100 mL of dichloromethane followed by addition of N-methylmorpholine (4 eq, 7.6 mL, d 0.920). The reaction mixture was stirred at 0 °C overnight. All the volatiles were removed under vacuum and the residue was dissolved in 500 mL of ethyl acetate. The organic layer was washed with water (2 x 100 mL), aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to afford the product **65g** (8.17 g, 84%) as a colorless oil.

Step G:



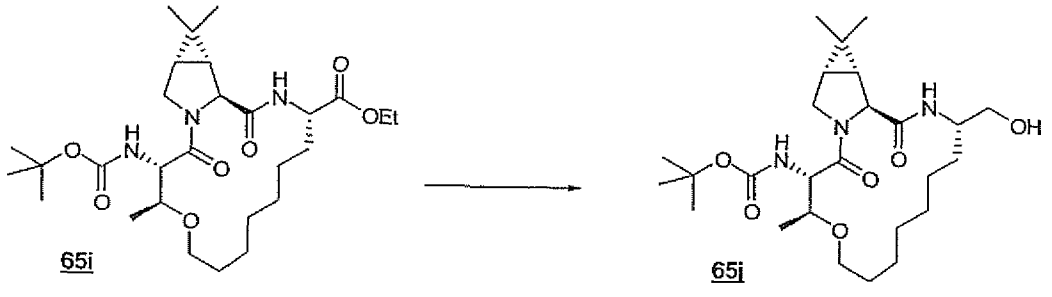
A solution of diene **65g** (8.17 g) in 1.5 L of toluene was degassed for 30 min (argon bubbling) and treated with Grubb's catalyst (0.2 eq, 2.38 g). The pink solution was heated to 60 °C for 18 h (the solution became dark after 10 min of heating). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to give the alkene product **65h** (7.0 g, 90%) as a mixture of E- and Z-isomers (approx 4:1).

Step H:



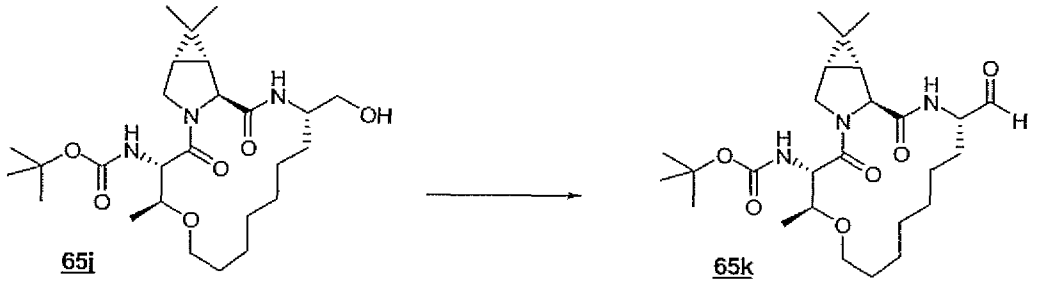
A solution of alkene **65h** (7.0 g) in 300 mL of methanol was treated with palladium on carbon (0.1 mol%, 1.37 g of 10% Pd/C). The mixture was hydrogenated at 35 psi until all the starting material had been consumed (approx 3 h). The reaction mixture was diluted with 300 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated and the residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to afford the product **65i** (5.33 g, 76%) as a white solid.

Step I:



A solution of ethyl ester **65i** (5.33 g) in 100 mL of dry THF was treated with lithium borohydride (2.1 eq, 10.4 mL of a 2M soln in THF). The reaction mixture was stirred at room temperature and monitored by TLC (acetone/hexanes; 3:7) for disappearance of the starting material. After 2 h, more lithium borohydride solution was added (1 eq) and stirring was continued for 1h. The excess lithium borohydride was quenched by addition of aqueous saturated ammonium chloride solution. The mixture was partitioned between ethyl acetate (300 mL) and aqueous saturated sodium bicarbonate solution (100 mL). The aqueous layer was back extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (acetone/hexanes; 3:7) to afford the product **65j** (3.93 g, 80%) as a white solid.

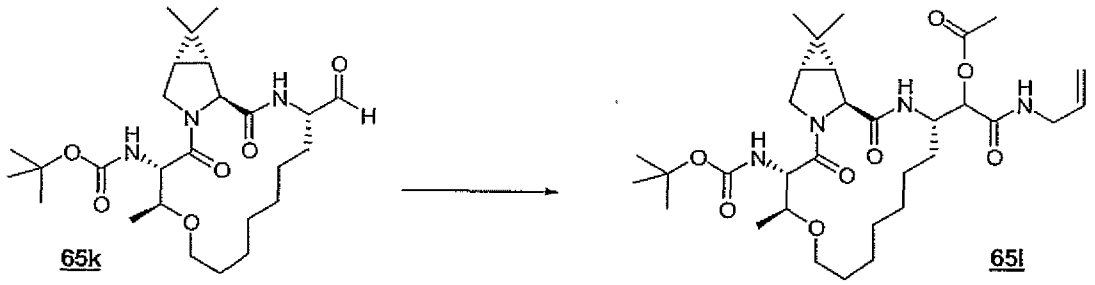
Step J:



65j 65k

A solution of alcohol **65j** (1.0 g) in 40 mL of dry dichloromethane was treated with Dess-Martin periodinane (1.5 eq, 1.28 g). The reaction mixture was stirred at room temperature for 3 h. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (30 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 4:6 to 8:2) to afford the product **65k** (750 mg, 75%) as a colorless solid.

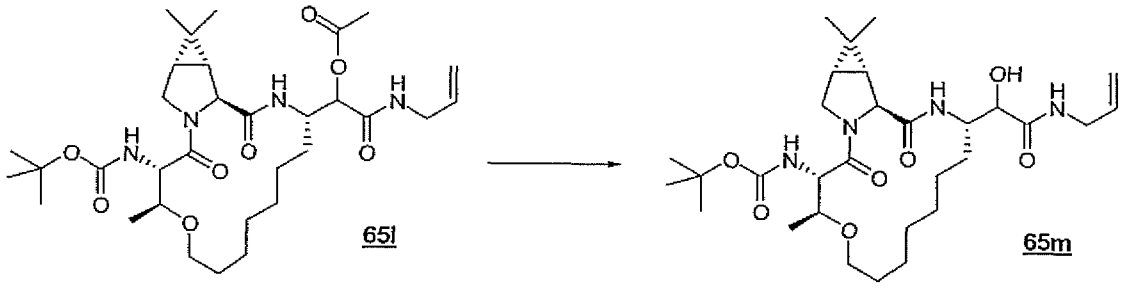
Step K:



65k 65l

A solution of aldehyde **65k** (750 mg) in 20 mL of dry dichloromethane was treated with allylisocyanide (2 eq, 0.26 mL, d 0.8) and acetic acid (2 eq, 0.17 mL, d 1.049). The mixture was stirred at room temperature for about 5 h. All the volatiles were removed under vacuum and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **65l** (700 mg, 74%) as a white solid.

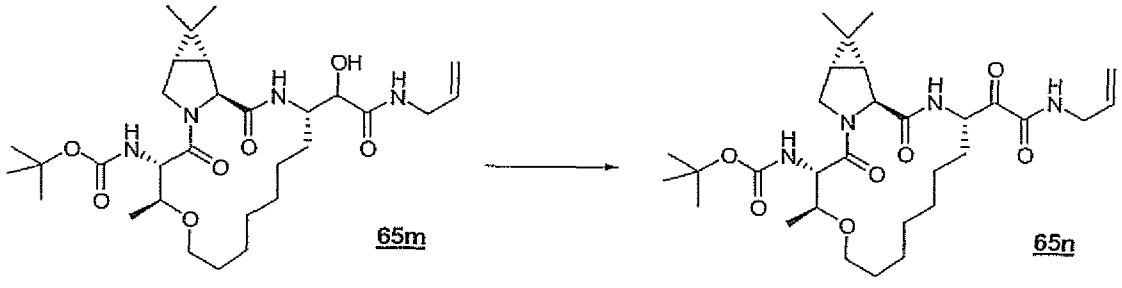
Step L:



65l 65m

A solution of acetate **65l** (700 mg) in 20 mL of a 2:1 mixture of THF/water was treated with lithium hydroxide monohydrate (2.5 eq, 118 mg) and stirred for approx 30 min until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 8:2). The reaction mixture was diluted with 50 mL of aqueous saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the product **65m** (651 mg, 98%) as a colorless semi-solid which was used without further purification.

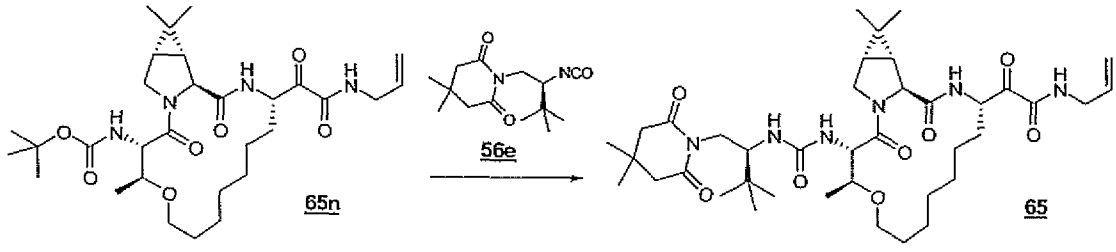
Step M:



65m 65n

A solution of hydroxyamide **65m** (1.127 mmol) in 25 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 956 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (20 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (30 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **65n** (585 mg, 90%) as white solid.

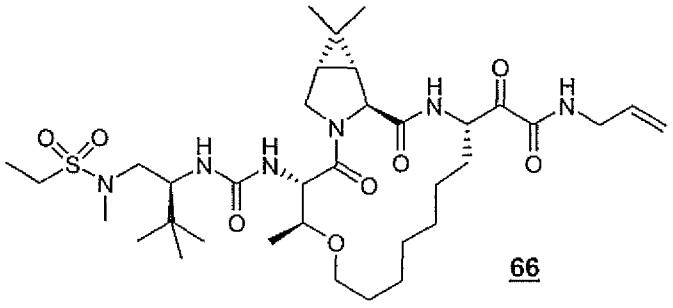
Step N:



The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **56e** was added dropwise (1.2 eq, 0.57 mL of a 0.216M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 5:5) to afford the product **65** (50 mg, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.42-7.82 (br s, 1H), 6.30 (br s, 1H), 5.90 (ddt, 1H, J = 5.6, 10.4, 17.0 Hz), 5.71 (br s, 1H), 5.38 (br s, 1H), 5.27 (dd, 1H, J = 1.2, 17.0 Hz), 5.23 (dd, 1H, J = 1.2, 10.4 Hz), 4.63 (dd, 1H, J = 7.8, 8.1 Hz), 4.50 (br s, 1H), 4.23 (d, 1H, J = 10.4 Hz), 4.05 (m, 2H), 3.98 (dd, 1H, J = 5.6, 5.9 Hz), 3.95 (d, 1H, J = 11.0 Hz), 3.88 (dd, 1H, J = 10.7, 10.8 Hz), 3.82 (q, 1H, J = 11.6 Hz), 3.71 (m, 1H), 3.62 (ddd, 1H, J = 5.0, 5.3, 9.4 Hz), 3.20 (m, 1H), 2.55 (d, 2H, J = 16.7 Hz), 2.47 (d, 2H, J = 16.7 Hz),

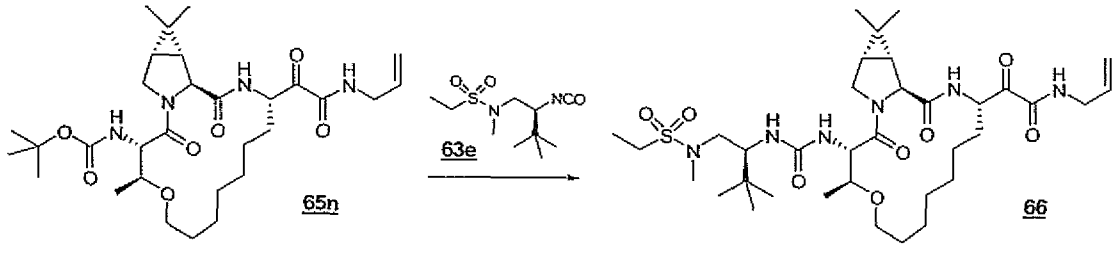
1.73-1.97 (m, 4H), 1.14 (d, 3H, J = 6.0 Hz), 1.10 (s, 6H), 1.00 (s, 3H), 0.99 (s, 9H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.0, 172.8, 171.5, 159.4, 157.8, 117.7, 75.5, 68.1, 60.8, 57.2, 55.9, 48.7, 46.8, 42.3, 35.2, 29.3, 28.7, 28.3, 27.8, 27.6, 26.9, 26.8, 24.7, 24.4, 19.4, 16.3, 13.6 ppm; HRMS calcd for $C_{39}H_{63}N_6O_8$ $[M+H]^+$: 743.4707, found 743.4717.

Preparative Example 66: Preparation of:



66

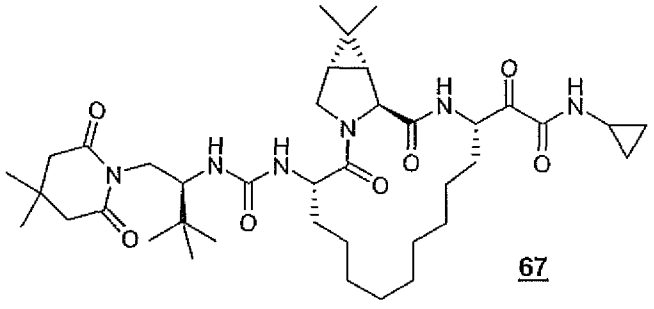
Step A:



The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **63e** was added dropwise (1.2 eq, 0.95 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **66** (55 mg, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 6.6 Hz), 7.58-7.77 (br s, 1H), 6.13 (br s, 1H), 5.90 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.76 (br s, 1H), 5.27 (dd, 1H, J = 1.2, 17.0 Hz), 5.22 (dd, 1H, J = 1.2, 10.0 Hz), 5.15 (d, 1H, J = 9.1 Hz), 4.69 (dd, 1H, J = 8.8, 8.8 Hz), 4.57 (s, 1H),

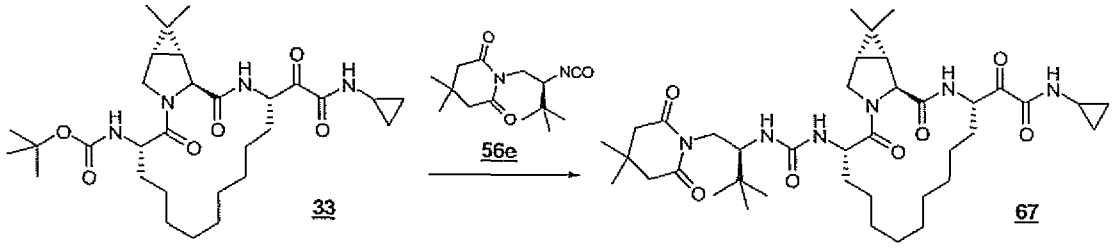
4.29 (d, 1H, J = 10.7 Hz), 3.91-4.09 (m, 4H), 3.61 (m, 2H), 3.47 (dd, 1H, J = 11.9, 13.5 Hz), 3.19 (m, 1H), 3.07 (m, 3H), 2.94 (s, 3H), 1.95 (m, 1H), 1.35 (t, 3H, J = 7.5 Hz), 1.27-1.69 (m, 12H), 1.22 (d, 3H, J = 6.3 Hz), 1.14 (m, 1H), 1.02 (s, 3H), 0.93 (s, 9H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.0, 172.8, 171.5, 159.3, 158.1, 133.5, 117.5, 75.8, 68.4, 60.7, 56.2, 50.4, 48.6, 45.6, 42.2, 34.7, 34.5, 32.0, 31.6, 28.6, 27.7, 27.0, 26.9, 26.7, 24.8, 24.6, 19.3, 16.2, 14.5, 13.5, 8.5 ppm; HRMS calcd for $C_{35}H_{61}N_6O_8S$ $[M+H]^+$: 725.4272, found 725.4285.

Preparative Example 67: Preparation of:



67

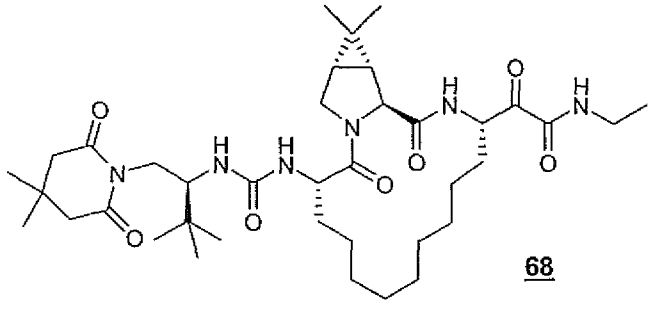
Step A:



The N-Boc amine **33** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.03 mL, d 0.920) was added. After 10 min, a soln of the isocyanate **56e** was added dropwise (1.5 eq, 0.8 mL of a 0.2M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aq 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to afford the product **67** (50 mg, 64%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, 1H, J = 6.9 Hz), 7.66-

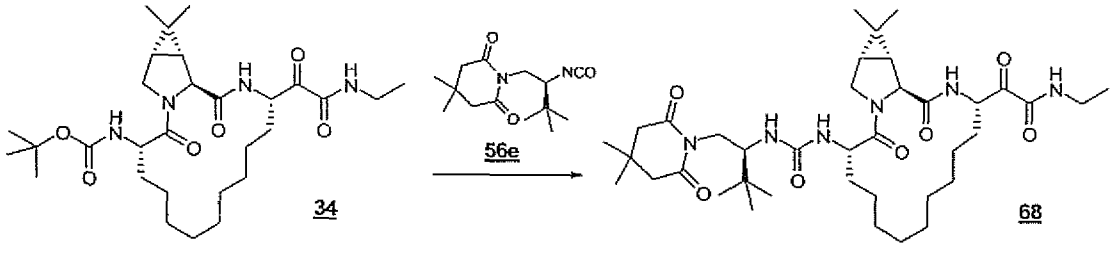
7.82 (br s, 1H), 6.11 (br s, 1H), 5.70 (br s, 1H), 5.32 (br s, 1H), 4.63 (br s, 1H), 4.60 (s, 1H), 4.19 (d, 1H, *J* = 10.0 Hz), 3.96 (dd, 1H, *J* 5.0, 10.0 Hz), 3.91 (m, 3H), 2.91 (ddd, 1H, *J* = 3.7, 7.8, 15.1 Hz), 2.57 (d, 2H, *J* = 16.7 Hz), 2.50 (d, 2H, *J* = 16.7 Hz), 1.86 (m, 3H), 1.69 (m, 1H), 1.18-1.61 (m, 16H), 1.10 (s, 6H), 1.01 (s, 3H), 0.95 (s, 9H), 0.89 (m, 2H), 0.87 (s, 3H), 0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.2, 173.5, 172.9, 171.9, 160.7, 158.0, 60.5, 56.6, 51.5, 48.5, 46.8, 39.9, 35.0, 34.2, 31.4, 29.4, 28.1, 27.8, 27.6, 27.4, 27.3, 27.0, 26.9, 26.5, 26.1, 23.4, 23.1, 19.4, 13.6, 6.8, 6.7 ppm.

Preparative Example 68: Preparation of:



68

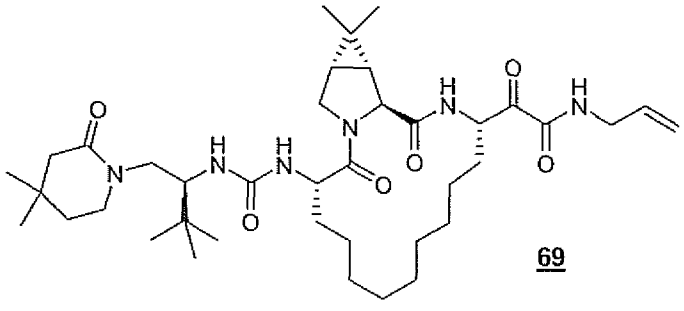
Step A:



The N-Boc amine **34** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.02 mL, d 0.920) was added. After 10 min, a soln of the isocyanate **56e** was added dropwise (1.4 eq, 0.6 mL of a 0.241M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aq 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **68** (44 mg,

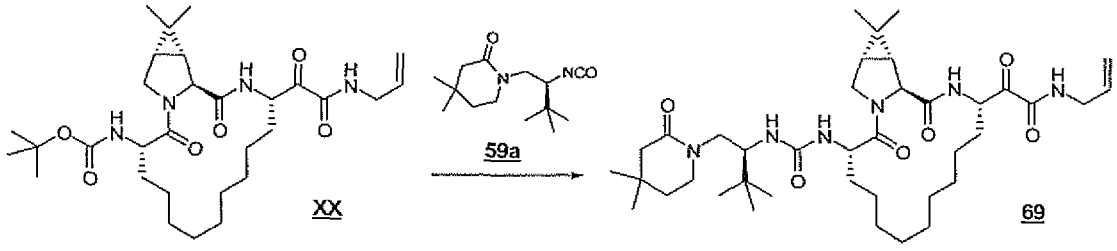
56%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (br s, 1H), 7.52-7.77 (br s, 1H), 6.06 (br s, 1H), 5.70 (br s, 1H), 5.26 (br s, 1H), 4.63 (m, 2H), 4.20 (d, 1H, J = 10.0 Hz), 3.97 (dd, 1H, J = 5.0, 10.0 Hz), 3.92 (m, 3H), 3.43 (m, 2H), 2.57 (d, 2H, J = 16.7 Hz), 2.50 (d, 2H, J = 16.7 Hz), 1.90 (m, 1H), 1.74 (m, 2H), 1.27 (t, 3H, J = 7.2 Hz), 1.20-1.62 (m, 17H), 1.11 (s, 6H), 1.02 (s, 3H), 0.96 (s, 9H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.1, 173.5, 172.9, 171.8, 159.3, 157.9, 60.6, 56.6, 51.5, 48.5, 46.8, 40.0, 34.9, 34.8, 34.1, 32.8, 29.4, 28.1, 27.8, 27.5, 27.4, 27.3, 27.0, 26.9, 26.5, 26.0, 25.1, 23.4, 19.4, 14.8, 13.6 ppm; HRMS calcd for $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715.4758, found 715.4751.

Preparative Example 69: Preparation of:



69

Step A:

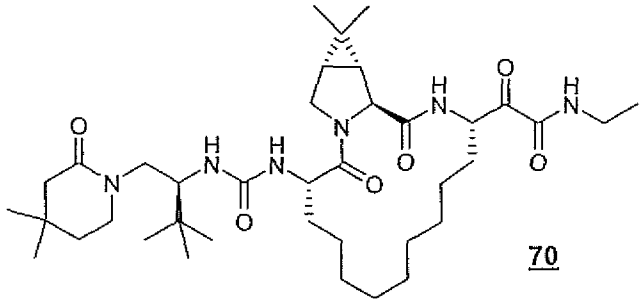


XX 59a 69

The N-Boc amine **XX** (93 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.04 mL, d 0.920) was added. After 10 min, a soln of the isocyanate **59a** in toluene was added dropwise (1.2 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aq 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient:

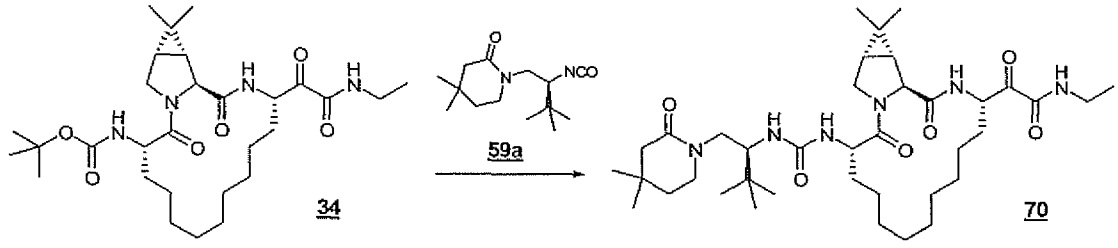
acetone/hexanes; 1:9 to 45:55) to afford the product **69** (45 mg, 38%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26-8.67 (br s, 1H), 8.17 (br s, 1H), 6.19 (br s, 1H), 5.92 (ddt, 1H, J = 5.6, 10.4, 17.3 Hz), 5.74 (dd, 1H, J = 8.8, 9.1 Hz), 5.41 (br s, 1H), 5.26 (dd, 1H, J = 1.2, 17.3 Hz), 5.20 (d, 1H, J = 10.0 Hz), 4.67 (br s, 1H), 4.62 (s, 1H), 4.35 (dd, 1H, J = 1.9, 12.9 Hz), 4.20 (d, 1H, J = 9.8 Hz), 3.99 (m, 4H), 3.58 (ddd, 1H, J = 5.9, 6.9, 12.6 Hz), 3.18 (ddd, 1H, J = 5.9, 5.9, 11.9 Hz), 2.69 (d, 1H, J = 10.7 Hz), 2.18 (d, 1H, J = 17.0 Hz), 2.12 (d, 1H, J = 17.0 Hz), 1.96 (m, 1H), 1.18-1.89 (m, 20H), 1.12 (m, 1H), 1.04 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.3, 173.3, 171.8, 171.1, 159.4, 158.2, 133.7, 117.3, 60.4, 55.3, 51.5, 48.3, 46.3, 45.0, 42.3, 35.8, 34.6, 34.0, 31.2, 30.3, 28.6, 27.8, 27.7, 27.6, 27.3, 27.2, 27.0, 26.3, 25.9, 25.4, 23.2, 19.3, 13.5 ppm.

Preparative Example 70: Preparation of:



70

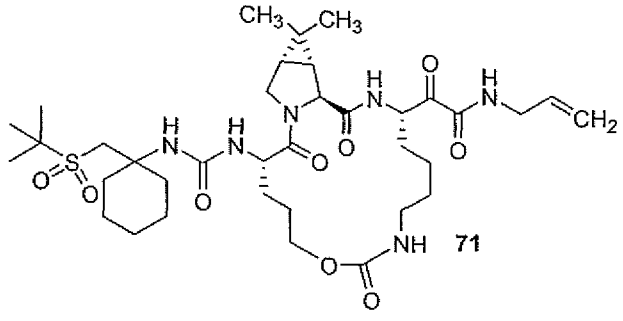
Step A:



The N-Boc amine **34** (73 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.03 mL, d 0.920) was added. After 10 min, a soln of the isocyanate **59a** in toluene was added dropwise (1.2 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aqueous 1M HCl (10 mL) and

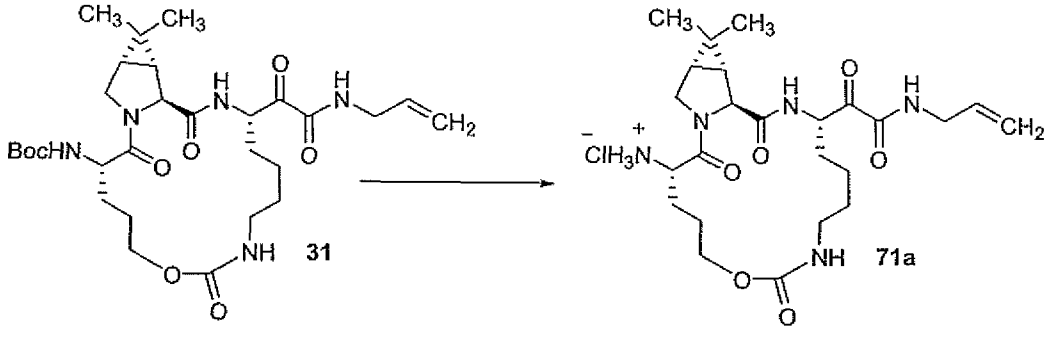
brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **70** (63 mg, 69%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20-8.43 (br s, 1H), 8.17 (br s, 1H), 6.20 (br s, 1H), 5.75 (dd, 1H, J = 8.2, 9.4 Hz), 5.41 (br s, 1H), 4.66 (d, 1H, J = 9.1 Hz), 4.63 (s, 1H), 4.36 (dd, 1H, J = 12.6, 13.2 Hz), 4.18 (d, 1H, J = 10.4 Hz), 3.96 (m, 2H), 3.57 (m, 1H), 3.41 (m, 2H), 3.18 (ddd, 1H, J = 5.9, 11.9 Hz), 2.69 (d, 1H, J = 13.2 Hz), 2.19 (d, 1H, J = 17.0 Hz), 2.14 (d, 1H, 17.0 HZ), 1.76-1.99 (m, 4H), 1.25 (t, 3H, J = 7.2 Hz), 1.18-1.75 (m, 17H), 1.12 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 173.3, 171.8, 171.1, 159.4, 158.2, 60.4, 55.2, 53.5, 51.5, 48.3, 46.3, 35.8, 34.8, 34.6, 31.3, 30.3, 28.7, 27.8, 27.7, 27.6, 27.3, 27.0, 26.4, 26.0, 23.2, 19.3, 14.8, 13.5 ppm; HRMS calcd for $C_{38}H_{65}N_6O_6$ $[M+H]^+$: 701.4966, found 701.4960.

Preparative Example 71: Preparation of:



71

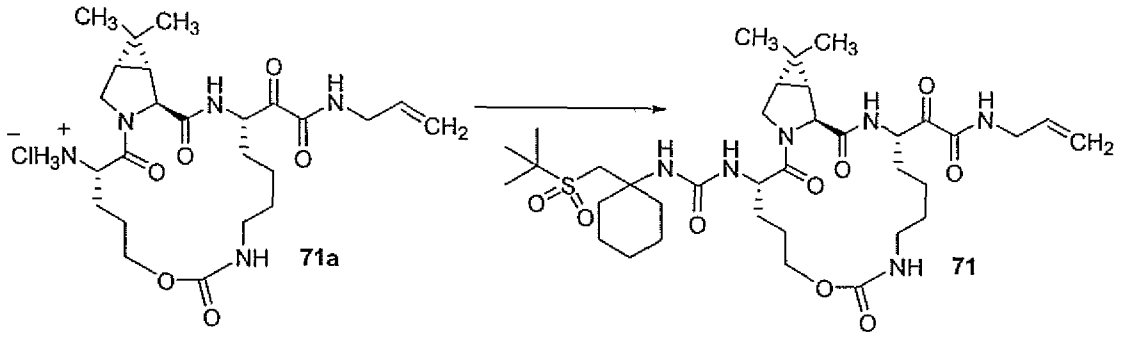
Step A:



31 **71a**

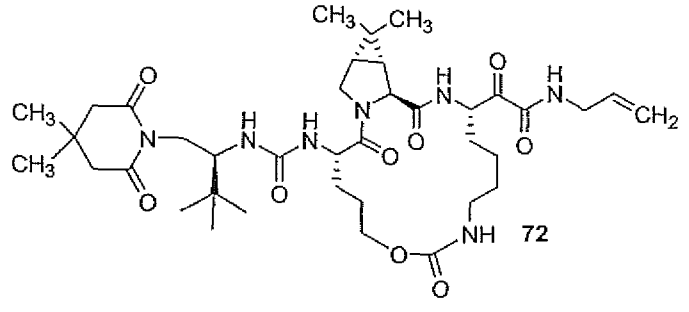
A solution of **31** (100 mg, 0.169 mmol) in 4 N. HCl in dioxane (5 ml) was stirred at room temperature for 1 hour. Solvent was removed to dryness to give **71a** (120 mg) which was used without further purification

Step B:

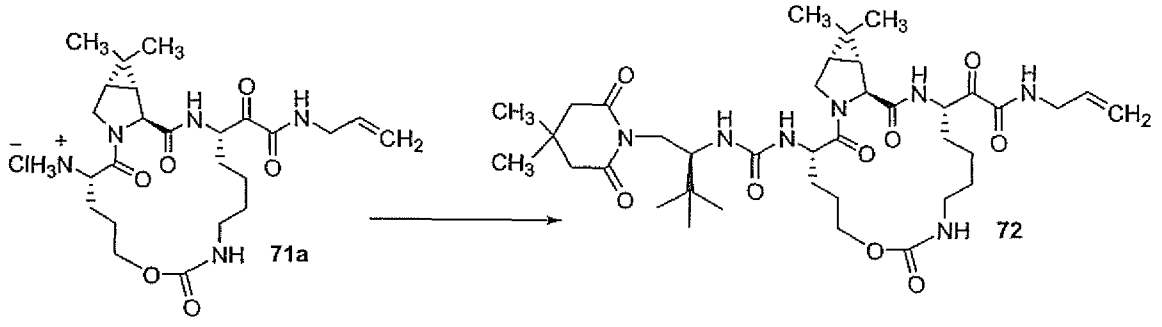


A solution of **71a** (89 mg, 0.169 mmol) in CH_2Cl_2 (10 ml) was treated with isocyanate **27b** (3 equiv), sat. $NaHCO_3$ (3 ml) and stirred vigorously for 2 hours. The solution was allowed to stand at 5 °C for 12 hours. The CH_2Cl_2 layer was separated, washed with water, brine and filtered through Na_2SO_4. Solvent was removed to dryness and the residue was purified on silica gel column (40% to 60% acetone/hexanes) to give **71** (73 mg). MS (ES) *m/z* relative intensity 773 [$(M+Na)^+$, 20]; 751 [$(M+1)^+$, 100]. Calcd. for $C_{36}H_{59}N_6O_9S$ [$M+1]^+$: 751.4064; Found 751.4075.

Preparative Example 72: Preparation of:



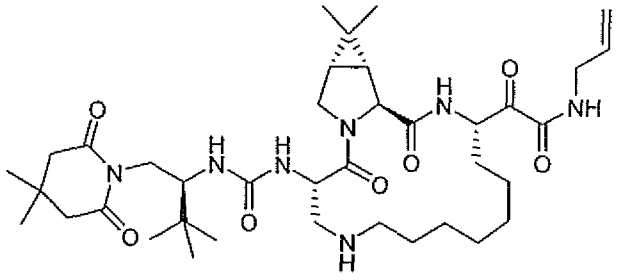
Step A:



A solution of **71a** (89 mg, 0.169 mmol) in CH_2Cl_2 (10 ml) was treated with isocyanate **51c** (1.5 equiv), sat. $NaHCO_3$ (4 ml) and stirred vigorously for 30 minutes. The solution was allowed to stand at 5 °C for 12 hours. The CH_2Cl_2 layer was separated, washed with water, brine and filtered through Na_2SO_4. Solvent was removed to dryness and the residue was purified on silica gel column (40% to 50% acetone/hexanes) to give **72** (95 mg). MS (ES) *m/z* relative intensity 790

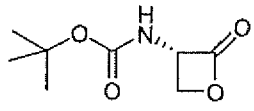
[(M+CH_3OH+1)$^+$, 40]; 758 [(M+1)$^+$, 100]. Calcd. for $C_{38}H_{59}N_7O_9$ [M+1]$^+$: 758.4453; Found 758.4449.

Preparative Example 73: Preparation of:



73

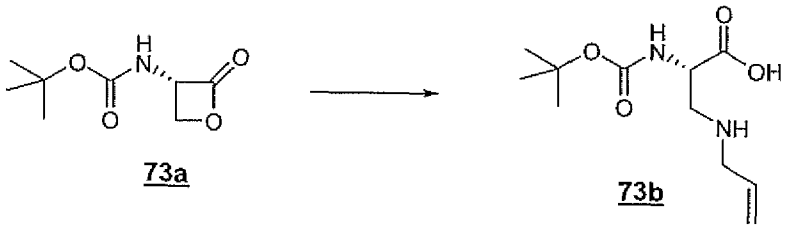
Step A:



73a

The N-(tert-Butoxycarbonyl)-L-serine-beta-lactone **73a** will be prepared according to the procedure described by Vederas and co-workers (Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105-7109) starting from commercially available N-Boc-L-Ser-OH.

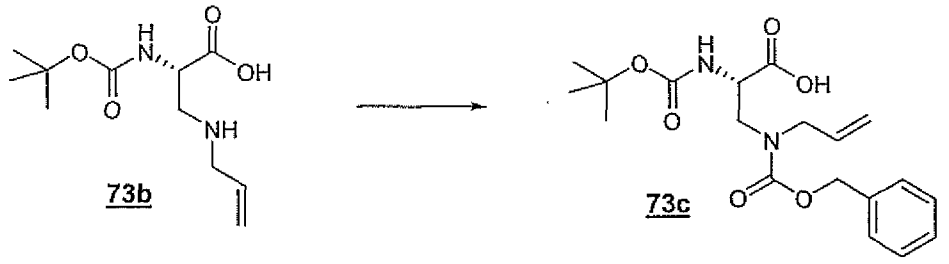
Step B:



73a **73b**

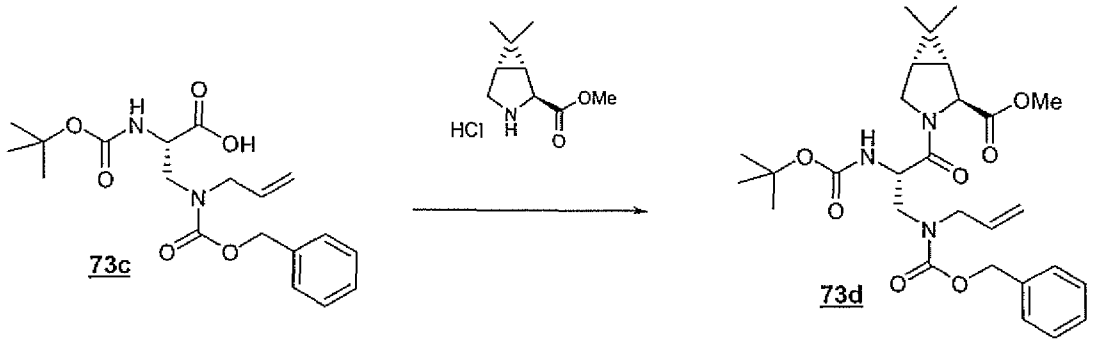
A solution of N-(tert-Butoxylcarbonyl)-L-serine-beta-lactone **73a** (1 mmol) in 20 mL of dry acetonitrile will be added dropwise at ambient temperature over 1 h to a stirred solution of allylamine (25 mmol) in 30 mL dry acetonitrile. After 2 h, the solution will be concentrated under reduced pressure. The residue will be slurried with acetonitrile and the acid product **73b** will be recovered by filtration.

Step C:



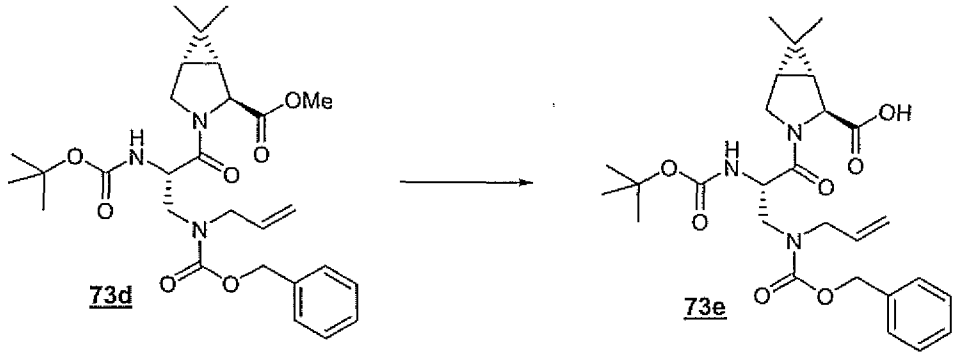
A solution of acid 2 (1 mmol) in aqueous saturated sodium bicarbonate solution (4 mL) and water (1 mL) at room temperature will be treated with benzyl chloroformate (1.12 mmol) in acetone (1 mL). The reaction mixture will be stirred for 2 h. The mixture will be partitioned between ether (20 mL) and water (20 mL). The aqueous layer will be cooled in an ice-water bath, brought to pH 2 using 5% aqueous HCl and extracted with dichloromethane (3 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered and concentrated to afford the acid product **73c**.

Step D:



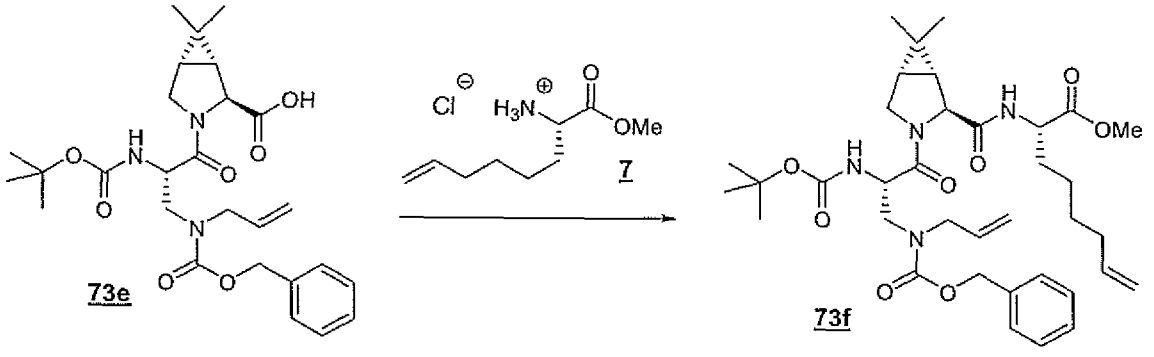
A solution of acid **73c** (1 mmol) in 10 mL of dry dichloromethane and 10 mL of dry DMF will be stirred at 0 °C and treated with HATU (1.4 mmol). The amine hydrochloride (1.3 mmol) and N-methylmorpholine (4 mmol) will be successively added. The reaction mixture will be gradually warmed to room temperature and stirred overnight. All the volatiles will be removed under vacuum and the residue will be taken into 100 mL of ethyl acetate. The organic layer will be washed with water (20 mL), aqueous 1N HCl (20 mL), aqueous saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic layer will be dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product **73d** will be purified by column chromatography on silica gel.

Step E:



A solution of methyl ester **73d** (1 mmol) in 15 mL of a mixture of THF/MeOH/H2O (1:1:1) will be treated with lithium hydroxide monohydrate (2.5 mmol) at 0 °C. The cooling bath will be removed and the reaction mixture stirred at room temperature and monitored by TLC (acetone/hexanes; 2:8). After 1 h, 10 mL of aqueous 1N HCl will be added and all the volatiles will be removed under reduced pressure. The residue will be partitioned between 30 mL of aqueous 1N HCl and 100 mL of dichloromethane. The aqueous layer will be back extracted with dichloromethane (2 x 50 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the acid product **73e**.

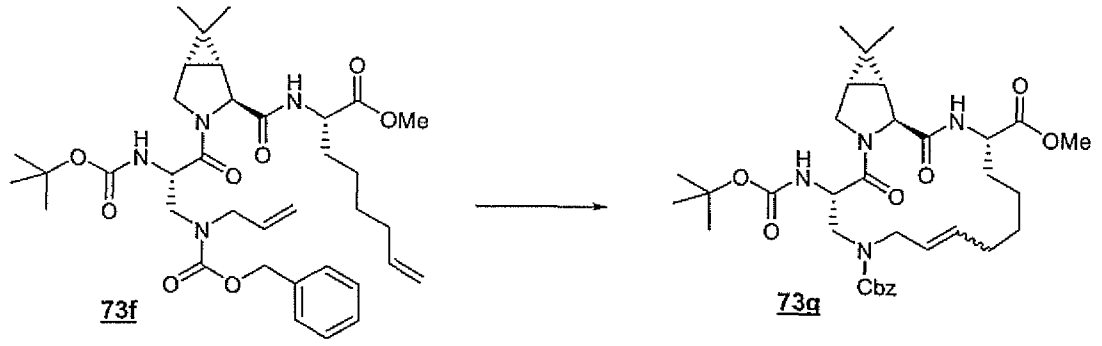
Step F:



A solution of acid **73e** (1 mmol) in 10 mL of dry dichloromethane and 10 mL of dry DMF will be stirred at 0 °C and treated with HATU (1.4 eq, 1.15 g). The amine hydrochloride **7** (1.2 mmol) will be added in 10 mL of dichloromethane followed by N-methylmorpholine (4 mmol). The reaction mixture will be stirred overnight (temp from 0 to 25 °C). All the volatiles will be removed under vacuum and the residue will be dissolved in 100 mL of ethyl acetate. The organic layer will be washed with water (20 mL), aqueous 1N HCl (20 mL), aqueous saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic layer will be dried over magnesium sulfate,

filtered and concentrated under reduced pressure. The product **73f** will be purified by column chromatography on silica gel.

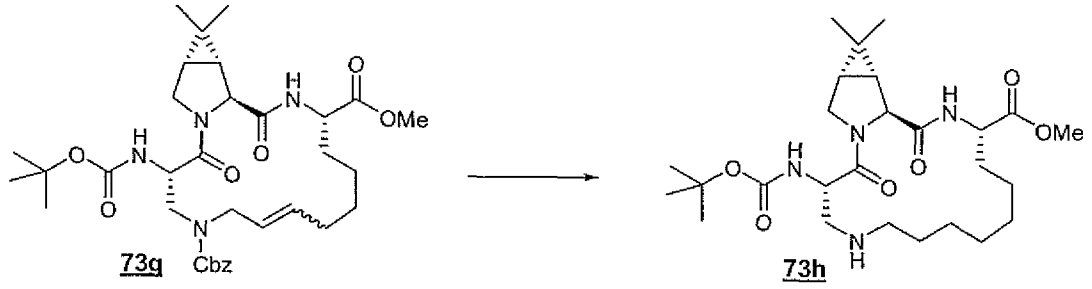
Step G:



73f 73g

A 0.01M solution of diene **73f** (1 mmol) in toluene will be degassed for 30 min (argon bubbling) and treated with Grubb's catalyst (0.2 mmol). The pink solution will be heated to 60 °C for 16 h. The solvent will be removed under reduced pressure and the residue will chromatographed on silica gel to afford the alkene product **73g** as a mixture of E- and Z-isomers.

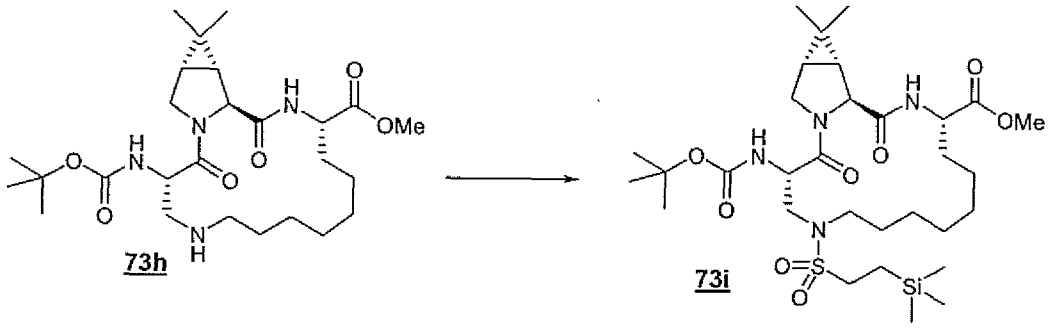
Step H:



73g 73h

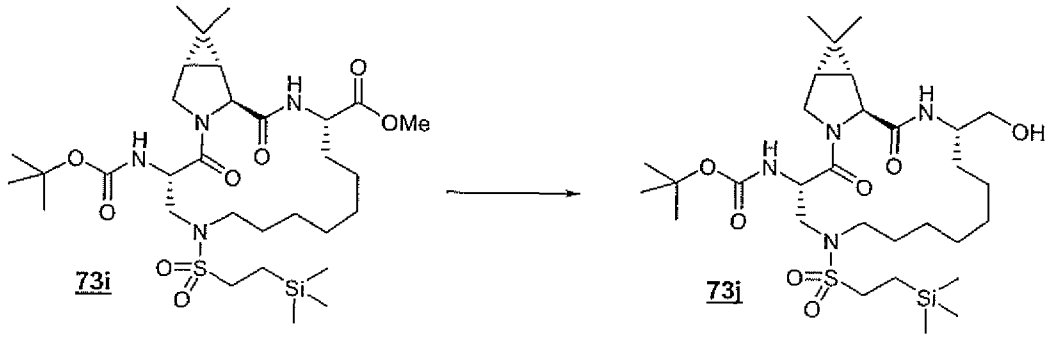
A solution of alkene **73g** (1 mmol) in 20 mL of methanol will be treated with 5% palladium on carbon (0.1 mol%). The mixture will be hydrogenated at 50 psi until all the starting material is consumed. The reaction mixture will be diluted with 100 mL of dichloromethane and filtered thru a short path of celite. The filtrate will be concentrated and the product **73h** will be purified by column chromatography on silica gel.

Step I:



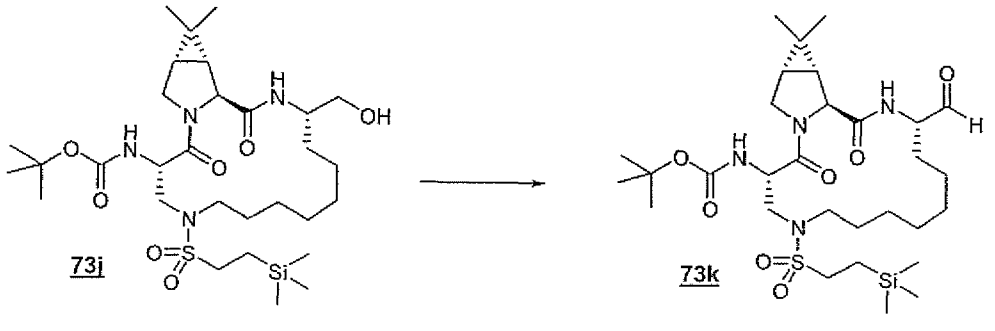
A solution of macrocyclic amine **73h** (1 mmol) in 10 mL of dichloromethane will be treated with potassium carbonate (2 mmol) and (trimethylsilyl)ethanesulfonyl chloride (1 mmol). The mixture is stirred for 1 day and solvent will be evaporated. The product **73i** will be purified by column chromatography on silica gel.

Step J:



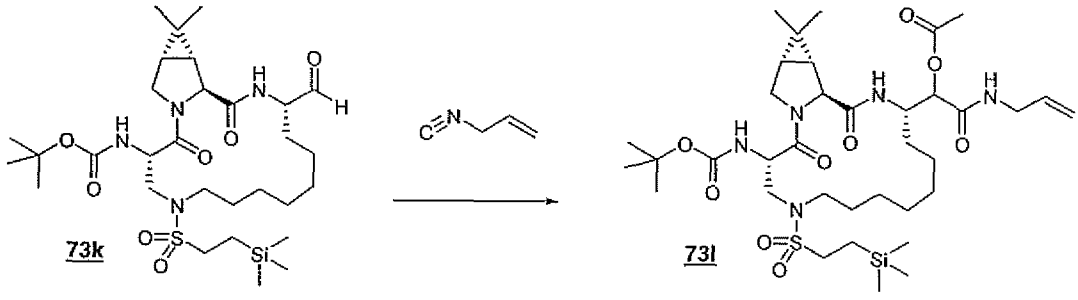
A solution of methyl ester **73i** (1 mmol) in 10 mL of dry THF will be treated with lithium borohydride (2.1 mmol). The reaction mixture will be stirred at room temperature. After 5 h, the excess lithium borohydride will be quenched by addition of aqueous saturated ammonium chloride solution (3 mL). The mixture will be partitioned between ethyl acetate (50 mL) and aqueous saturated sodium bicarbonate solution (30 mL). The aqueous layer will be back extracted with ethyl acetate (2 x 30 mL) and dichloromethane (2 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue will be chromatographed on silica gel to afford the product **73j**.

Step K:



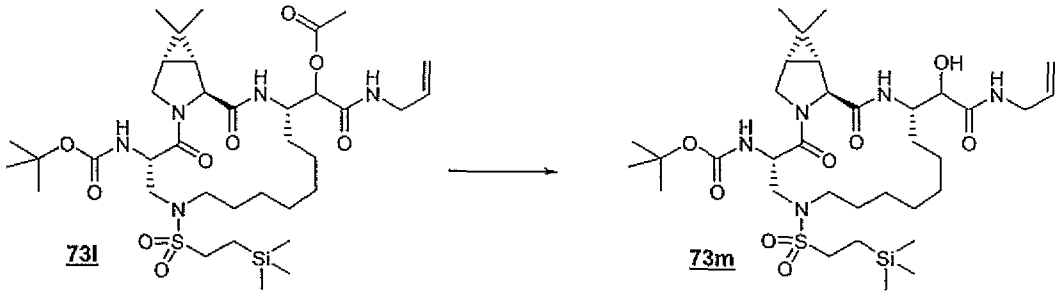
A solution of alcohol **73j** (1 mmol) in 20 mL of dry dichloromethane will be treated with Dess-Martin periodinane (1.5 mmol). The reaction mixture will be stirred at room temperature for 45 min. The mixture will be treated with aqueous 1M sodium thiosulfate solution (10 mL) and aqueous saturated sodium bicarbonate solution (20 mL) and stirred for 15 min. The mixture will be extracted with dichloromethane (3 x 40 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated. The residue will be chromatographed on silica gel to afford the aldehyde product **73k**.

Step L:



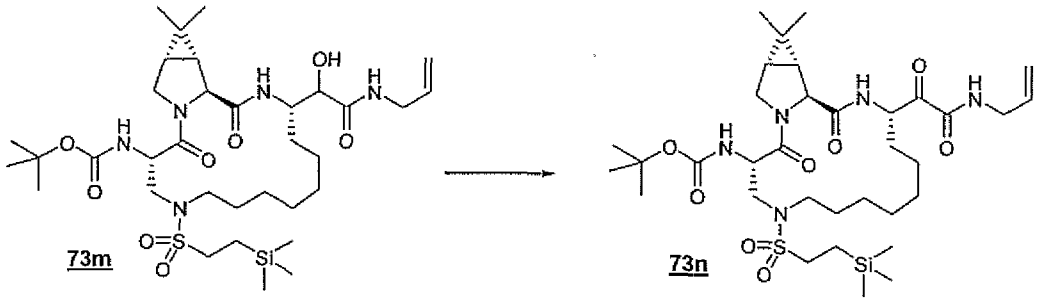
A solution of aldehyde **73k** (1 mmol) in 10 mL of dry dichloromethane will be treated with allylisocyanide (2 mmol) and acetic acid (2 mmol). The mixture will be stirred for about 5 h. All the volatiles will be removed under vacuum and the residue will be chromatographed on silica gel to afford the acetate product **73l**.

Step M:



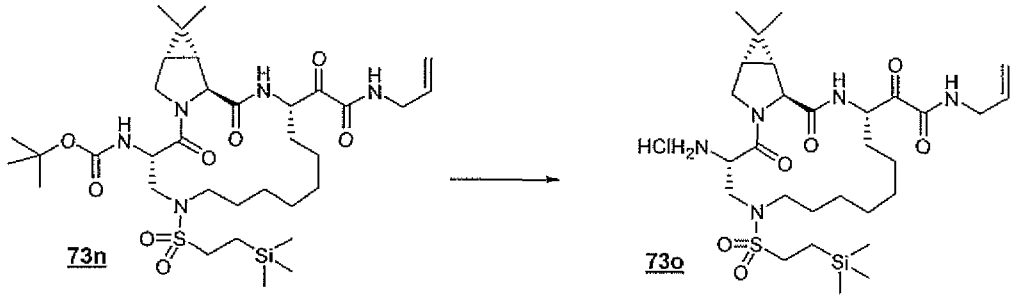
The acetate **73l** (1 mmol) will be dissolved in 16 mL of a 1:1 mixture of THF/water and treated with lithium hydroxide monohydrate (2.5 mmol). After 30 min the mixture will be partitioned between dichloromethane (50 mL) and aqueous saturated sodium bicarbonate solution (20 mL). The aqueous layer will be back extracted with dichloromethane (3 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated. The hydroxyamide product **73m** will be used without further purification.

Step N:



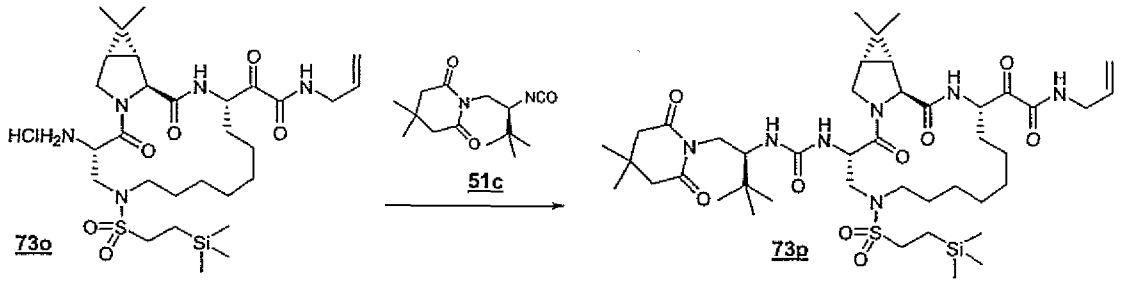
A solution of hydroxyamide **73m** (1 mmol) in 20 mL of dry dichloromethane will be treated with Dess-Martin periodinane (2.5 mmol). The reaction mixture will be stirred at room temperature for 30 min. The mixture will be treated with aqueous 1M sodium thiosulfate solution (20 mL) and aqueous saturated sodium bicarbonate solution (10 mL) and stirred for 15 min. The mixture will be extracted with dichloromethane (3 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated. The ketoamide product **73n** will be purified by column chromatography.

Step O:



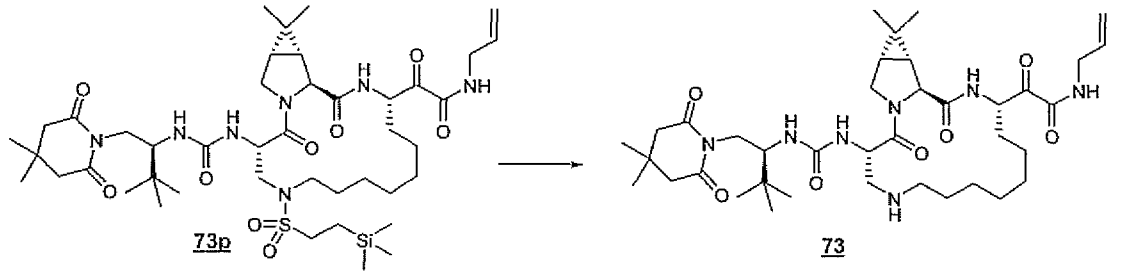
The N-Boc protected amine **73n** (0.1 mmol) will be dissolved in 5 mL of 4M HCl solution in dioxanes. The resulting solution will be stirred for 30 min and then evaporated under reduced pressure to give the amine hydrochloride product **73o**.

Step P:



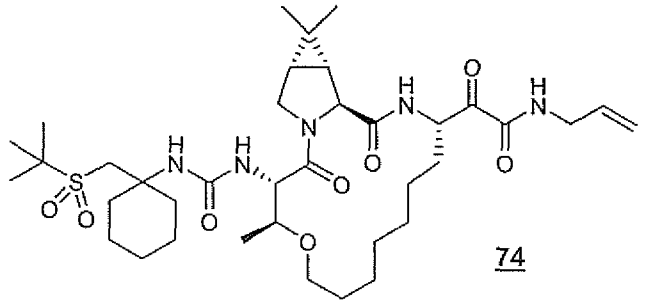
The amine hydrochloride **73o** (0.1 mmol) will be dissolved in 5 mL of dichloromethane and treated with 20 drops of aqueous saturated sodium bicarbonate solution followed by a solution of isocyanate **51c** (0.12 mmol) in toluene. The mixture will be stirred for 5 h and then diluted with 50 mL of dichloromethane and dried over magnesium sulfate. The mixture will be filtered, and concentrated under reduced pressure. The product **73p** will be purified by column chromatography on silica gel.

Step Q:

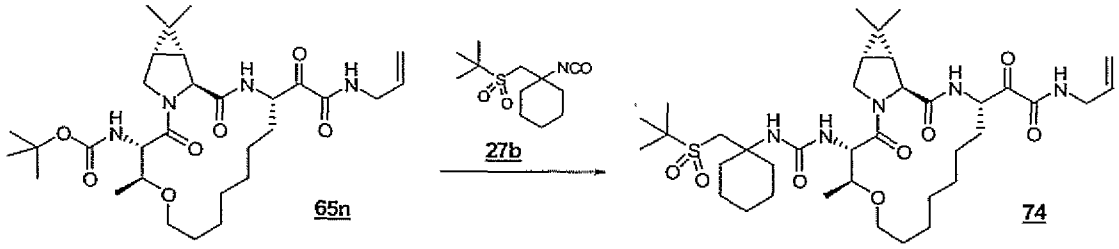


The SES-protected amine **73p** (0.1 mmol) will be dissolved in 2 mL of DMF and treated with cesium fluoride (0.4 mmol). The reaction mixture will be stirred at room temperature for 4 h and poured onto water (10 mL). The mixture will be extracted with ethyl acetate (3 x 20 mL). The combined organic layers will be dried over magnesium sulfate, filtered and concentrated under reduced pressure. The macrocyclic amine **73** will be purified by column chromatography on silica gel.

Preparative Example 74: Preparation of:

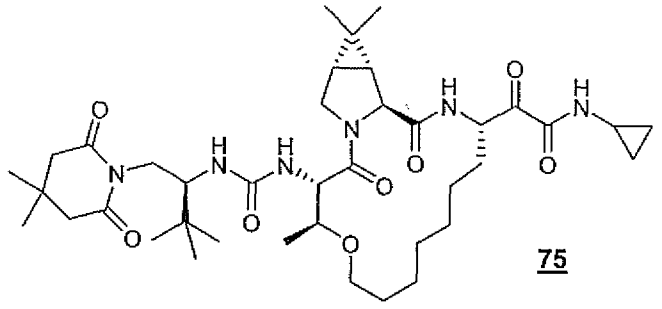


Step A:



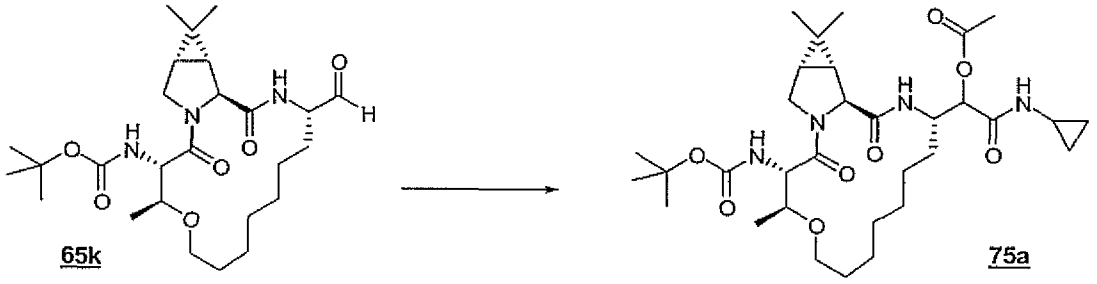
The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln. of the isocyanate **27b** in toluene (1.2 eq, 0.6 mL of a 0.2M soln. in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **74** (45 mg, 59%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.40-7.69 (br s, 1H), 6.08-6.43 (br s, 1H), 5.91 (ddt, 1H, J = 5.6, 10.4, 17.3 Hz), 5.70 (br s, 1H), 5.29 (dd, 1H, J = 1.2, 17.3 Hz), 5.24 (dd, 1H, J = 1.2, 10.4 Hz), 4.66 (d, 1H, J = 9.4 Hz), 4.46 (br s, 1H), 4.38 (m, 1H), 4.25 (d, 1H, J = 10.7 Hz), 4.06 (m, 2H), 3.98 (m, 1H), 3.71 (dq, 5.6, 11.6 Hz), 3.64 (ddd, 1H, J = 5.0, 5.3, 9.7 Hz), 3.25 (m, 1H), 2.88 (d, 1H, J = 13.5 Hz), 2.47 (br s, 1H), 2.19 (d, 1H, J = 11.6 Hz), 1.39 (s, 9H), 1.28-1.99 (m, 22H), 1.21 (d, 3H, J = 5.6 Hz), 1.13 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7, 173.0, 171.3, 159.4, 157.0, 133.4, 117.7, 75.2, 67.7, 61.2, 60.8, 55.6, 54.6, 48.7, 42.2, 36.3, 31.6, 28.9, 27.9, 27.8, 27.1, 26.8, 25.9, 24.8, 24.0, 23.6, 21.9, 21.5, 19.4, 15.8, 13.4 ppm; HRMS calcd for $C_{37}H_{62}N_5O_8S$ $[M+H]^+$: 736.4319, found 736.4325.

Preparative Example 75: Preparation of:



75

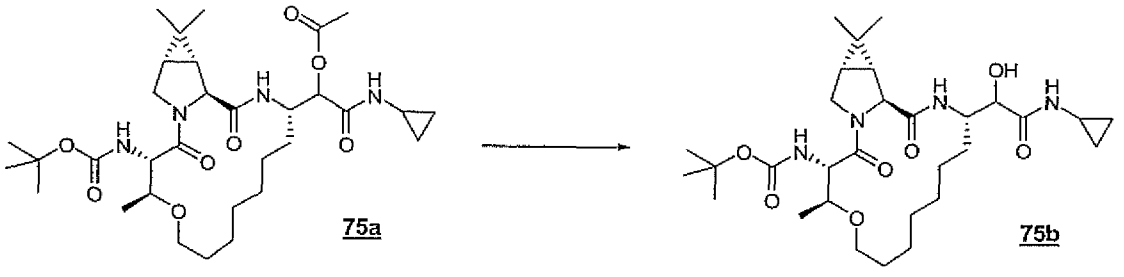
Step A:



65k 75a

A solution of aldehyde **65k** (710 mg) in 30 mL of dry dichloromethane was treated with cyclopropylisocyanide (Oakwood Prod., 2.0 eq, 0.25 mL, d 0.8) and acetic acid (2 eq, 0.16 mL, d 1.049). The mixture was stirred at room temp for 5 h. All the volatiles were removed under reduced pressure and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 55:45) to afford the product **75a** (740 mg, 83%) as a white solid.

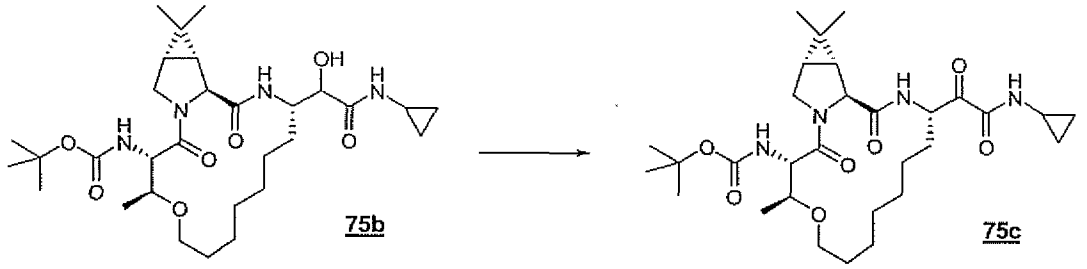
Step B:



75a 75b

A solution of acetate **75a** (740 mg) in 20 mL of a 2:1 mixture of THF/water was treated with lithium hydroxide monohydrate (2.5 eq, 125 mg) and stirred for approx 30 min until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 8:2). The reaction mixture was diluted with 50 mL of aqueous saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the product **75b** (688 mg, 98%) as a colorless semi-solid which was used without further purification.

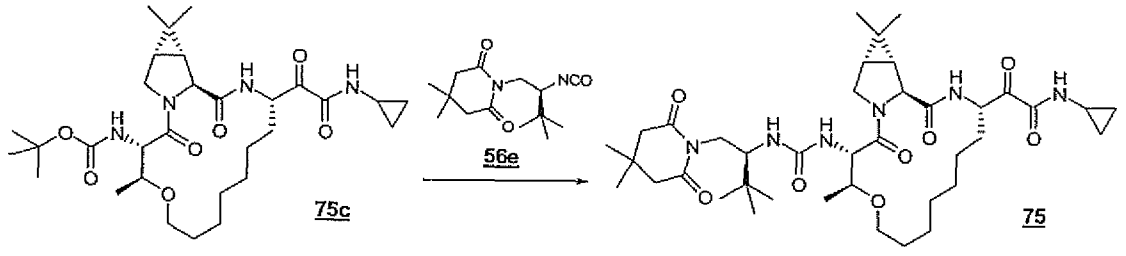
Step C:



75b 75c

A solution of hydroxyamide **75b** (1.192 mmol) in 25 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 1.01 g). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (30 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (30 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 4:6) to afford the product **75c** (476 mg, 69%) as white solid.

Step D:

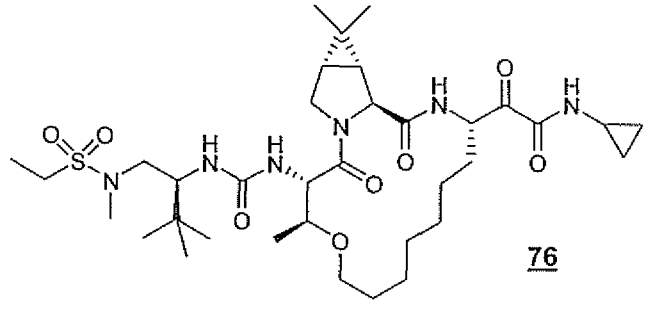


75c 56e 75

The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **56e** was added dropwise (1.2 eq, 0.59 mL of a 0.216M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **75** (41 mg, 53%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (br s, 1H), 7.40-7.70 (br s, 1H), 6.28 (br s, 1H), 5.68 (br s, 1H), 5.37 (br

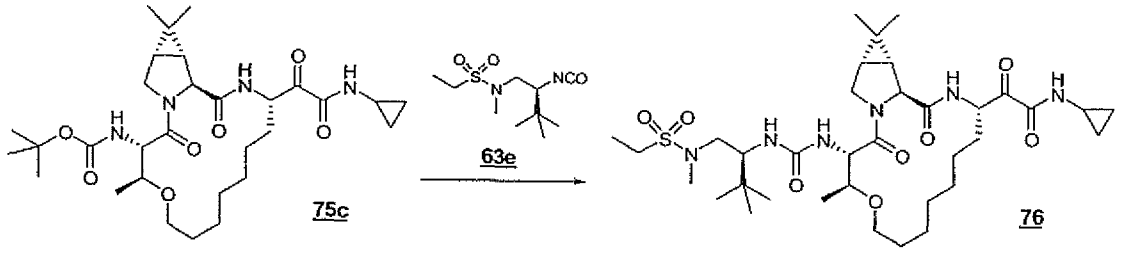
s, 1H), 4.62 (s, 1H), 4.49 (br s, 1H), 4.22 (d, 1H, J = 10.7 Hz), 4.05 (dd, 1H, J = 5.0, 10.4 Hz), 3.94 (d, 1H, J = 1.6 Hz), 3.88 (dd, 1H, J = 10.4, 10.7 Hz), 3.82 (q, 1H, J = 11.0 Hz), 3.69 (m, 1H), 3.62 (ddd, 1H, J = 5.0, 5.6, 9.4 Hz), 3.20 (m, 1H), 2.89 (ddd, 1H, J = 3.4, 7.2, 14.8 Hz), 2.55 (d, 2H, J = 17.0 Hz), 2.48 (d, 2H, J = 17.0 Hz), 1.79-1.99 (m, 4H), 1.28-1.69 (m, 10H), 1.14 (d, 3H, J = 6.0 Hz), 1.10 (s, 6H), 1.00 (s, 3H), 0.99 (s, 9H), 0.90 (m, 2H), 0.83 (s, 3H), 0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 172.8, 171.5, 160.9, 157.8, 75.5, 68.1, 60.8, 57.2, 55.9, 48.7, 46.8, 35.2, 29.3, 28.6, 28.3, 27.7, 26.9, 26.8, 24.8, 24.4, 23.1, 19.3, 16.3, 13.6, 6.8 ppm; HRMS calcd for $C_{39}H_{63}N_6O_8$ $[M+H]^+$: 743.4707, found 743.4686.

Preparative Example 76: Preparation of:



76

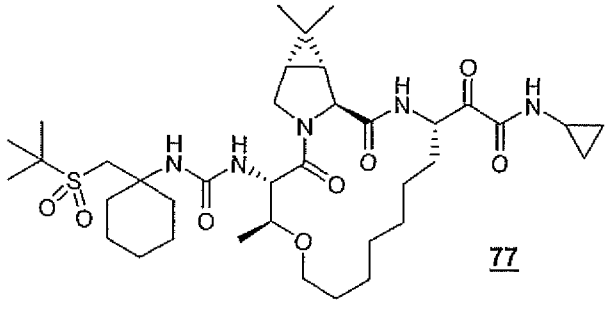
Step A:



The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln. of the isocyanate **63e** was added dropwise (1.2 eq, 0.95 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to

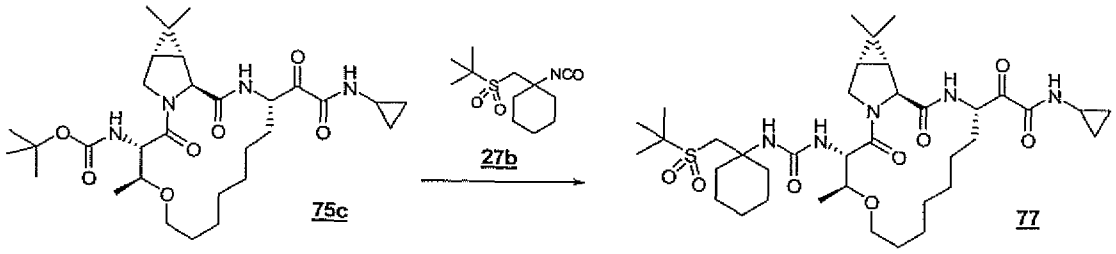
6:4) to afford the product **76** (54 mg, 72%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.58 (br s, 1H), 6.13 (br s, 1H), 5.75 (br s, 1H), 5.15 (d, 1H, J = 8.5 Hz), 4.68 (br s, 1H), 4.56 (s, 1H), 4.28 (d, 1H, J = 10.7 Hz), 4.06 (dd, 1H, J = 4.7, 10.4 Hz), 3.99 (dd, 1H, J = 9.1, 9.7 Hz), 3.60 (m, 2H), 3.47 (dd, 1H, J 12.2, 13.2 Hz), 3.19 (m, 1H), 3.07 (m, 3H), 2.94 (s, 3H), 2.87 (ddd, 1H, J = 4.0, 7.8, 15.1 Hz), 1.72-1.99 (m, 4H), 1.37 (t, 3H, J = 7.5 Hz), 1.27-1.68 (m, 9H), 1.21 (d, 3H, J = 6.0 Hz), 1.13 (m, 1H), 1.01 (s, 3H), 0.92 (s, 9H), 0.89 (s, 3H), 0.87 (m, 2H), 0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.5, 172.8, 171.6, 160.8, 158.1, 75.8, 68.4, 60.6, 56.2, 54.4, 50.4, 48.5, 45.7, 34.7, 34.5, 32.1, 31.6, 28.6, 27.8, 27.7, 27.0, 26.9, 26.7, 24.9, 24.6, 23.0, 19.2, 16.2, 13.5, 8.5, 6.7 ppm; HRMS calcd for $C_{35}H_{61}N_6O_8S$ $[M+H]^+$: 725.4272, found 725.4292.

Preparative Example 77: Preparation of:



77

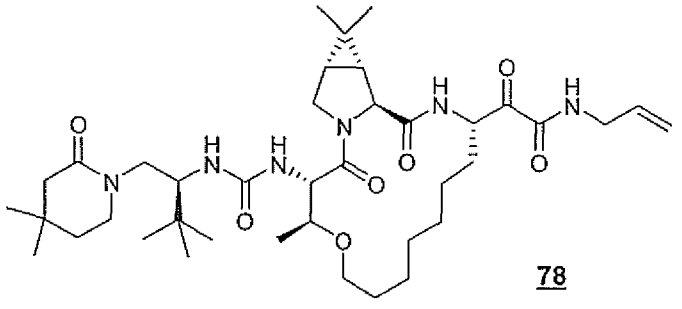
Step A:



The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln of the isocyanate **27b** in toluene (1.2 eq, 0.6 mL of a 0.2M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium

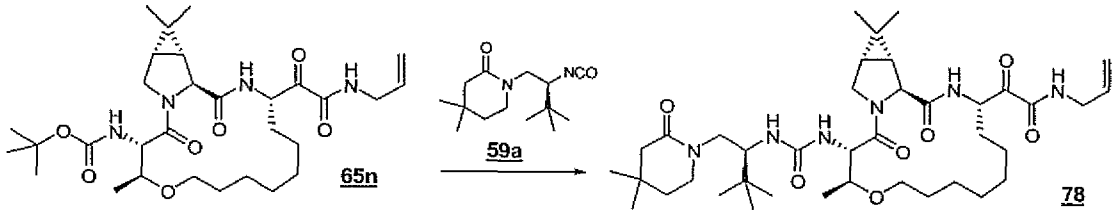
sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **77** (50 mg, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (br s, 1H), 7.33-7.63 (br s, 1H), 6.07-6.47 (br s, 1H), 5.67 (br s, 1H), 4.65 (d, 1H, J = 9.7 Hz), 4.45 (br s, 1H), 4.37 (m, 1H), 4.24 (d, 1H, J = 10.7 Hz), 4.07 (dd, 1H, J =5.0, 10.7 Hz), 3.70 (dq, 1H, 5.9, 9.7 Hz), 3.64 (ddd, 1H, J = 5.0, 5.6, 9.7 Hz), 3.24 (m, 1H), 2.89 (ddd, 1H, J = 3.7, 7.5, 14.5 Hz), 2.88 (m, 1H), 2.47 (br s, 1H), 2.18 (d, 1H, J = 12.6 Hz), 1.74-1.97 (m, 5H), 1.39 (s, 9H), 1.27-1.73 (m, 17H), 1.20 (d, 3H, J = 6.3 Hz), 1.11 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H), 0.90 (m, 2H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7, 173.0, 171.3, 161.0, 157.0, 75.2, 67.8, 61.1, 60.8, 55.5, 54.6, 50.1, 48.6, 36.3, 31.6, 28.8, 27.9, 27.0, 26.9, 25.9, 24.8, 24.0, 23.6, 23.1, 21.9, 21.5, 19.4, 15.8, 13.4, 6.9, 6.8 ppm. HRMS calcd for $C_{37}H_{62}N_5O_8S$ $[M+1]^+$: 736.4319, found 736.4329.

Preparative Example 78



78

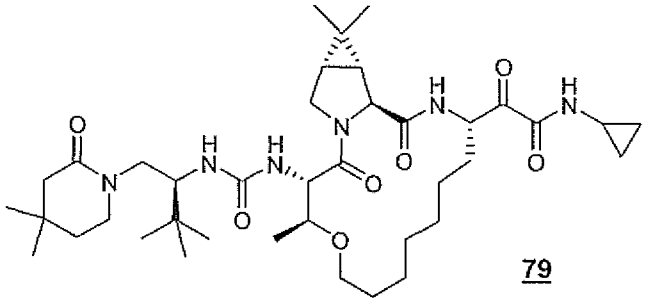
Step A:



The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **59a** in toluene (1.2 eq, 0.6 mL of a 0.2M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h.

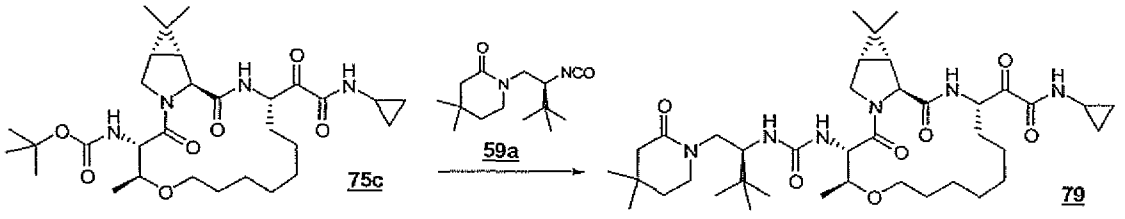
The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/(hexanes-dichloromethane; 1:1); 1:9 to 1:1) to afford the product **78** (51 mg, 67%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (br s, 1H), 6.42-6.79 (br s, 1H), 5.90 (ddt, 1H, J = 5.6, 10.7, 17.0 Hz), 5.73 (br s, 1H), 5.57 (br s, 1H), 5.27 (d, 1H, J = 17.0 Hz), 5.22 (d, 1H, J = 10.0 Hz), 4.62 (dd, 1H, J = 9.1, 9.7 Hz), 4.52 (br s, 1H), 4.29 (m, 2H), 3.86-4.11 (m, 4H), 3.64 (m, 3H), 3.17 (m, 2H), 2.74 (d, 1H, J = 11.9 Hz), 2.24 (d, 1H, J = 17.3 Hz), 2.10 (d, 1H, J = 17.0 Hz), 1.95 (m, 4H), 1.24-1.68 (m, 11H), 1.16 (d, 3H, J = 5.9 Hz), 1.11 (m, 1H), 1.02 (s, 3H), 1.01 (s, 6H), 0.95 (s, 9H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.8, 172.9, 171.6, 170.7, 159.4, 158.2, 133.6, 117.5, 75.7, 68.2, 60.8, 56.0, 55.3, 48.5, 46.8, 46.2, 44.9, 42.3, 35.7, 34.8, 32.3, 31.6, 30.2, 28.6, 28.4, 27.8, 27.7, 27.1, 27.0, 26.8, 24.8, 24.5, 19.3, 16.5, 13.6 ppm. HRMS calcd for $C_{39}H_{65}N_6O_7$ $[M+1]^+$: 729.4915, found 729.4917.

Preparative Example 79



79

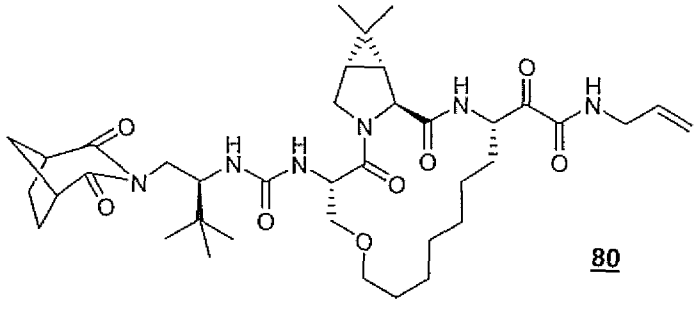
Step A:



The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **59a** in toluene (1.2 eq, 0.6 mL of a 0.2M soln in toluene) and stirring was continued for 10

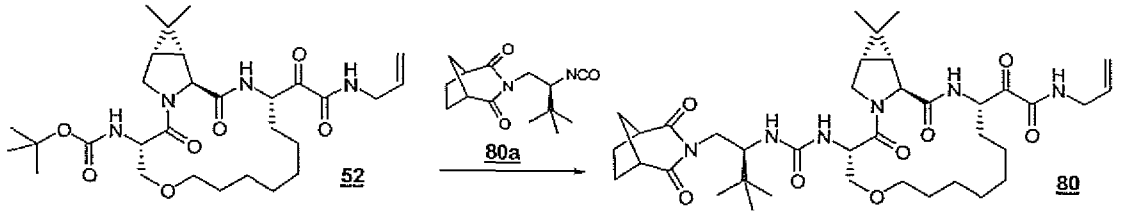
min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/(hexanes-dichloromethane, 1:1); 1:9 to 1:1) to afford the product **79** (36 mg, 48%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (br s, 1H), 6.38-6.70 (br s, 1H), 5.73 (br s, 1H), 5.55 (d, 1H, J = 7.8 Hz), 4.61 (t, 1H, J = 9.7 Hz), 4.51 (br s, 1H), 4.27 (m, 2H), 4.05 (dd, 1H, J = 5.0, 10.4 Hz), 3.95 (dd, 1H, J = 9.4, 9.7 Hz); 3.62 (m, 3H), 3.18 (m, 2H), 2.90 (ddd, 1H, J = 3.7, 7.2, 14.8 Hz), 2.73 (d, 1H, J = 12.6 Hz), 2.21 (d, 1H, J = 17.0 Hz), 2.09 (d, 1H, J = 17.3 Hz), 1.93 (br s, 4H), 1.27-1.68 (m, 11H), 1.15 (d, 3H, J = 5.9 Hz), 1.11 (m, 1H), 1.02 (s, 3H), 1.00 (s, 6H), 0.94 (s, 9H), 0.87 (m, 2H), 0.86 (s, 3H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.1, 172.9, 171.6, 170.6, 160.9, 158.2, 75.6, 68.3, 60.7, 56.0, 55.3, 48.5, 46.7, 46.3, 44.9, 35.7, 34.8, 32.4, 31.6, 30.2, 29.7, 28.6, 28.5, 27.8, 27.7, 27.0, 26.7, 24.8, 24.7, 23.1, 19.3, 16.5, 13.6, 6.7, 6.6 ppm. HRMS calcd for $C_{39}H_{65}N_6O_7$ $[M+1]^+$: 729.4915, found 729.4926.

Preparative Example 80



80

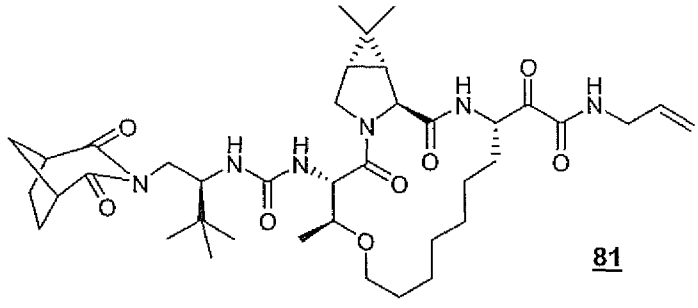
Step A:



The N-Boc amine **52** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **80a** in

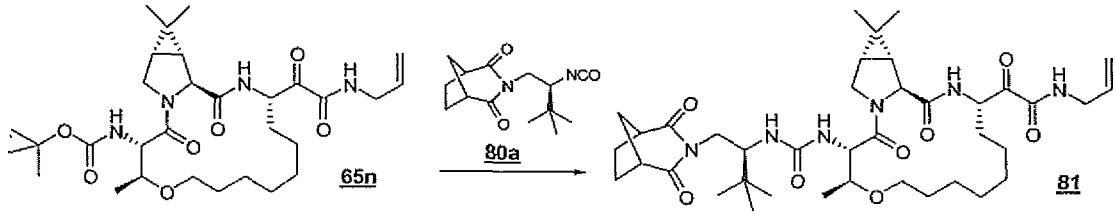
toluene (1.2 eq, 0.8 mL of a 0.155M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **80** (41 mg, 61%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ, 8.01 (d, 1H, J = 8.2 Hz), 7.65 (br s, 1H), 6.01 (br s, 1H), 5.91 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.68 (dd, 1H, J = 9.1, 9.4 Hz), 5.27 (dd, 1H, J = 1.2, 17.0 Hz), 5.23 (dd, 1H, J = 1.2, 10.0 Hz), 5.20 (m, 1H), 4.98 (br s, 1H); 4.59 (s, 1H), 4.13 (d, 1H, J = 10.7 Hz), 4.01 (m, 3H), 3.89 (ddd, 1H, J = 2.2, 10.4, 10.7 Hz), 3.79 (dd, 1H, J = 3.4, 12.9 Hz), 3.76 (m, 1H), 3.56 (m, 2H), 3.36 (dd, 1H, J = 4.1, 7.5 Hz), 3.31 (m, 1H), 3.18 (brs, 1H), 3.14 (br s, 1H), 2.22 (d, 1H, J = 10.7 Hz), 2.07 (br s, 2H), 1.73-2.00 (m, 5H), 1.25-1.70 (m, 11H), 1.16 (m, 1H), 1.02 (s, 3H), 0.96 (s, 9H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 177.4, 172.1, 171.3, 159.3, 157.9, 133.4, 117.7, 71.4, 70.7, 60.7, 56.7, 53.4, 50.8, 48.6, 45.4, 45.2, 42.2, 39.4, 34.7, 33.1, 32.2, 31.0, 28.7, 27.7, 27.5, 27.3, 26.9, 24.3, 19.3, 13.5 ppm. HRMS calcd for $C_{38}H_{59}N_6O_8$ $[M+1]^+$: 727.4394, found 727.4387.

Preparative Example 81



81

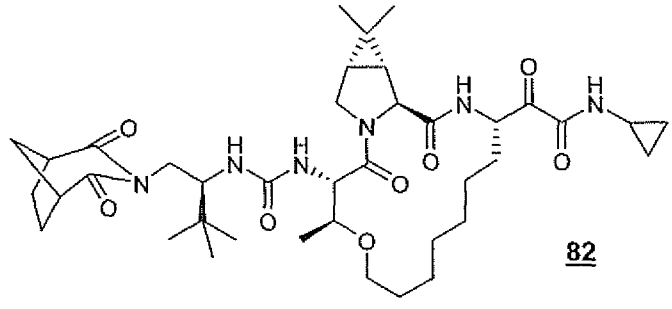
Step A:



The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry

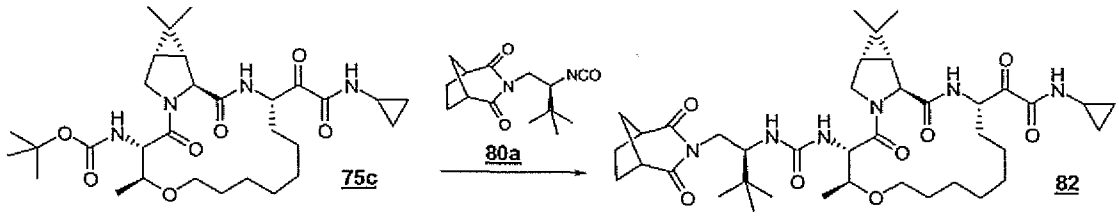
dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **80a** in toluene (1.2 eq, 0.8 mL of a 0.155M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **81** (54 mg, 70%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ, 8.12 (br s, 1H), 7.39-7.79 (br s, 1H), 6.29 (br s, 1H), 5.91 (ddt, 1H, J = 5.9, 10.4, 17.0 Hz), 5.71 (br s, 1H), 5.40 (br s, 1H), 5.27 (dd, 1H, J = 1.2, 17.0 Hz), 5.23 (dd, 1H, J = 1.2, 10.4 Hz), 4.67 (dd, 1H, J = 7.8, 8.1 Hz); 4.50 (br s, 1H), 4.24 (d, 1H, J = 10.7 Hz), 4.07 (dd, 1H, J = 5.3, 10.4 Hz), 4.03 (m, 1H), 3.97 (ddd, 1H, J = 5.6, 5.9, 15.7 Hz), 3.81 (m, 2H), 3.73 (m, 1H), 3.67 (d, 1H, J = 12.2 Hz), 3.62 (m, 1H), 3.20 (s, 2H), 3.07 (s, 1H), 2.29 (d, 1H, J = 11.0 Hz), 2.07 (br s, 3H), 1.93 (br s, 2H), 1.83 (br s, 3H), 1.28-1.68 (m, 10H), 1.17 (d, 3H, J = 5.9 Hz), 1.11 (m, 1H), 1.01 (s, 3H), 0.99 (s, 9H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5, 177.1, 172.8, 171.5, 159.4, 158.0, 133.4, 117.7, 75.5, 68.1, 60.8, 57.4, 55.9, 48.7, 45.4, 42.3, 40.4, 34.8, 32.8, 31.7, 28.6, 27.8, 27.6, 27.4, 26.9, 26.8, 24.7, 24.4, 19.4, 16.2, 13.5 ppm. HRMS calcd for $C_{39}H_{61}N_6O_8$ $[M+1]^+$: 741.4551, found 741.4543.

Preparative Example 82



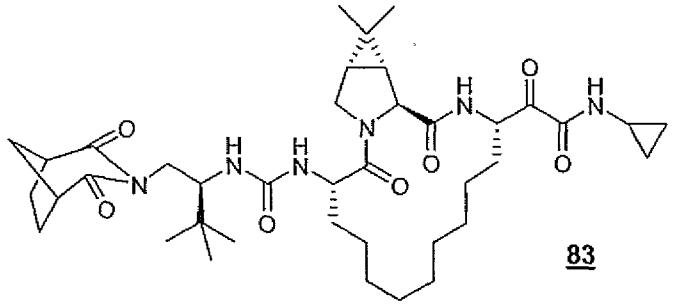
82

Step A:



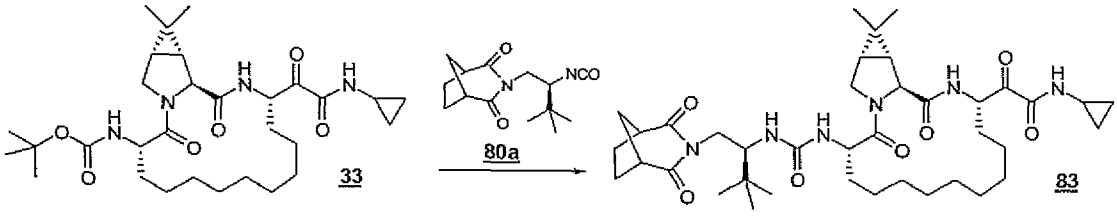
The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **80a** in toluene (1.2 eq, 0.8 mL of a 0.155M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **82** (50 mg, 65%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (br s, 1H), 7.38-7.68 (br s, 1H), 6.28 (br s, 1H), 5.68 (br s, 1H), 5.39 (br s, 1H), 4.66 (dd, 1H, J = 7.5, 7.5 Hz), 4.49 (br s, 1H), 4.23 (d, 1H, J = 10.4 Hz), 4.06 (dd, 1H, J = 5.0, 10.4 Hz); 3.81 (m, 2H), 3.71 (m, 1H), 3.67 (d, 1H, J = 12.2 Hz), 3.61 (m, 1H), 3.19 (br s, 2H), 3.07 (s, 1H), 2.89 (ddd, 1H, J = 3.7, 7.5, 14.8 Hz), 2.29 (d, 1H, J = 11.0 Hz), 1.98-2.13 (m, 3H), 1.75-1.96 (m, 6H), 1.26-1.67 (m, 9H), 1.17 (d, 3H, J = 5.9 Hz), 1.10 (m, 1H), 1.00 (s, 3H), 0.98 (s, 9H), 0.90 (m, 2H), 0.83 (s, 3H), 0.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.9, 178.8, 172.8, 171.5, 160.9, 158.0, 75.5, 68.1, 60.8, 57.4, 55.9, 48.7, 45.4, 40.2, 34.8, 32.8, 31.7, 28.6, 27.8, 27.7, 27.4, 26.9, 26.8, 24.8, 24.4, 23.1, 19.3, 16.2, 13.5, 6.9, 6.8 ppm.

Preparative Example 83



83

Step A:

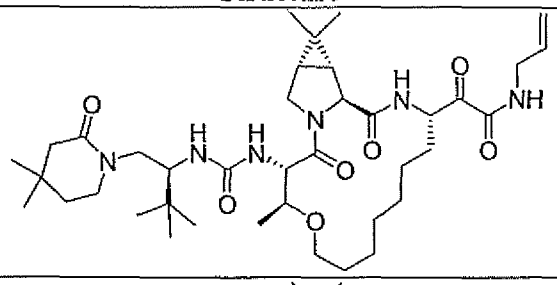
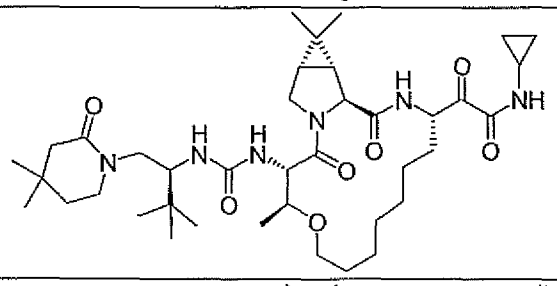
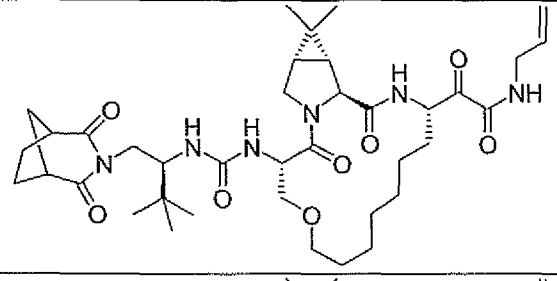
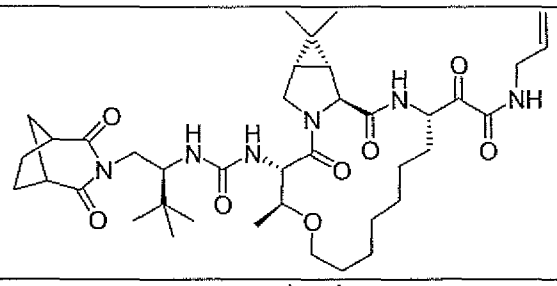
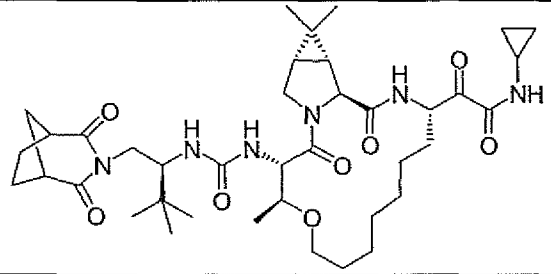
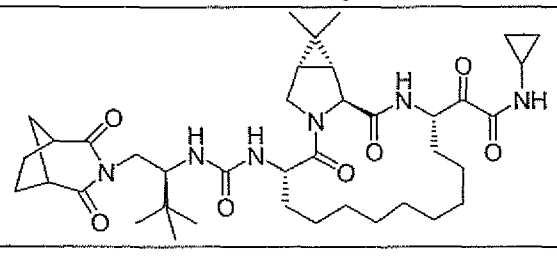


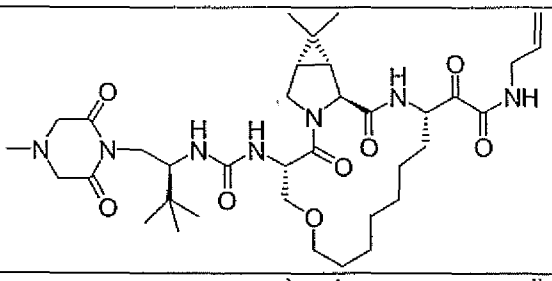
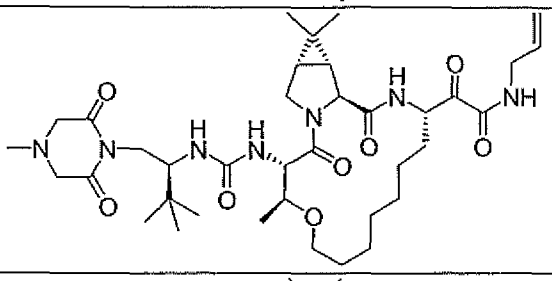
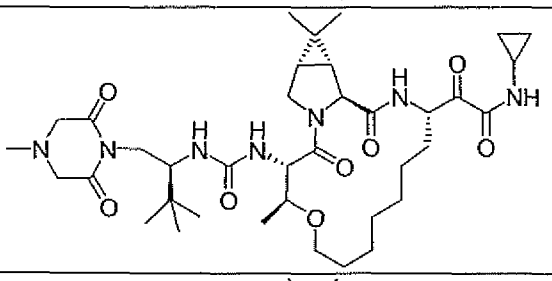
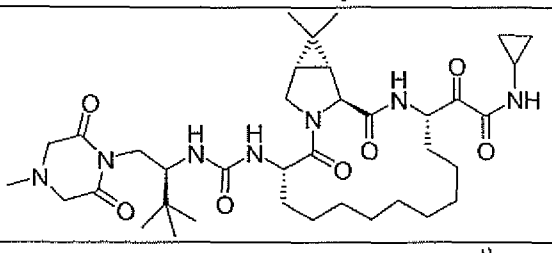
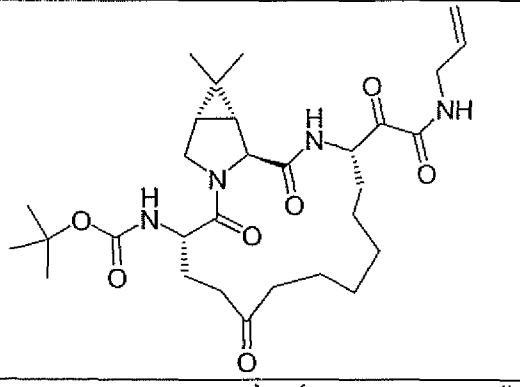
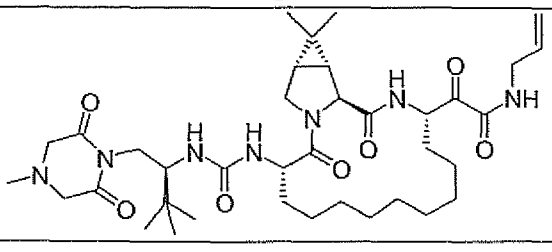
The N-Boc amine **33** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **80a** in toluene (1.2 eq, 0.8 mL of a 0.155M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **83** (63 mg, 81%) as a white solid.

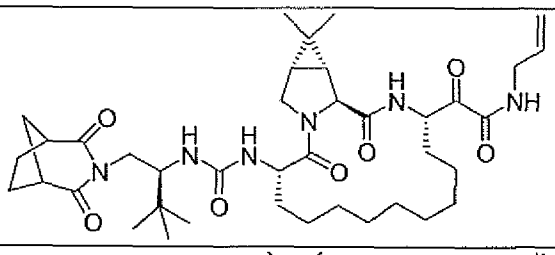
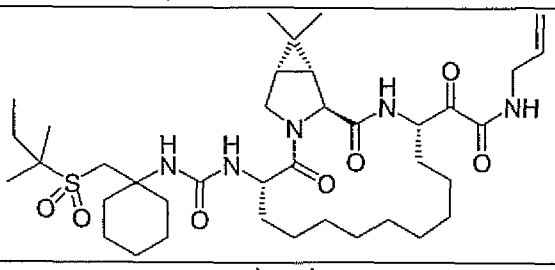
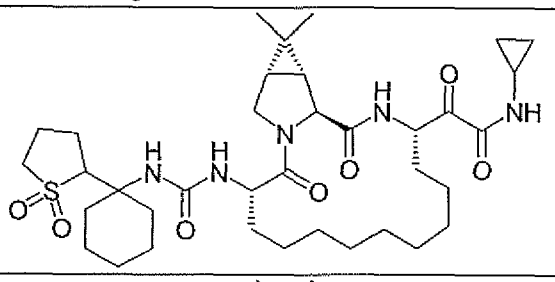
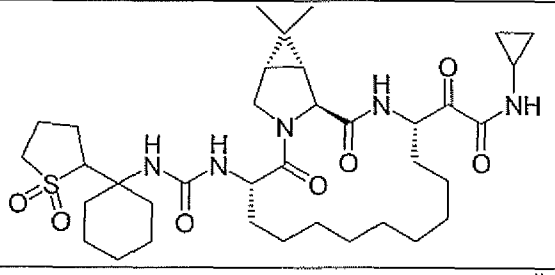
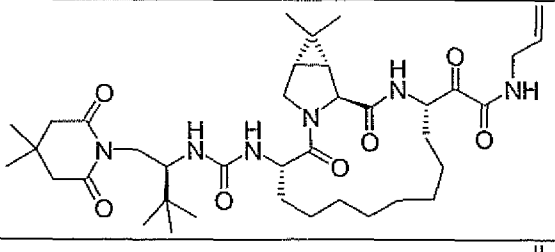
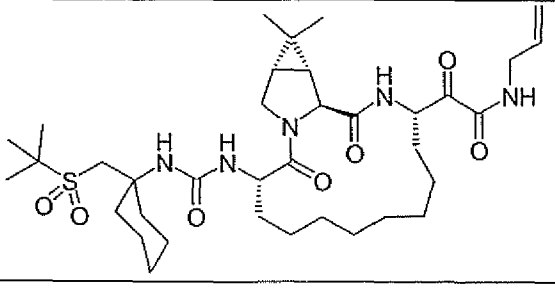
Example compounds are shown in **Table1**. The Ki values for the compounds are rated as follows:

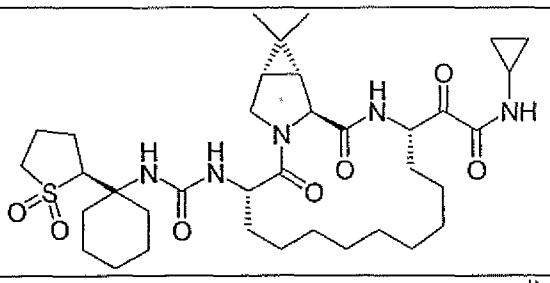
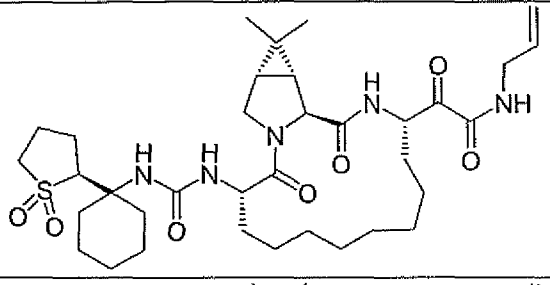
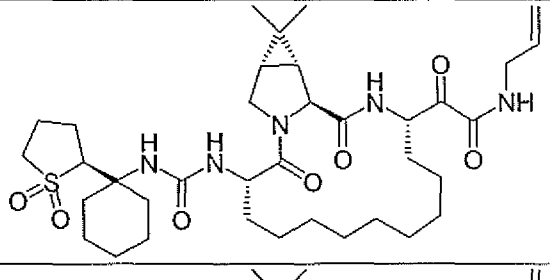
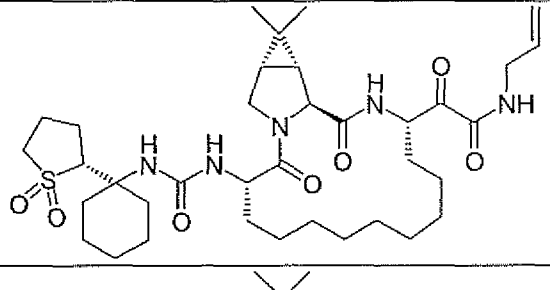
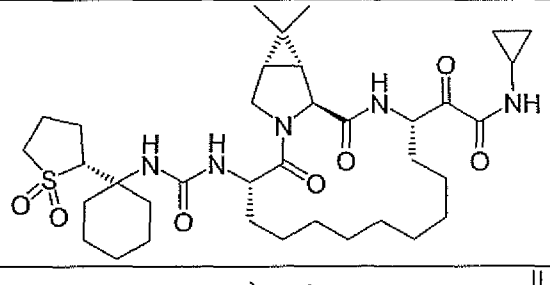
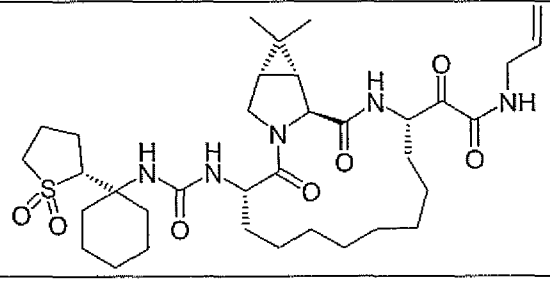
Category "A" for Ki values less than 100nM, category "B" for Ki values greater than or equal to 100nM but less than 1μM and category "C" for Ki values greater than or equal to 1μM.

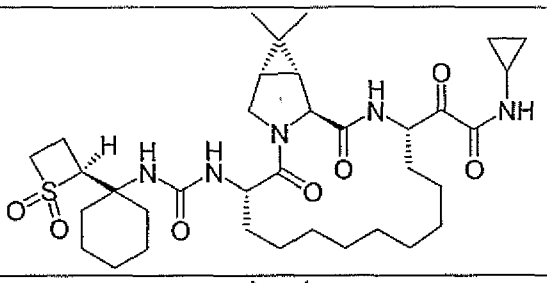
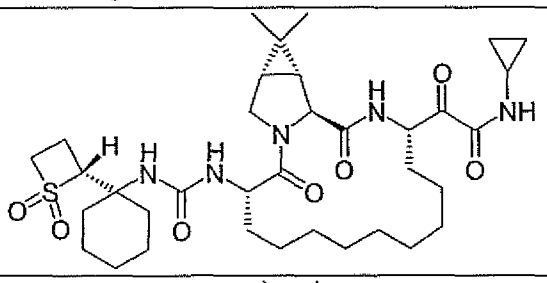
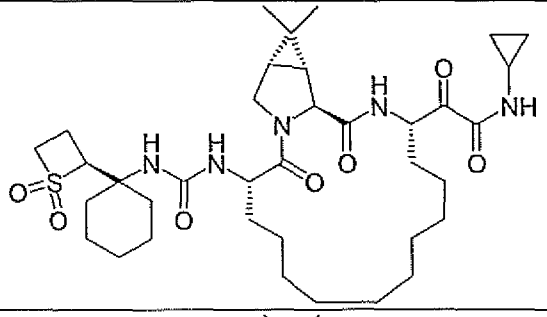
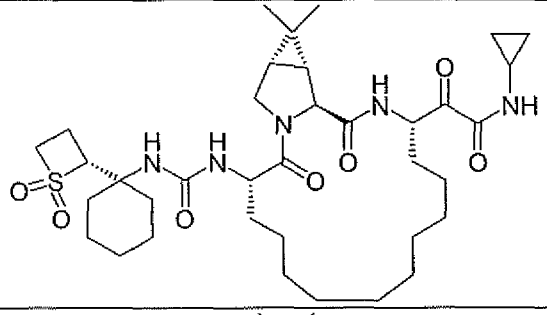
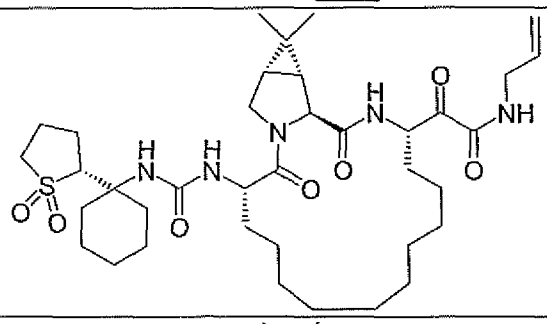
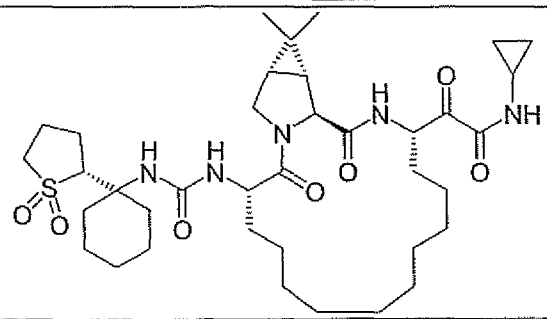
Table 1

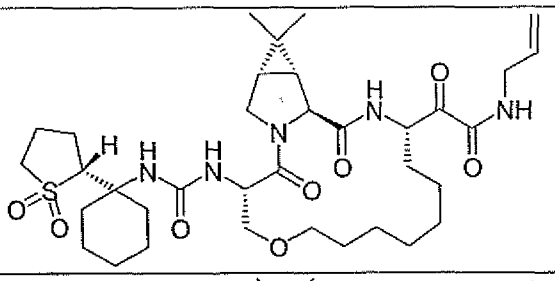
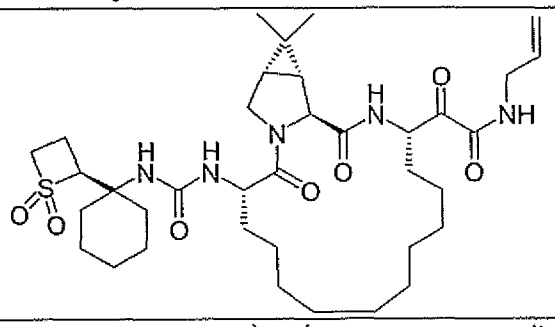
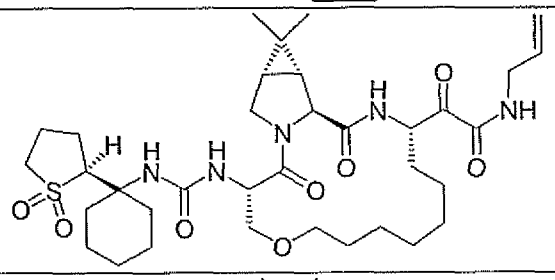
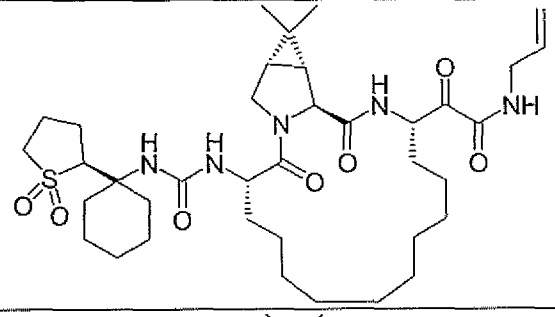
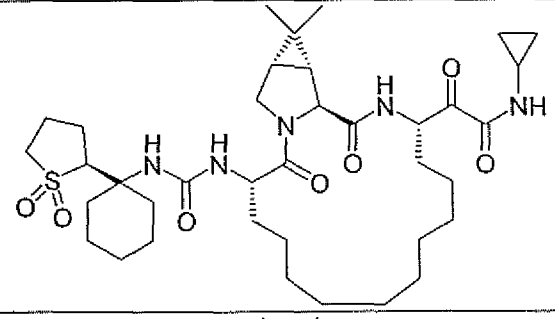
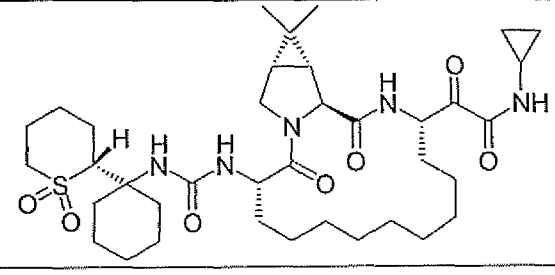
Example	Structure
1Z	
2Z	
3Z	
4Z	
5Z	
6Z	

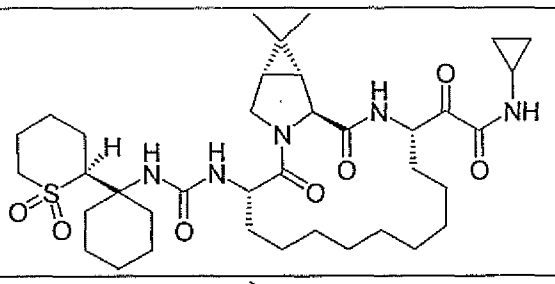
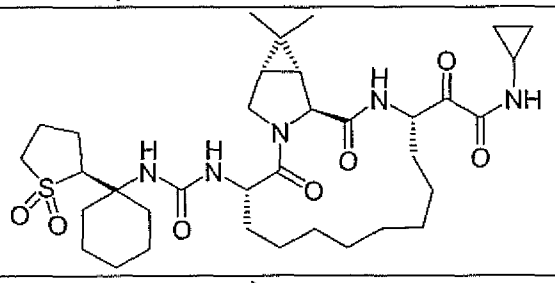
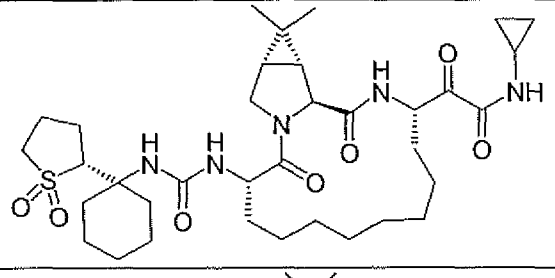
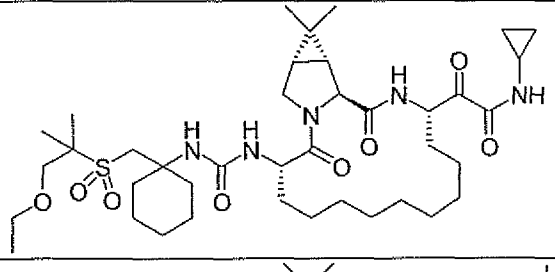
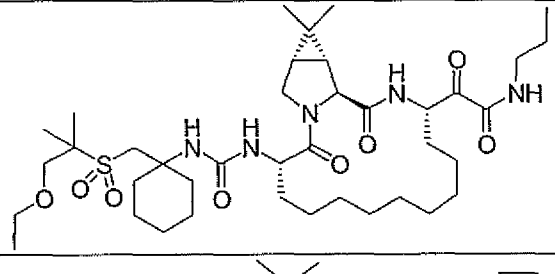
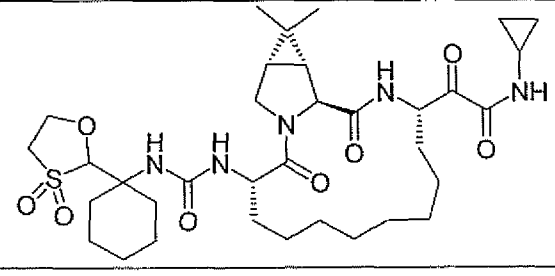
7Z	
8Z	
9Z	
10Z	
11Z	
12Z	

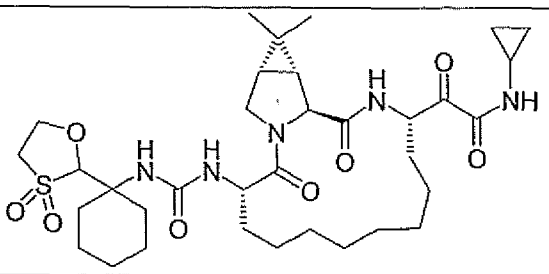
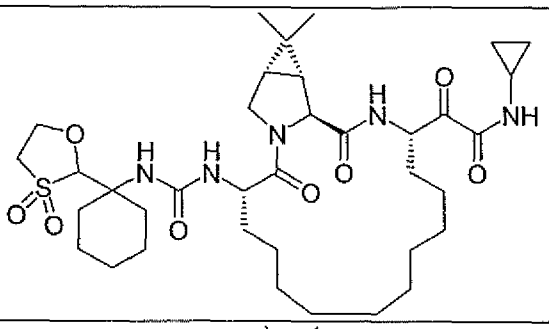
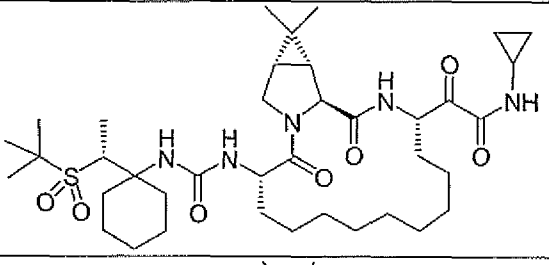
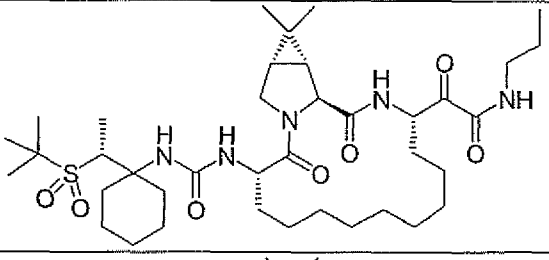
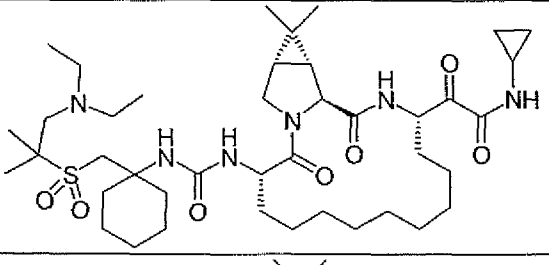
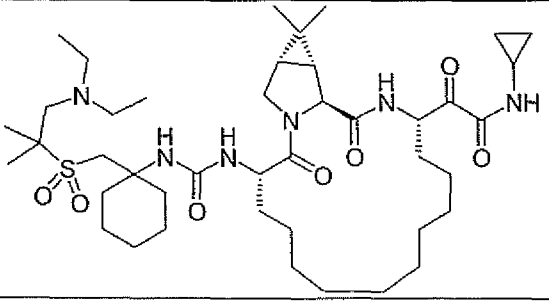
13Z	
14Z	
15Z	
16Z	
17Z	
18Z	

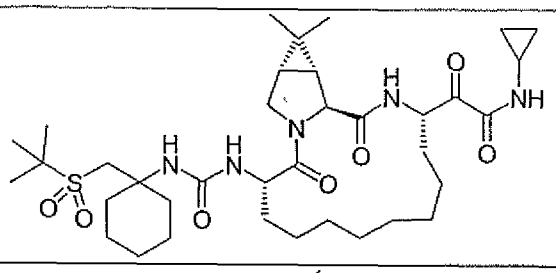
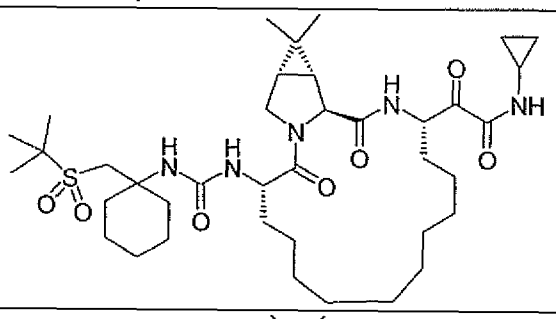
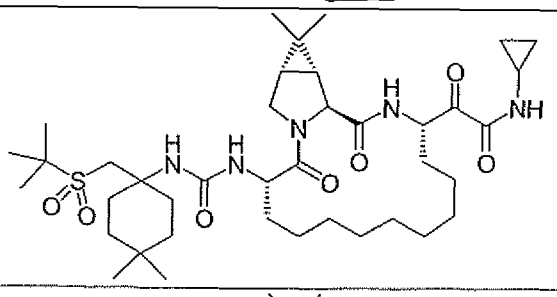
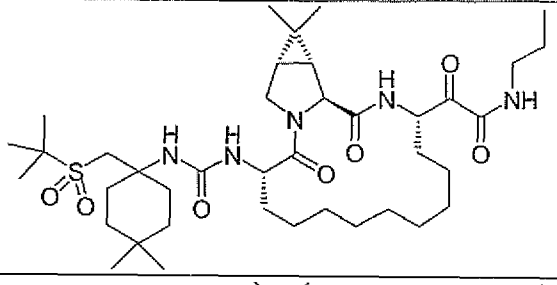
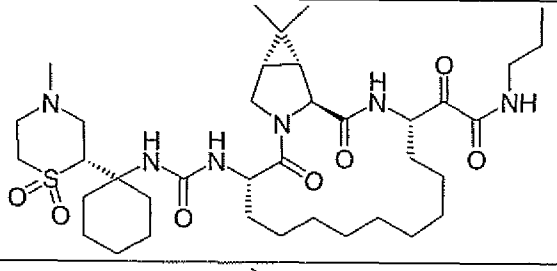
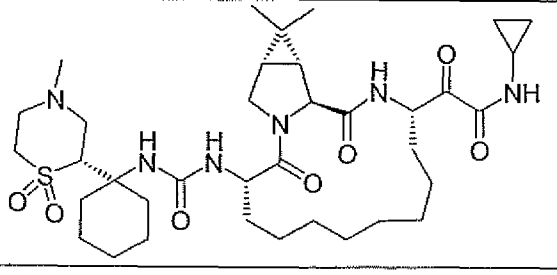
19Z	
20Z	
21Z	
22Z	
23Z	
24Z	

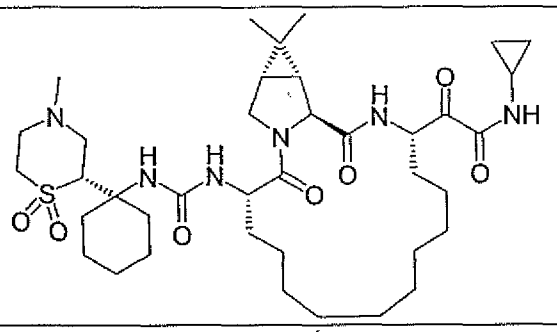
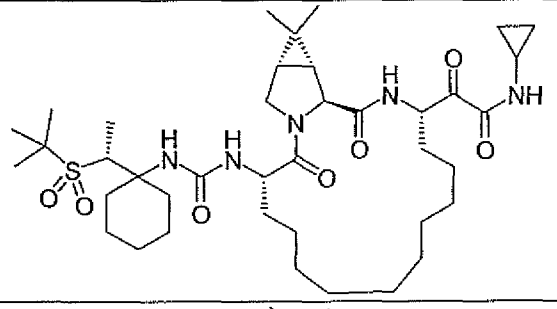
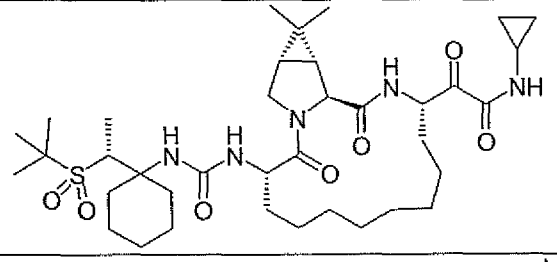
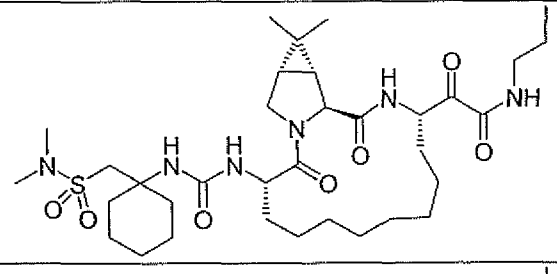
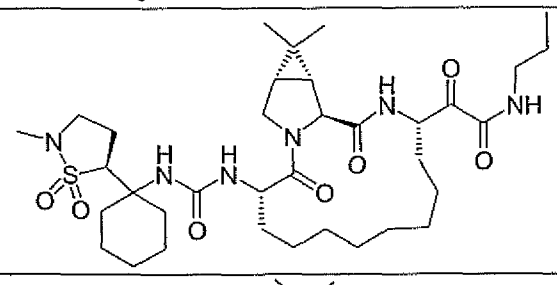
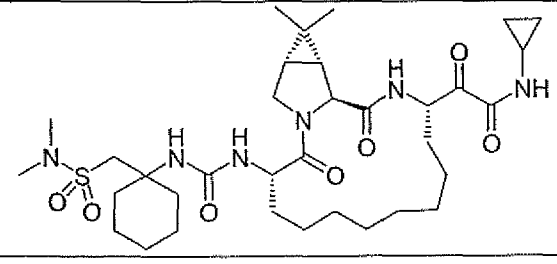
25Z	
26Z	
27Z	
28Z	
29Z	
30Z	

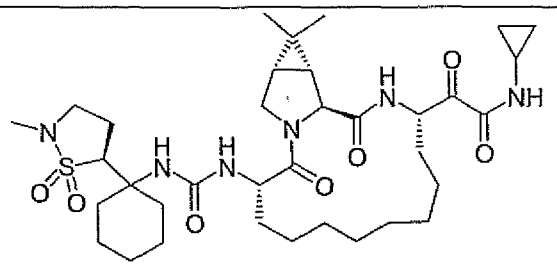
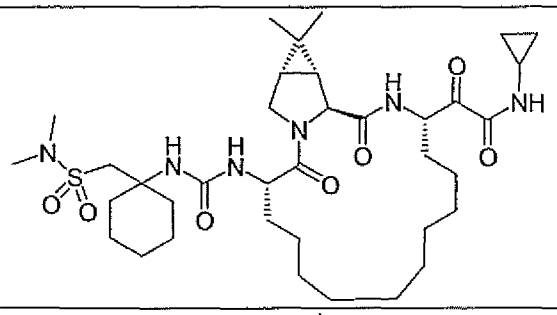
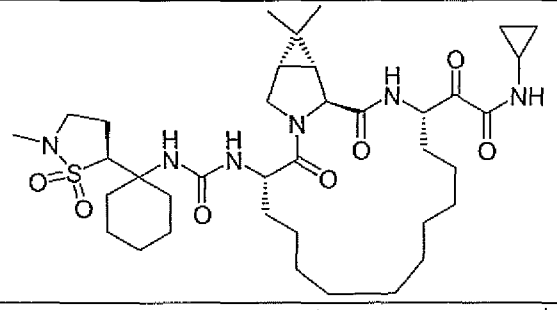
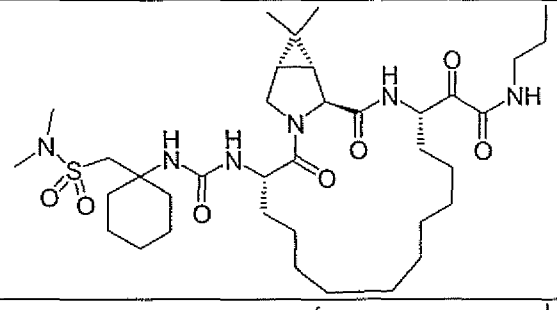
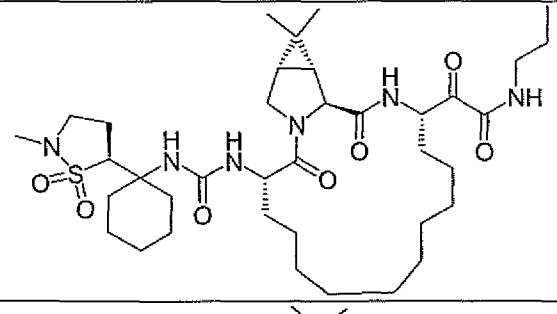
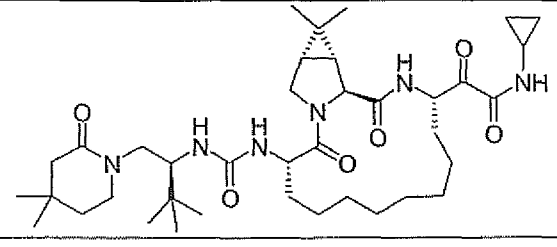
31Z	
32Z	
33Z	
34Z	
35Z	
36Z	

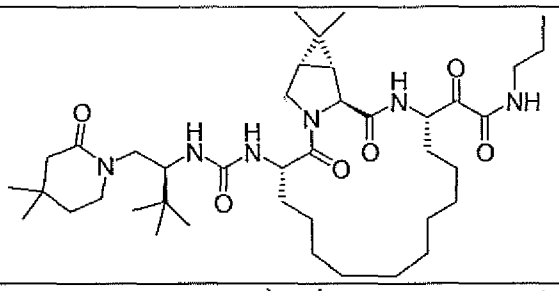
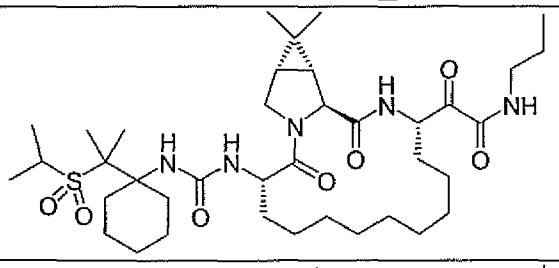
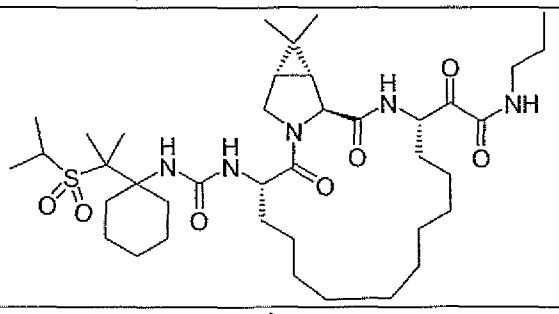
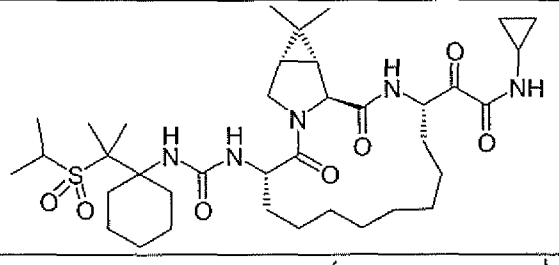
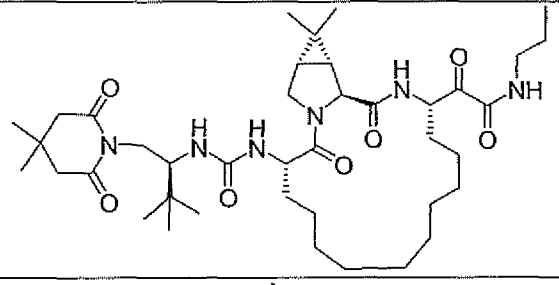
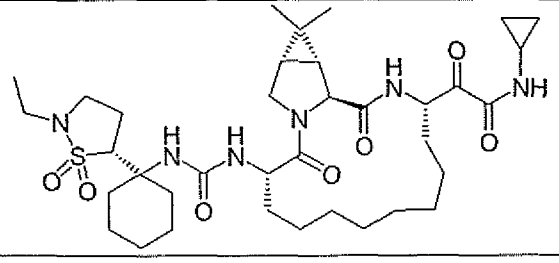
37Z	
38Z	
39Z	
40Z	
41Z	
42Z	

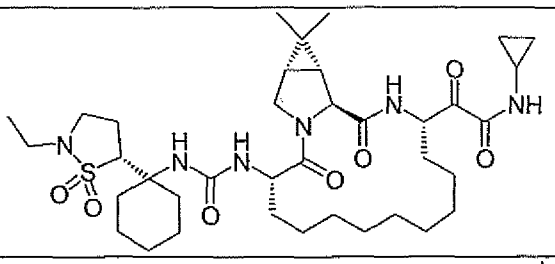
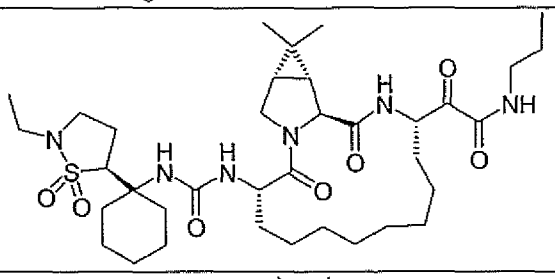
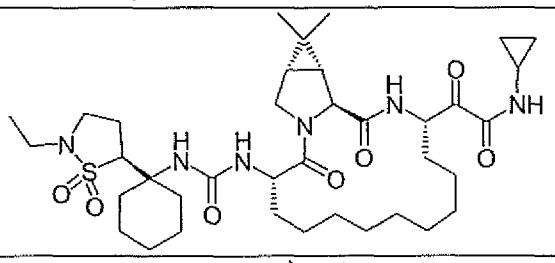
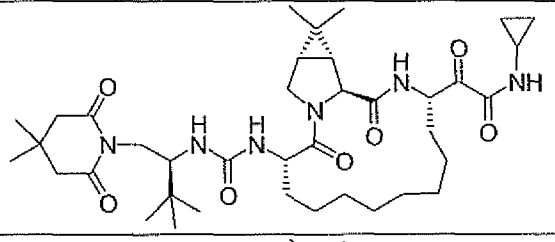
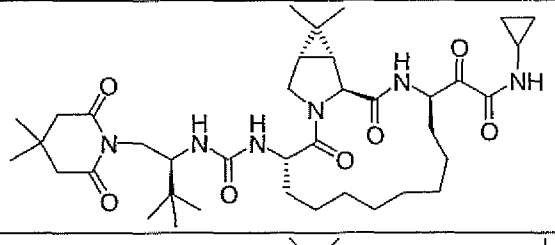
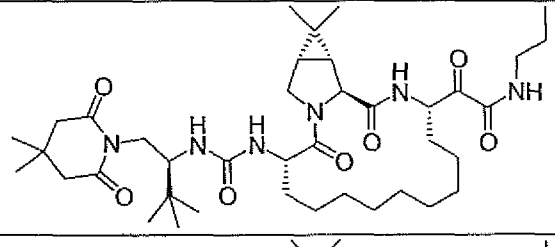
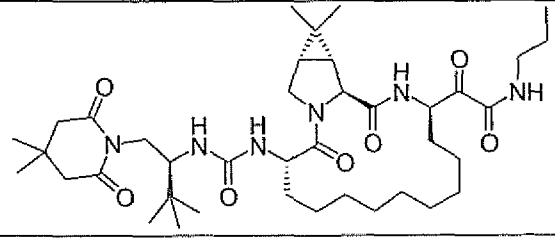
43Z	
44Z	
45Z	
46Z	
47Z	
48Z	

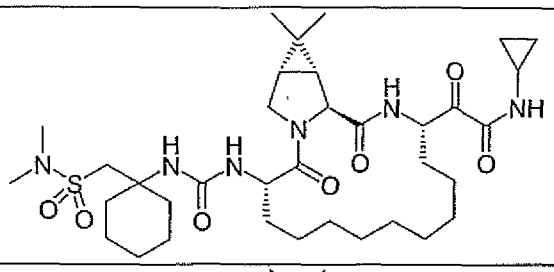
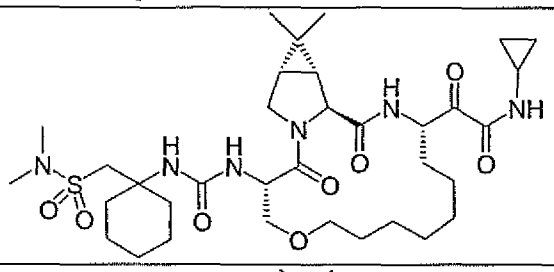
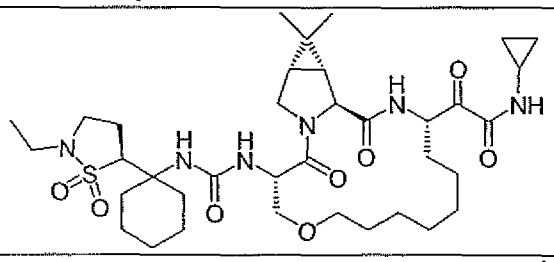
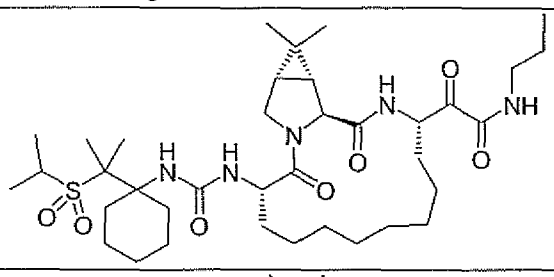
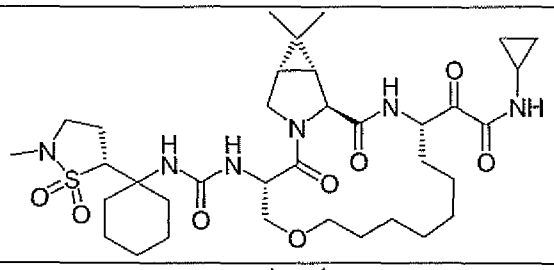
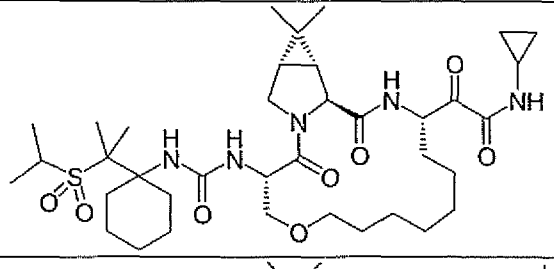
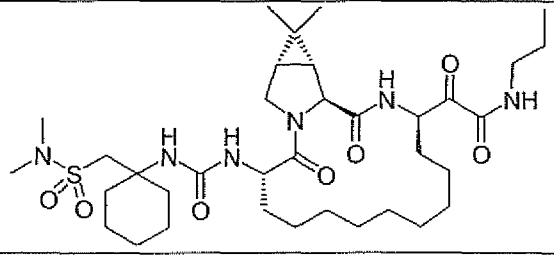
49Z	
50Z	
51Z	
52Z	
53Z	
54Z	

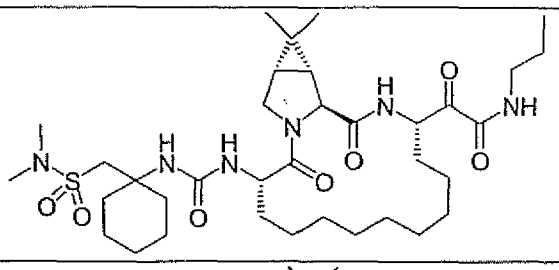
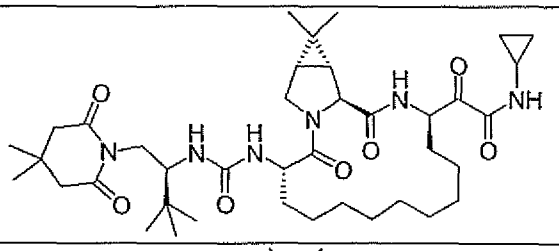
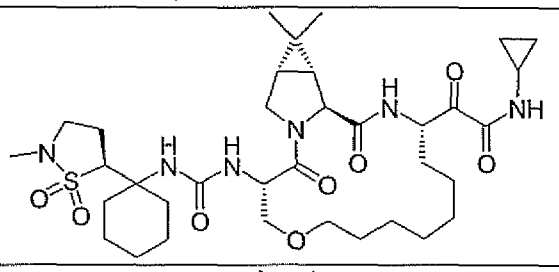
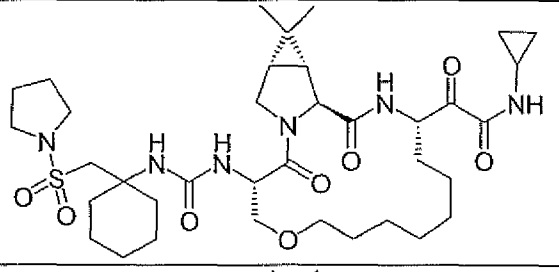
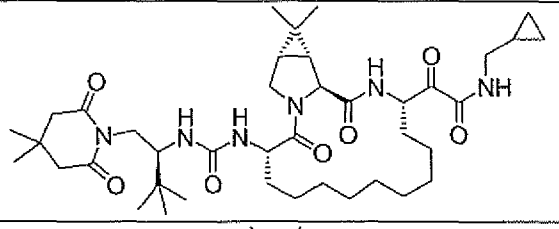
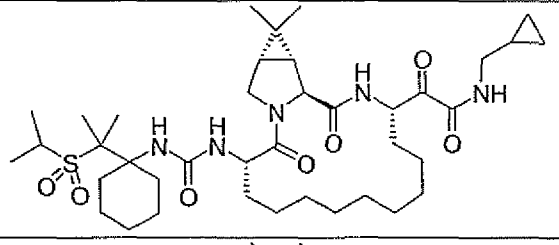
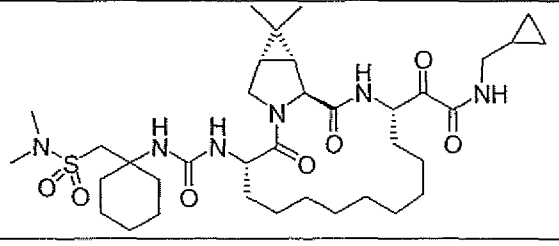
55Z	
56Z	
57Z	
58Z	
59Z	
60Z	

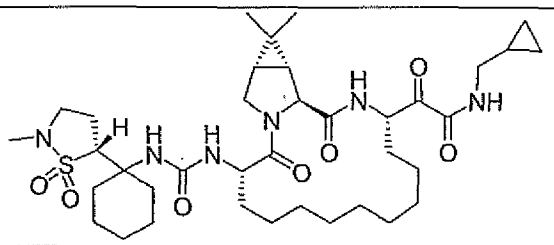
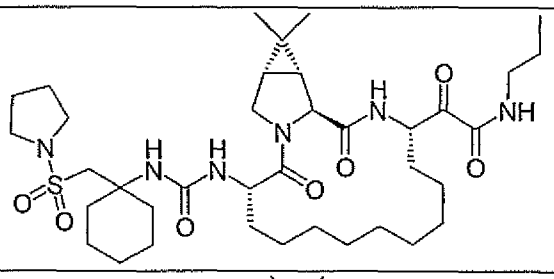
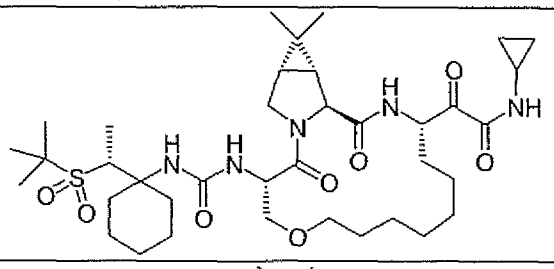
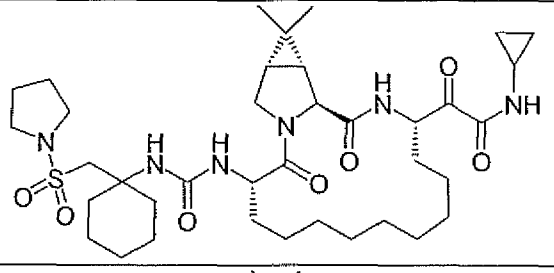
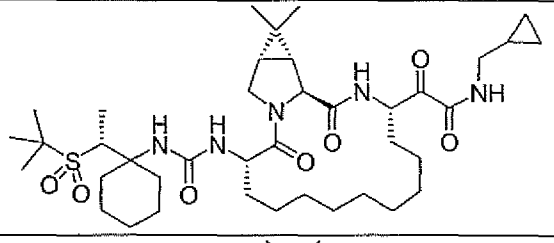
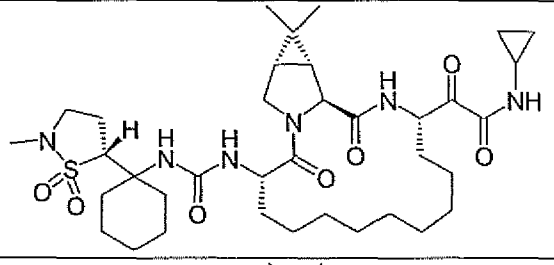
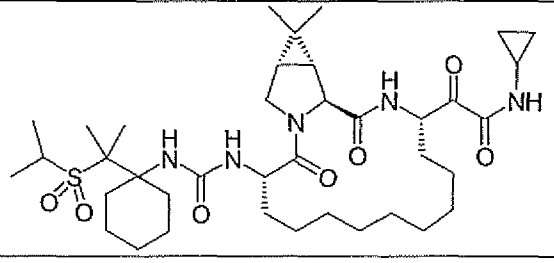
61Z	
62Z	
63Z	
64Z	
65Z	
66Z	

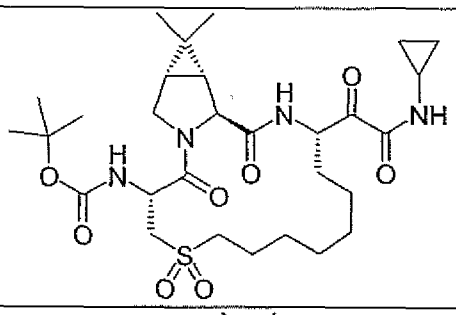
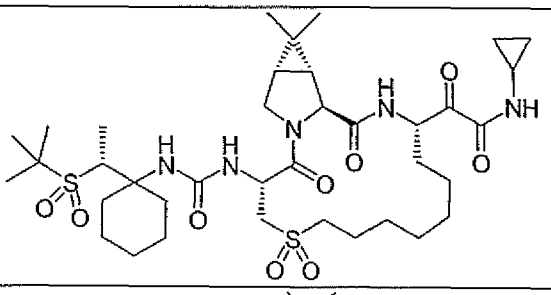
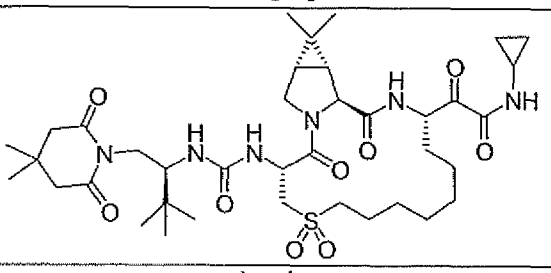
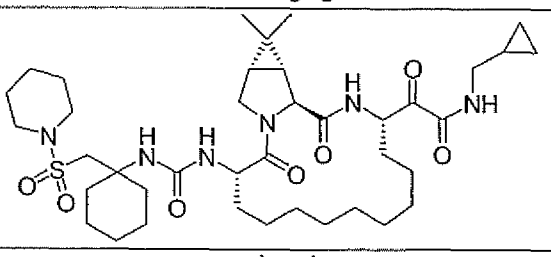
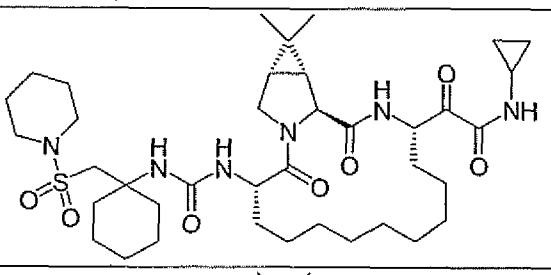
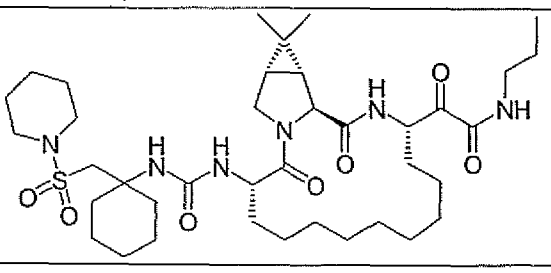
67Z	
68Z	
69Z	
70Z	
71Z	
72Z	

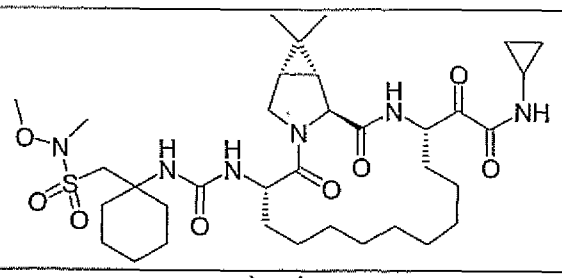
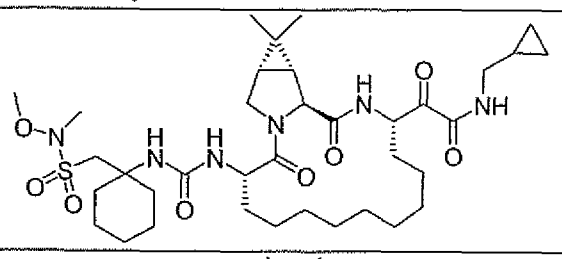
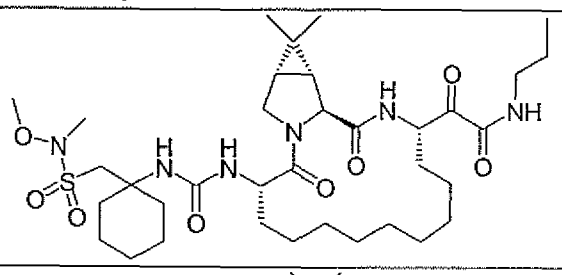
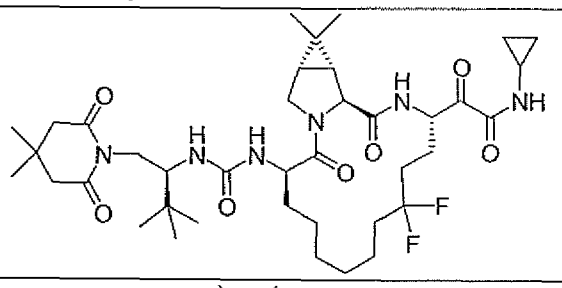
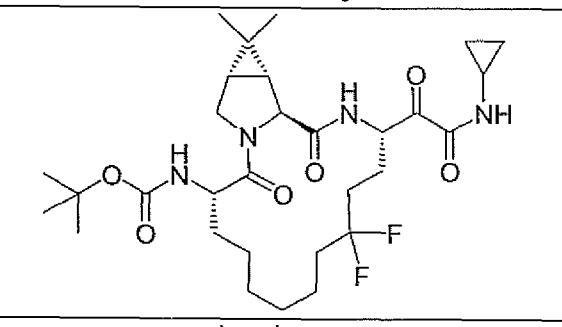
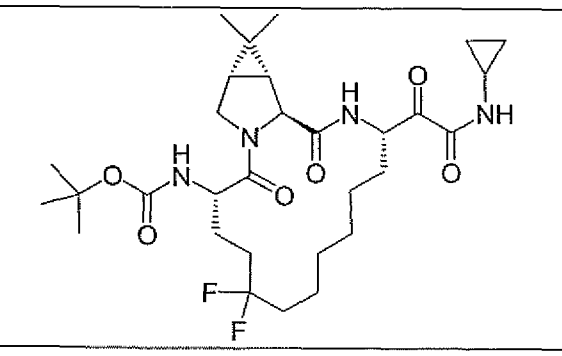
73Z	
74Z	
75Z	
76Z	
77Z	
78Z	
79Z	

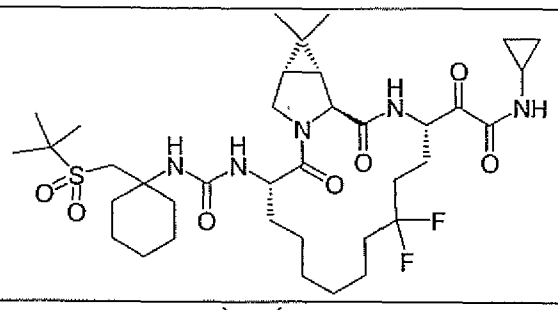
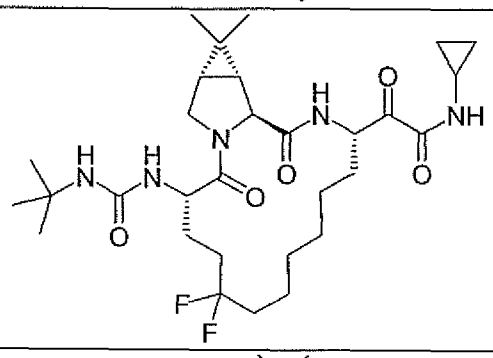
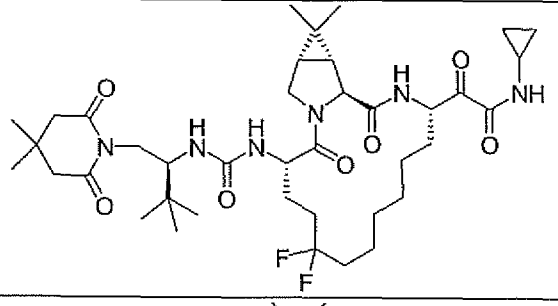
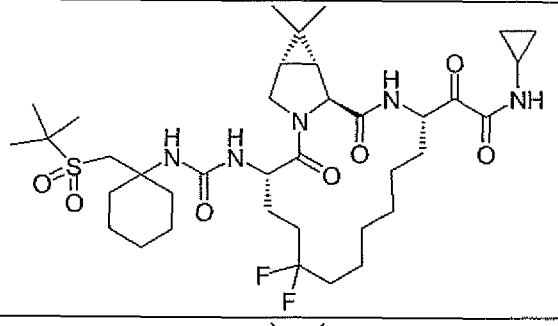
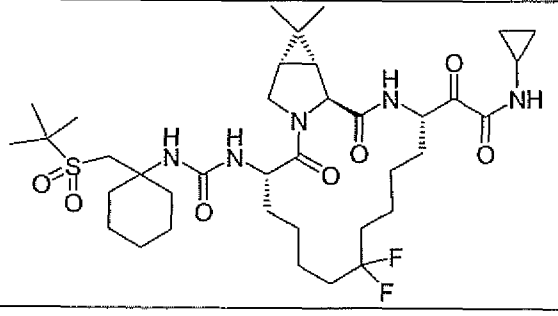
80Z	
81Z	
82Z	
83Z	
84Z	
85Z	
86Z	

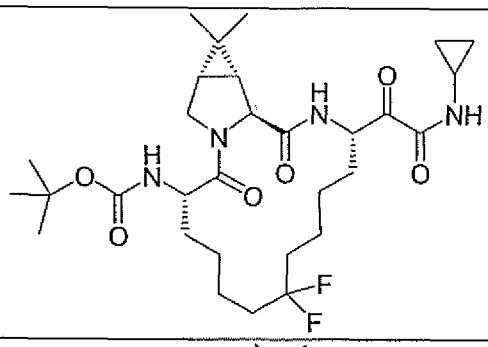
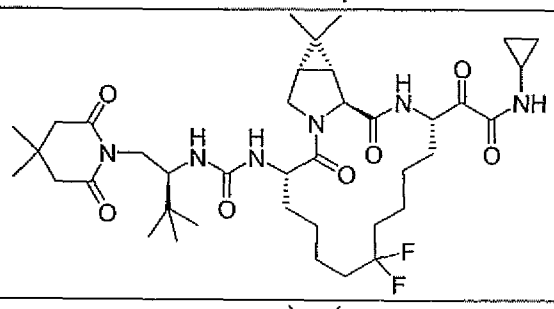
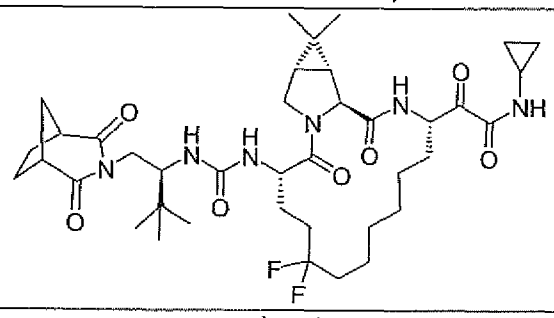
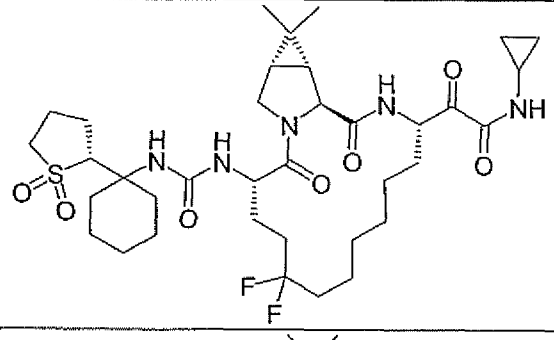
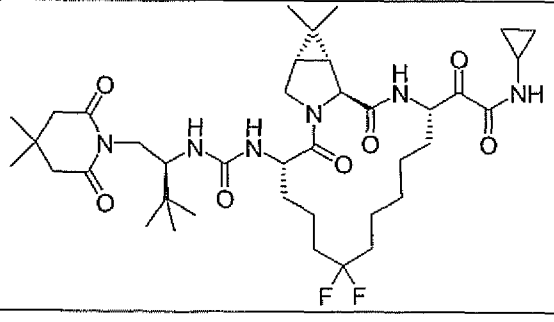
87Z	
88Z	
89Z	
90Z	
91Z	
92Z	
93Z	

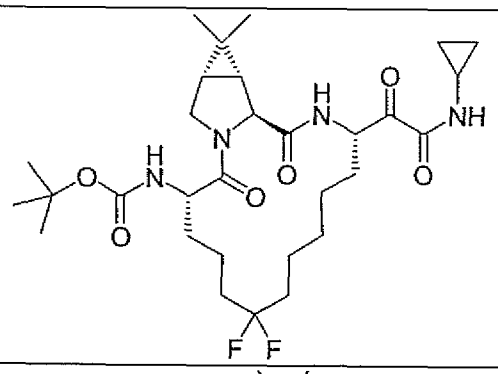
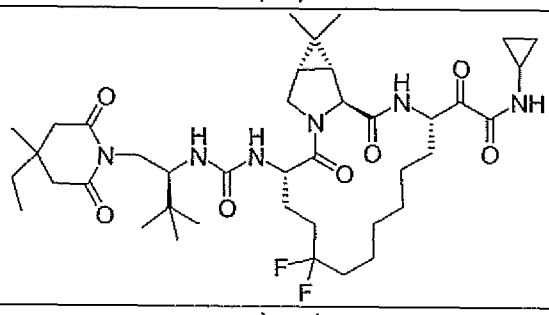
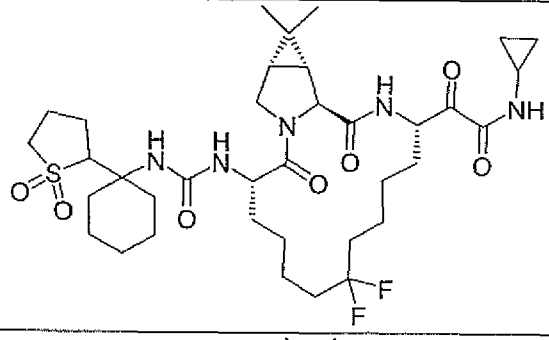
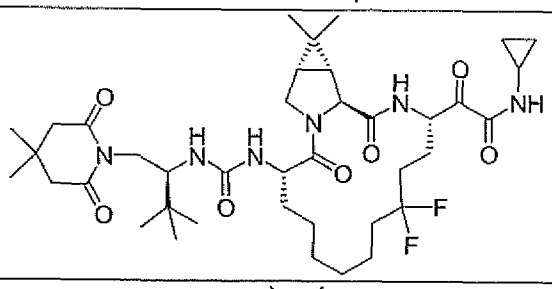
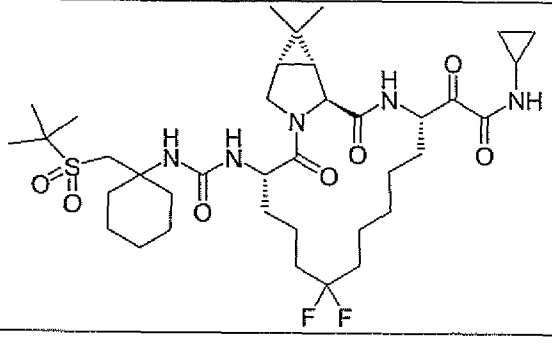
94Z	
95Z	
96Z	
97Z	
98Z	
99Z	
100Z	

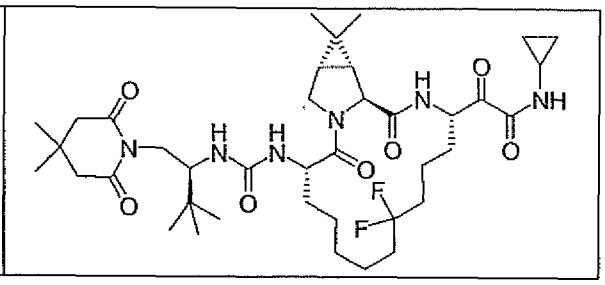
101Z	
102Z	
103Z	
104Z	
105Z	
106Z	

107Z	
108Z	
109Z	
110Z	
111Z	
112Z	

113Z	
114Z	
115Z	
116Z	
117Z	

118Z	
119Z	
120Z	
121Z	
122Z	

123Z	
124Z	
125Z	
126Z	
127Z	

128Z	

The compounds of **Table 1** have the following binding activity. Compounds 1Z-10Z, 12Z-51Z, 53Z-57Z, 59Z-100Z, 103Z-110Z, 112Z, 115Z-117Z, 119Z-122Z, 124Z, 125Z, 127Z and 128Z have category A binding activity. Compounds 52Z, 58Z, 102Z, 111Z, 114Z, 118Z, and 123Z have category B binding activity. Compound 113Z has category C binding activity.

The present invention relates to novel HCV protease inhibitors. This utility is manifested in their ability to inhibit the HCV NS2/NS4a serine protease as demonstrated by the following *in vitro* assays.

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assays for the HCV serine protease was performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates were derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or P) whose C-terminal carboxyl groups were esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Presented below are the synthesis, characterization and application of these novel spectrophotometric ester substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors.

Materials and Methods:

Materials: Chemical reagents for assay related buffers were obtained from Sigma Chemical Company (St. Louis, Missouri). Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) and Perseptive Biosystems (Framingham, Massachusetts). Peptides were synthesized manually or on an automated ABI model 431A synthesizer

(from Applied Biosystems). UV/VIS Spectrometer model LAMBDA 12 was from Perkin Elmer (Norwalk, Connecticut) and 96-well UV plates were obtained from Corning (Corning, New York). The prewarming block was from USA Scientific (Ocala, Florida) and the 96-well plate vortexer was from Labline Instruments (Melrose Park, Illinois). A Spectramax Plus microtiter plate reader with monochrometer was obtained from Molecular Devices (Sunnyvale, California).

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) was prepared by using the procedures published previously (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations were determined by the Biorad dye method using recombinant HCV protease standards previously quantified by amino acid analysis. Prior to assay initiation, the enzyme storage buffer (50 mM sodium phosphate pH 8.0, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside and 10 mM DTT) was exchanged for the assay buffer (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) utilizing a Biorad Bio-Spin P-6 prepacked column.

Substrate Synthesis and Purification: The synthesis of the substrates was done as reported by R. Zhang *et al*, (*ibid.*) and was initiated by anchoring Fmoc-Nva-OH to 2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al, Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides were subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments were cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in dichloromethane (DCM) for 30 min, or by 2% trifluoroacetic acid (TFA) in DCM for 10 min. The combined filtrate and DCM wash was evaporated azeotropically (or repeatedly extracted by aqueous Na_2CO_3 solution) to remove the acid used in cleavage. The DCM phase was dried over Na_2SO_4 and evaporated.

The ester substrates were assembled using standard acid-alcohol coupling procedures (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Peptide fragments were dissolved in anhydrous pyridine (30-60 mg/ml) to which 10 molar equivalents of chromophore and a catalytic amount (0.1 eq.) of para-toluenesulfonic acid (pTSA) were added. Dicyclohexylcarbodiimide (DCC, 3 eq.) was added to initiate the coupling reactions. Product formation was monitored by HPLC and found to be

complete following 12-72 hour reaction at room temperature. Pyridine solvent was evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester was deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate was purified by reversed phase HPLC on a C3 or C8 column with a 30% to 60% acetonitrile gradient (using six column volumes). The overall yield following HPLC purification was approximately 20-30%. The molecular mass was confirmed by electrospray ionization mass spectroscopy. The substrates were stored in dry powder form under desiccation.

Spectra of Substrates and Products: Spectra of substrates and the corresponding chromophore products were obtained in the pH 6.5 assay buffer. Extinction coefficients were determined at the optimal off-peak wavelength in 1-cm cuvettes (340 nm for 3-Np and HMC, 370 nm for PAP and 400 nm for 4-Np) using multiple dilutions. The optimal off-peak wavelength was defined as that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD).

Protease Assay: HCV protease assays were performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) were optimized for the NS3/NS4A heterodimer (D. L. Sali *et al, ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor were placed in wells (final concentration of DMSO ≤4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, was then used to initiate the reaction (final volume 200 µl).The plates were monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore was monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters was performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities were determined using linear regression and kinetic constants were obtained by fitting the data to the Michaelis-

Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) were calculated assuming the enzyme was fully active.

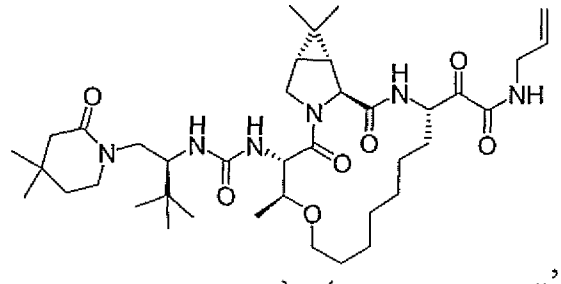
Evaluation of Inhibitors and Inactivators: The inhibition constants (Ki*) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH were determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o/(K_i (1 + [S]_o/K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data were fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_o/K_m)$, was used to calculate the Ki* value.

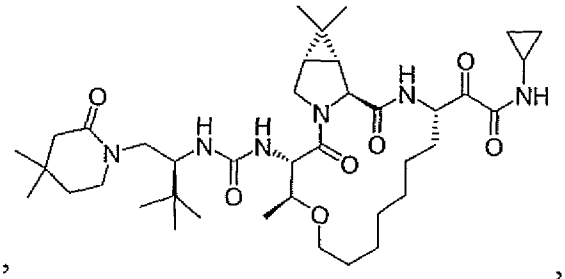
The obtained K_i values for the various macrocycles of the present invention are given in **Table 1**. From these test results, it would be apparent to the skilled artisan that the compounds of the invention have excellent utility as NS3-serine protease inhibitors.

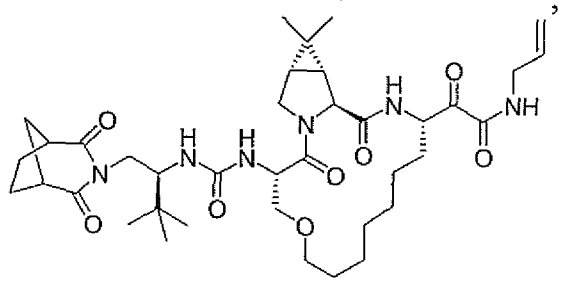
CLAIMS

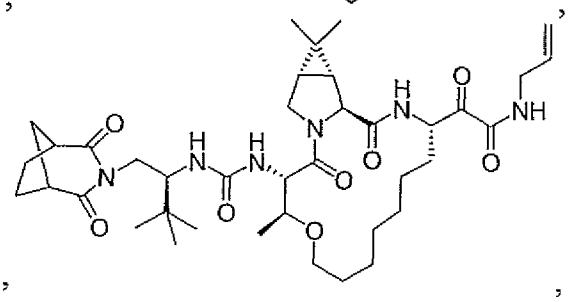
What is claimed is:

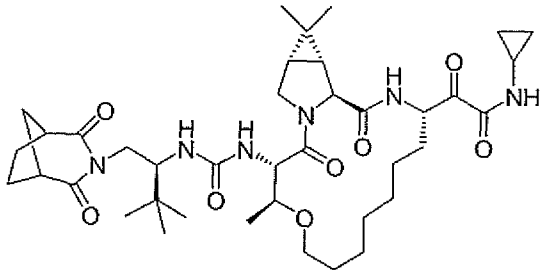
1. A compound exhibiting HCV protease inhibitory activity, or an enantiomer, stereoisomer, rotamer, tautomer, or racemate of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound or of said enantiomer, stereoisomer, rotamer, tautomer, or racemate, said compound being selected from the group consisting of the compounds of structures listed below:

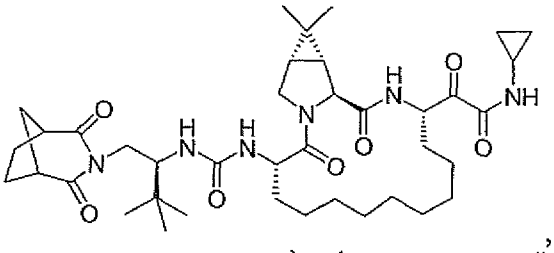


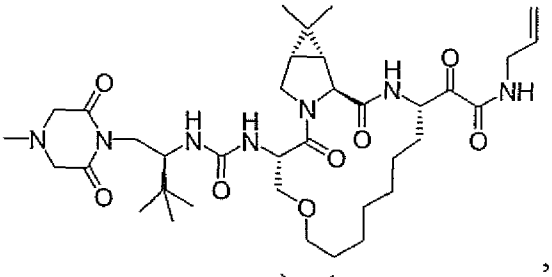


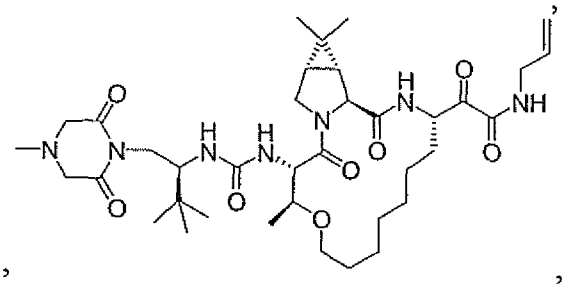


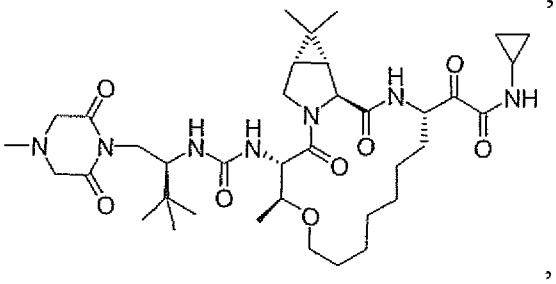


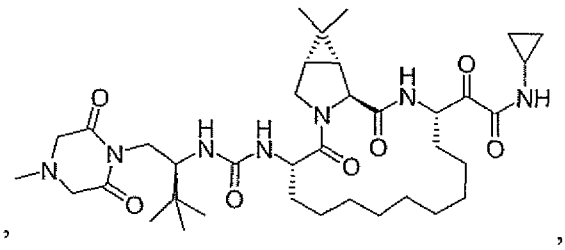


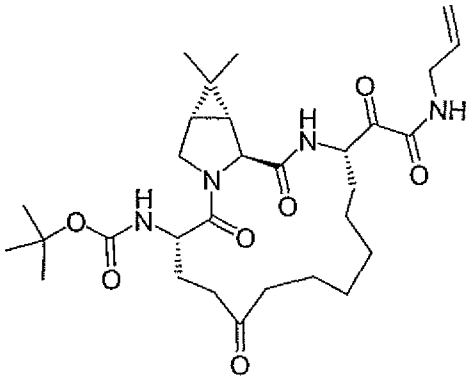












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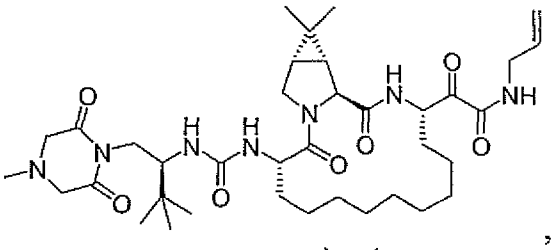

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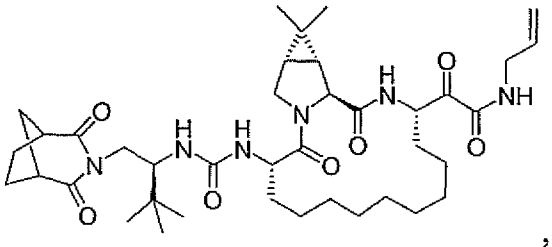

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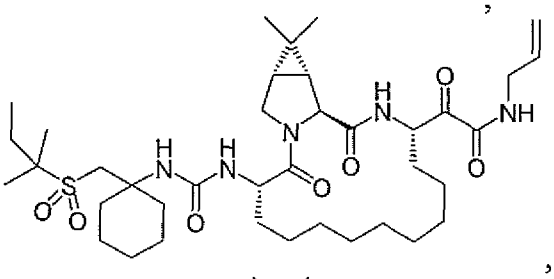

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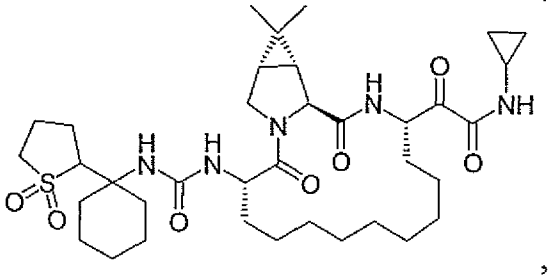

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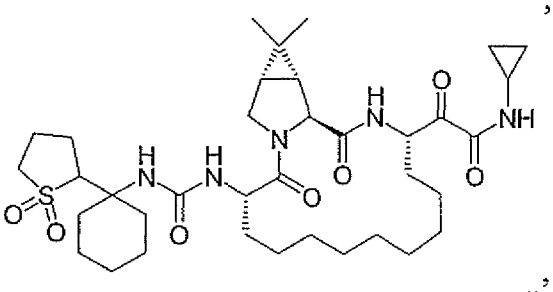

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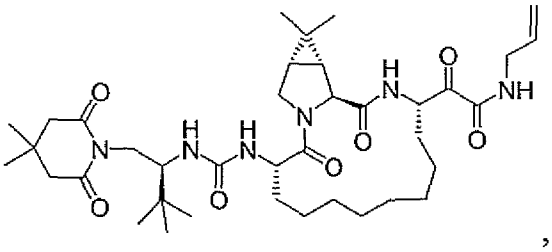

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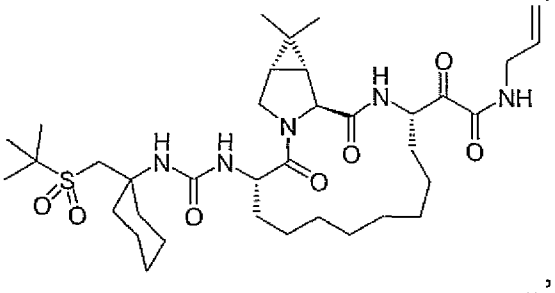

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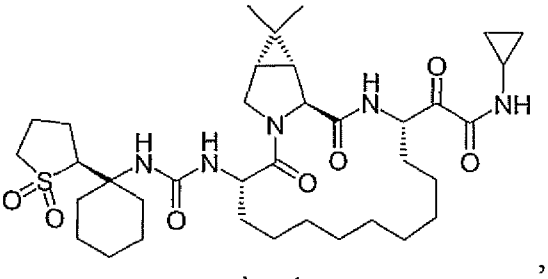

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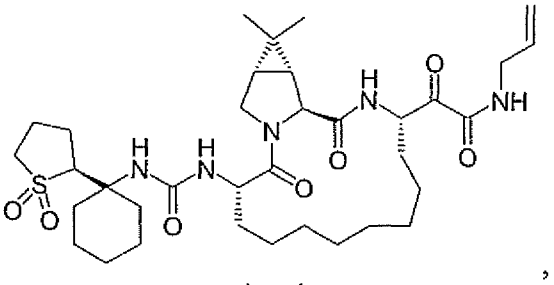

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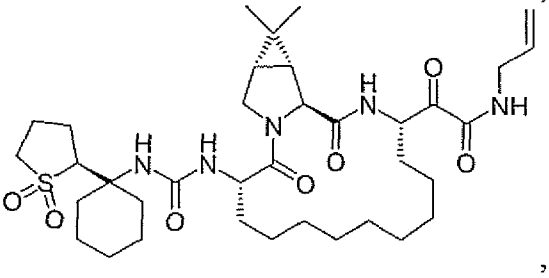

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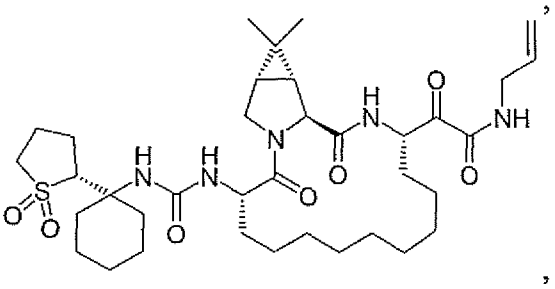

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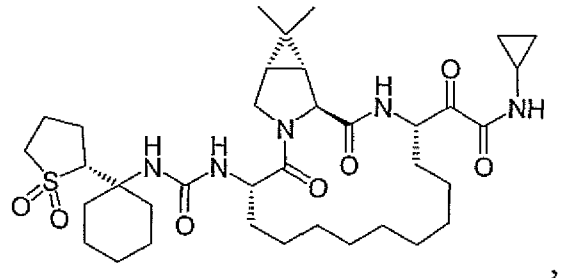
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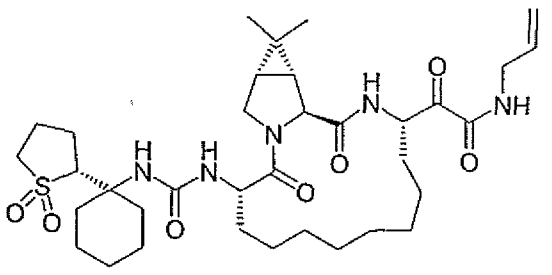
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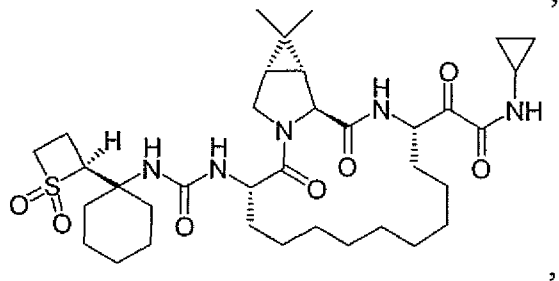
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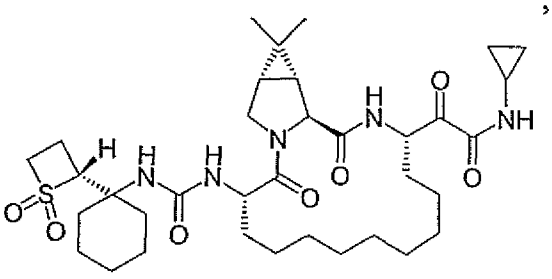
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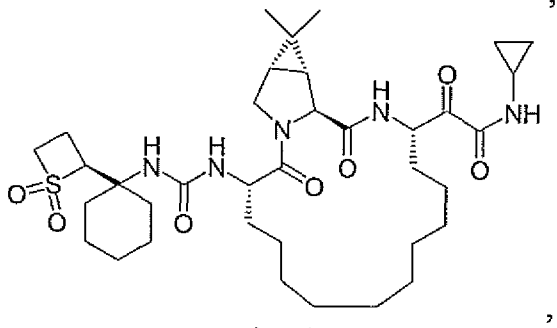
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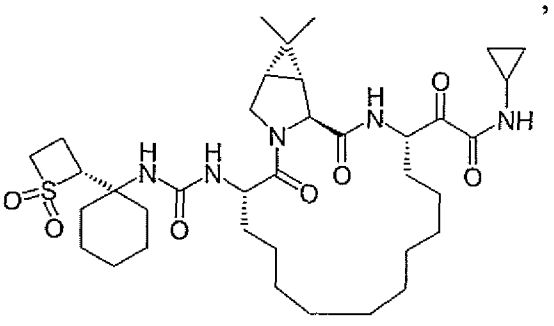
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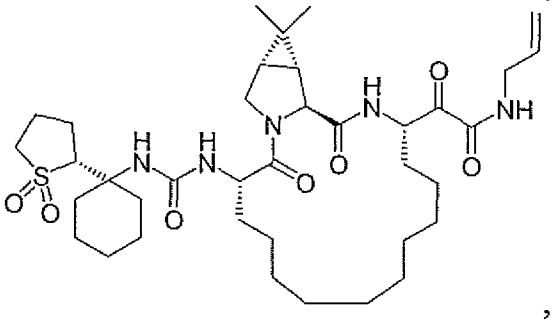
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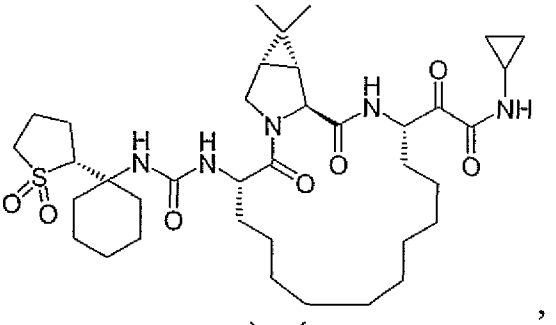
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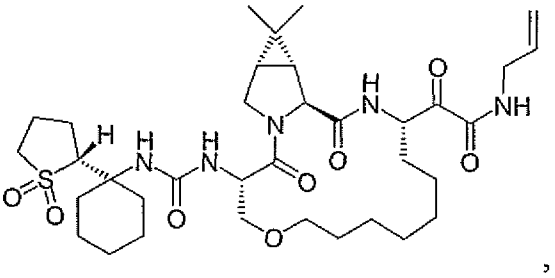
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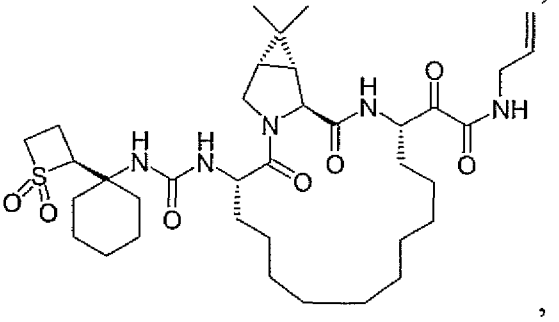
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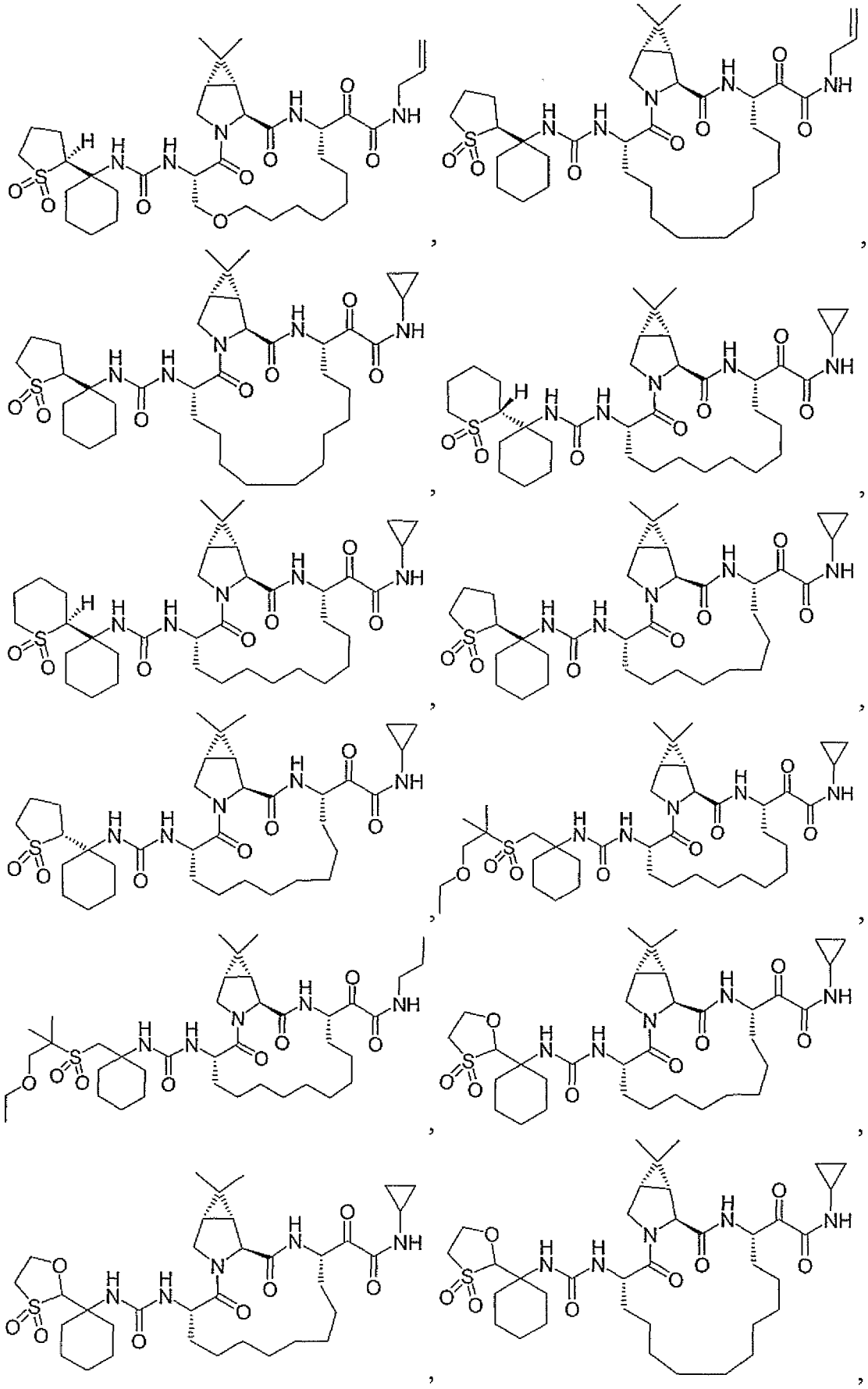

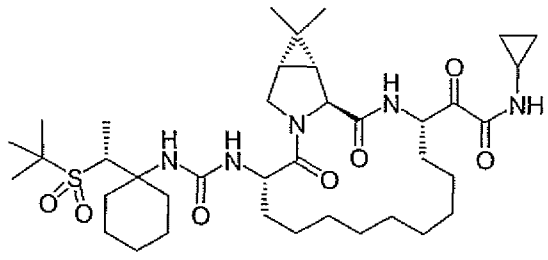
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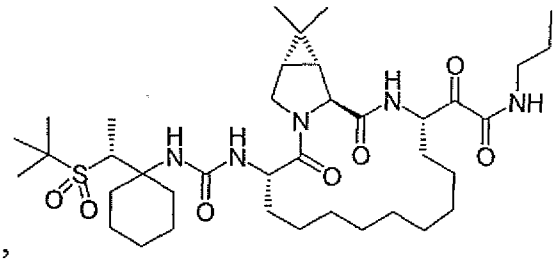
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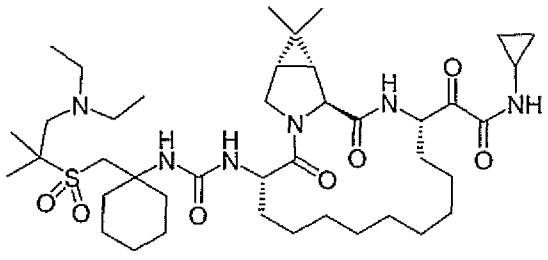
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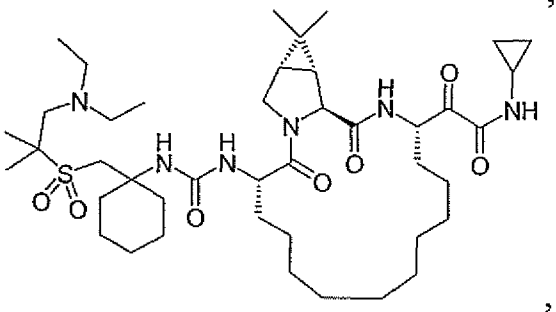
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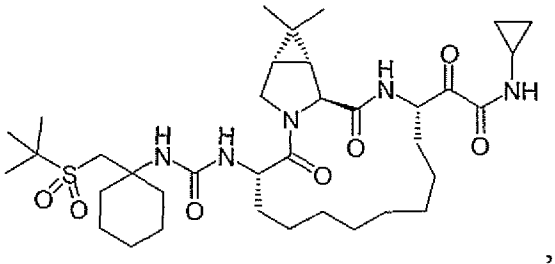
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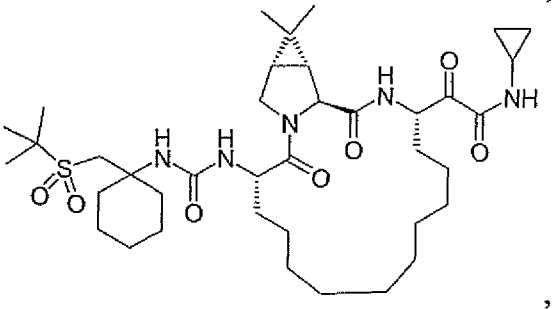
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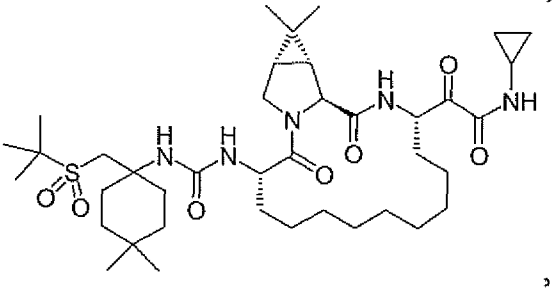
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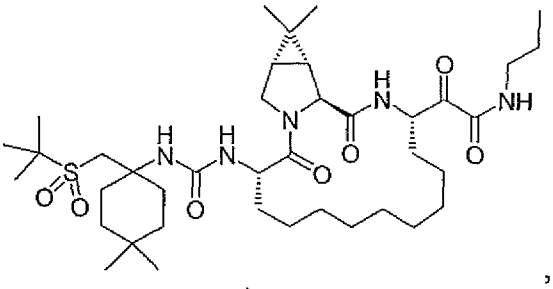
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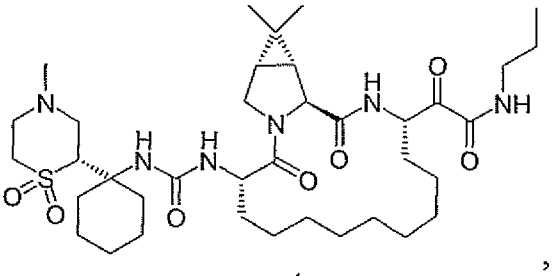
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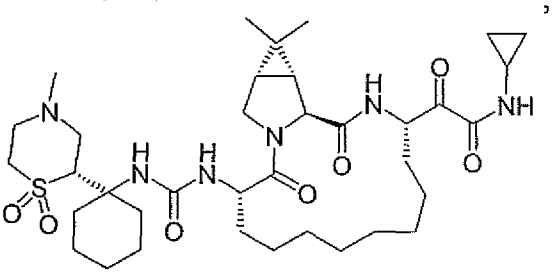
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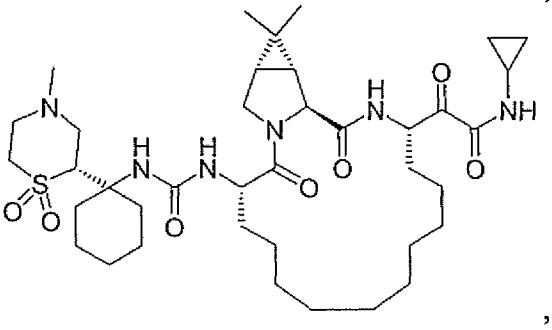
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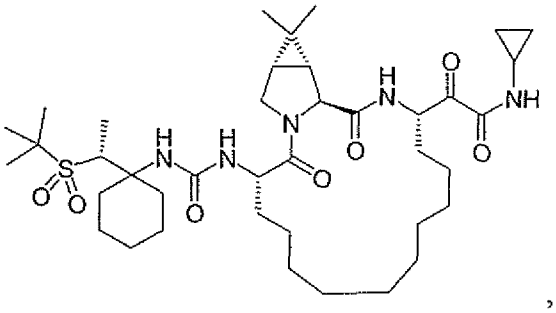
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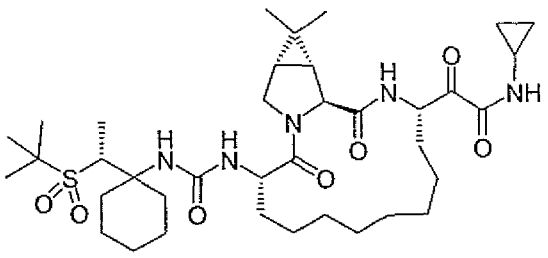
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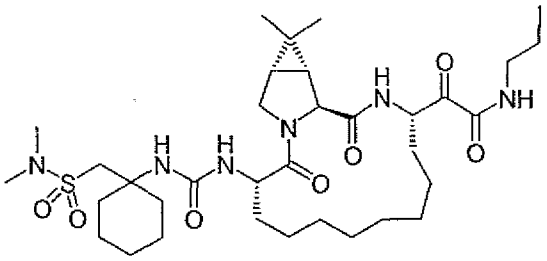
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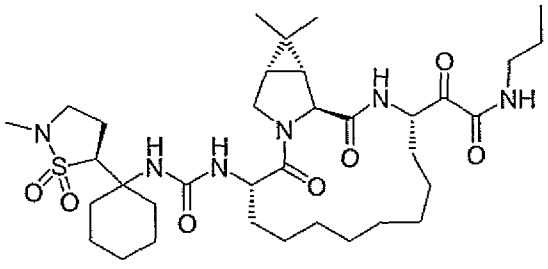
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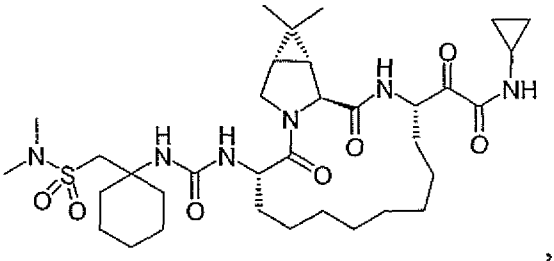
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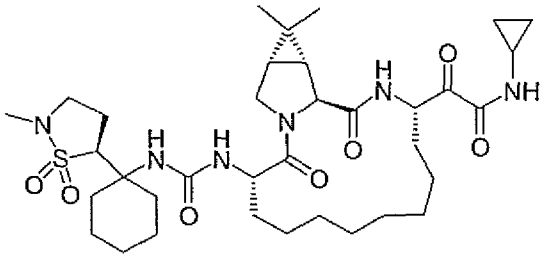
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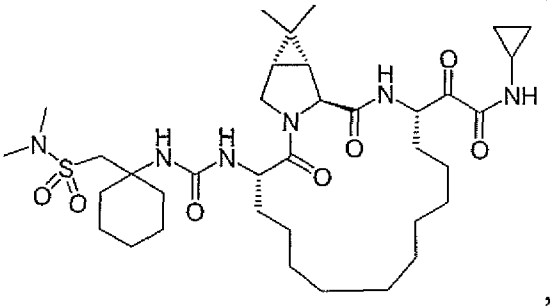
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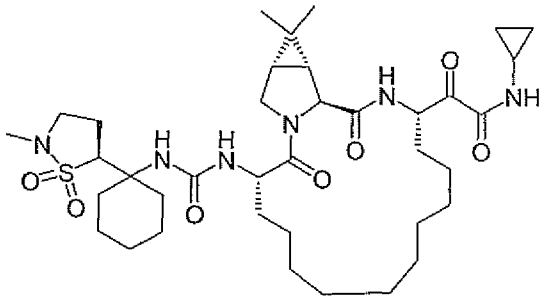
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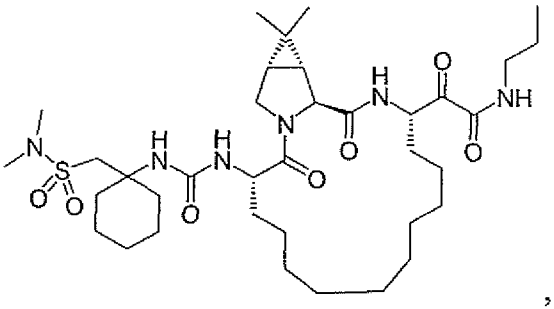
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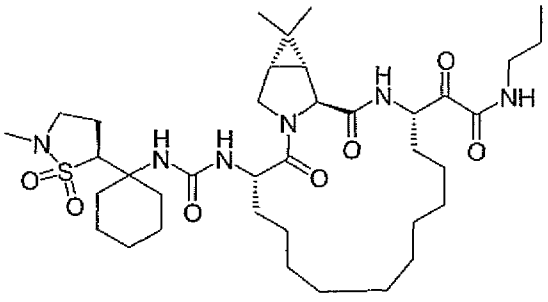
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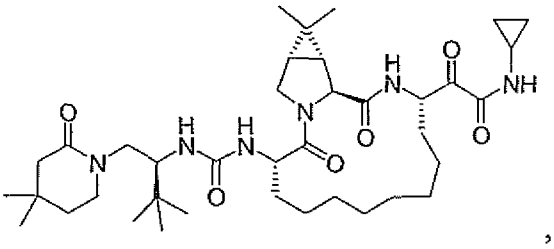
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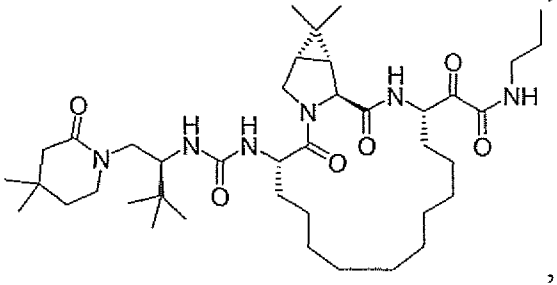
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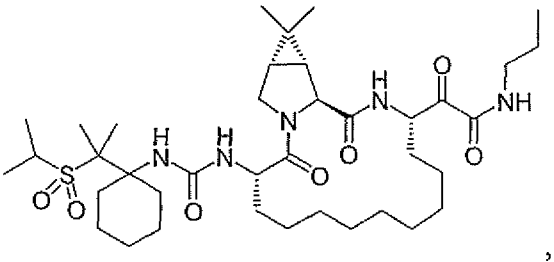
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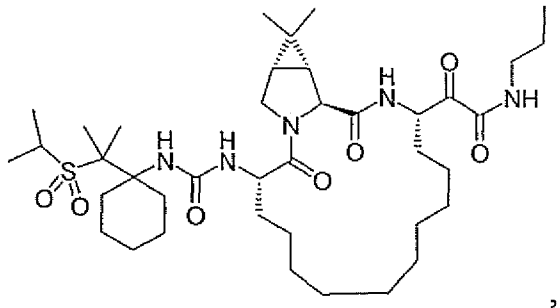
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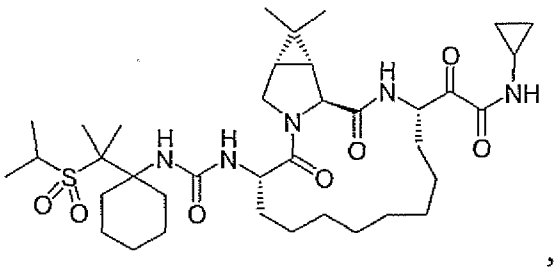
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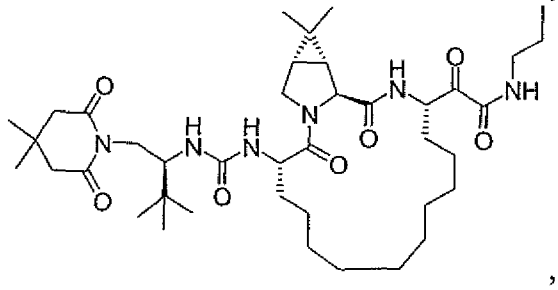
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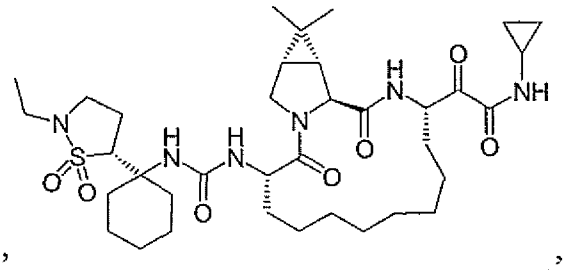
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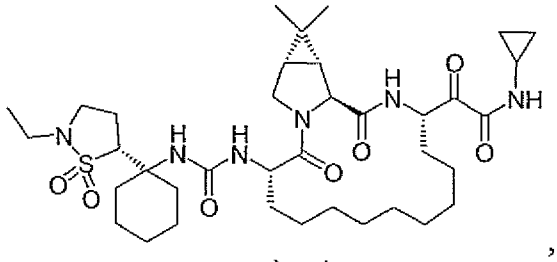
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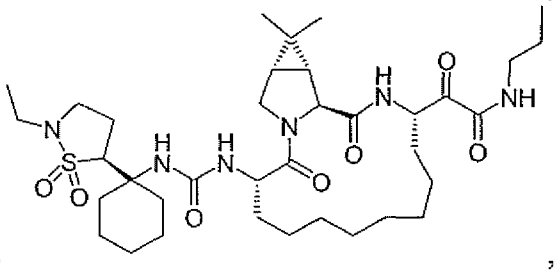
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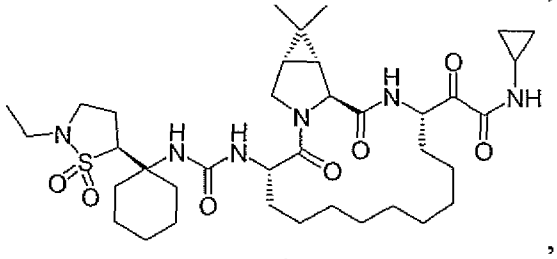
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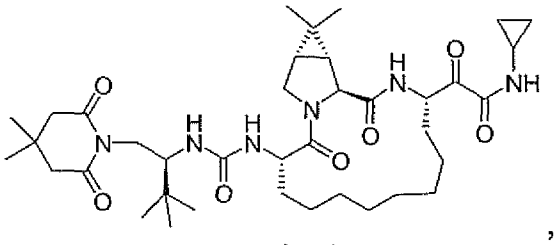
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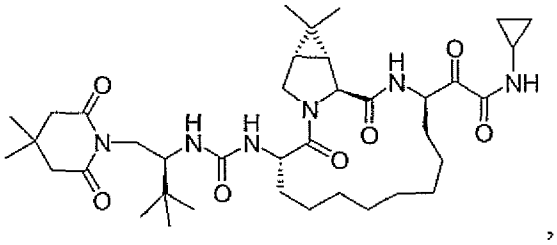
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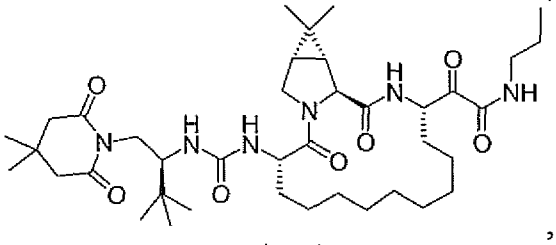
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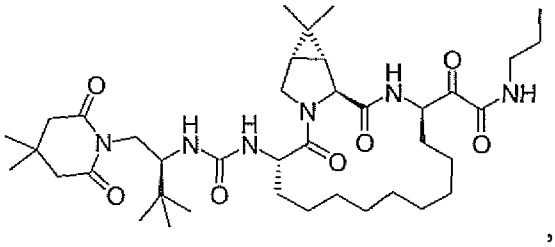
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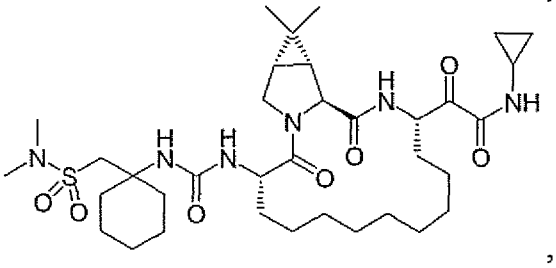
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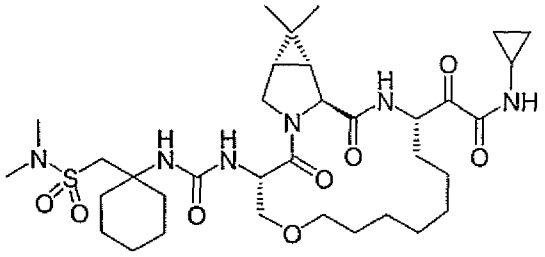
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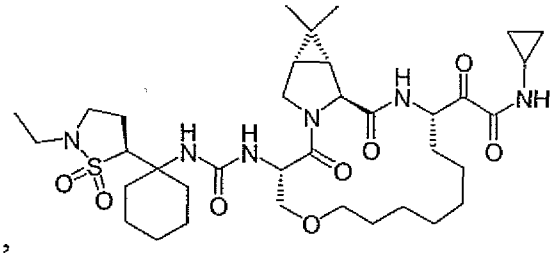
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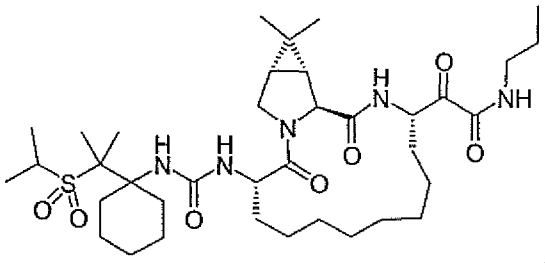
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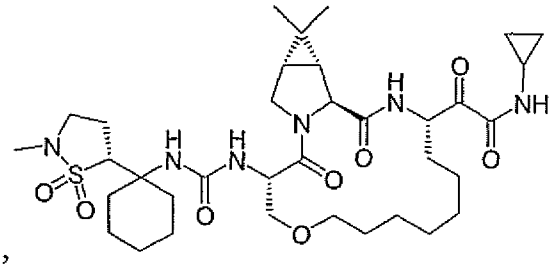
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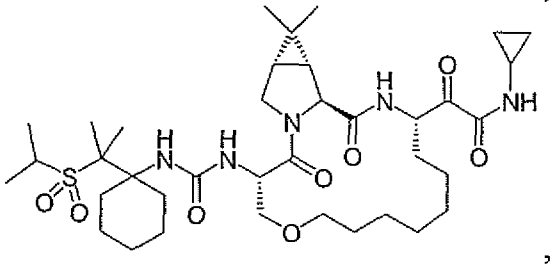
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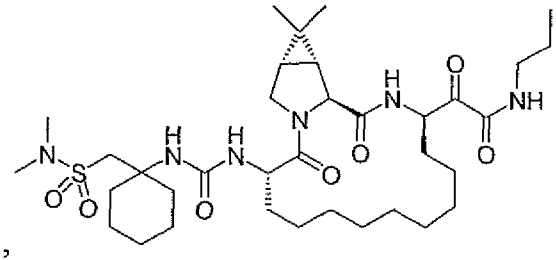
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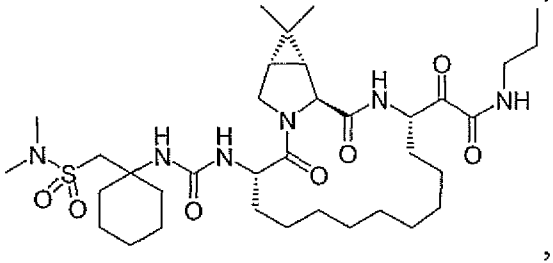
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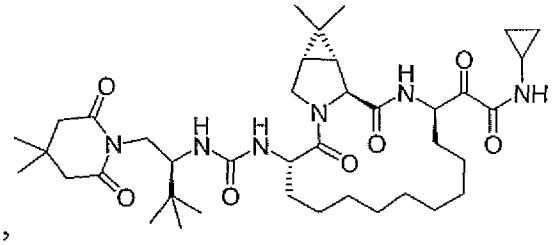
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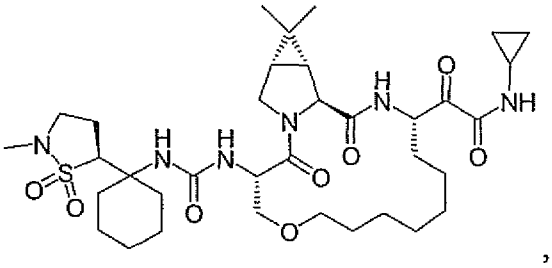
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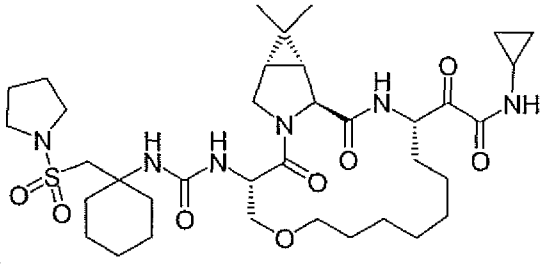
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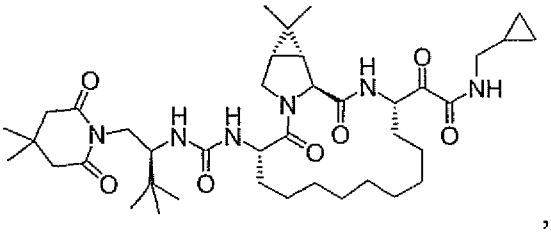
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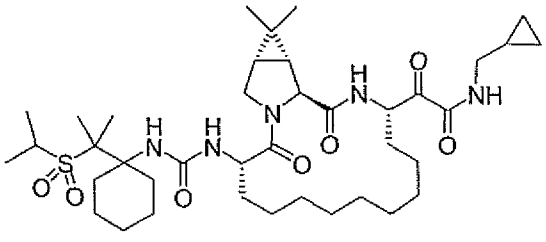
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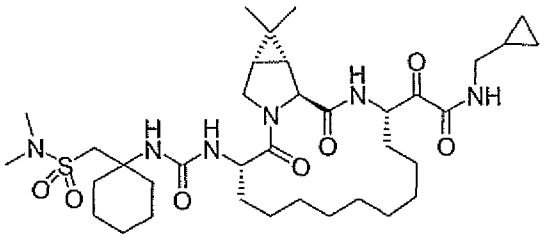
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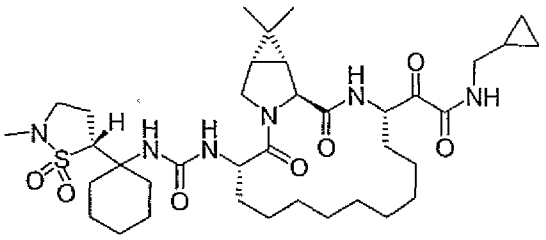
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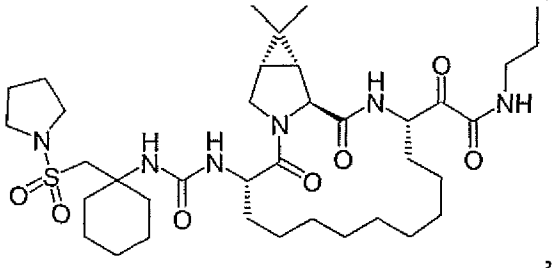
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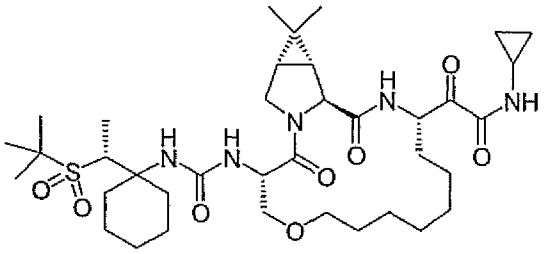
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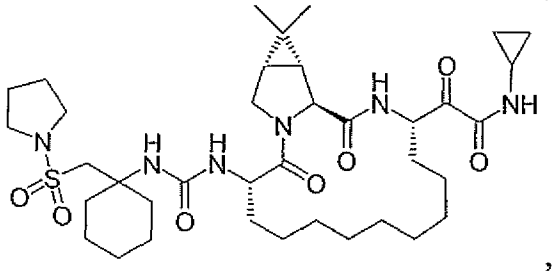
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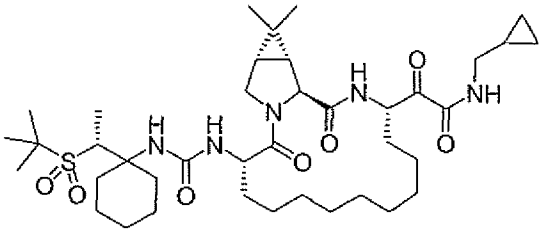
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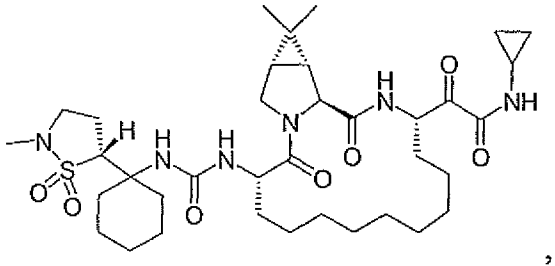
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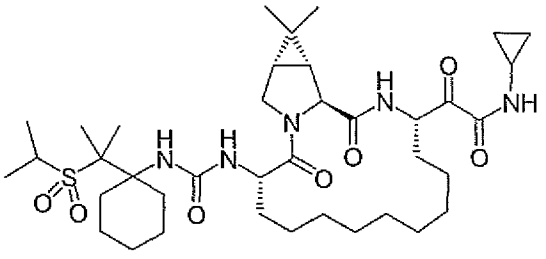
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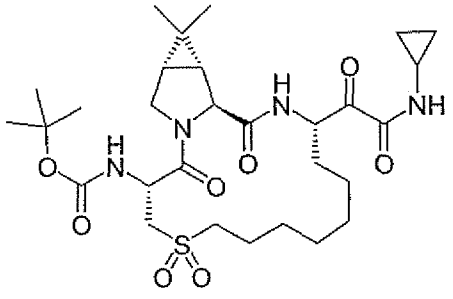
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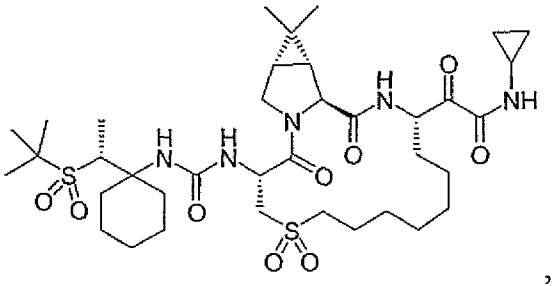
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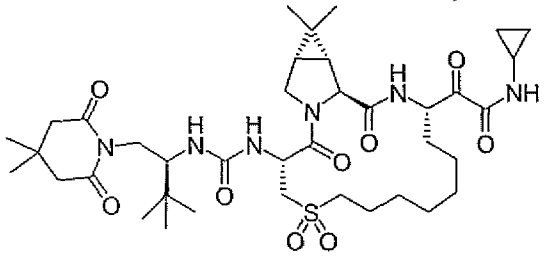
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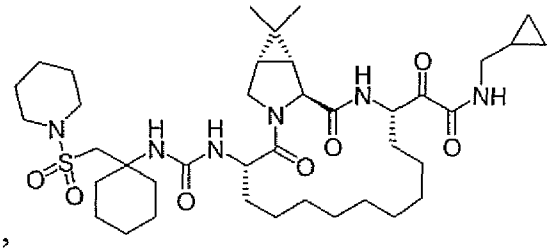
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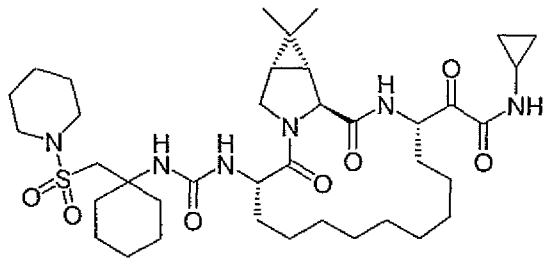
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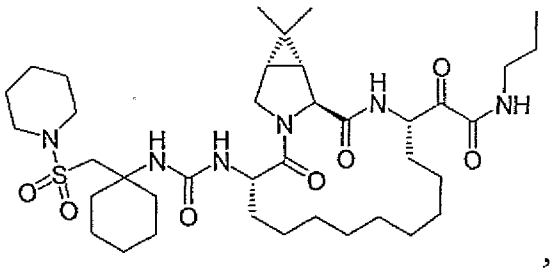
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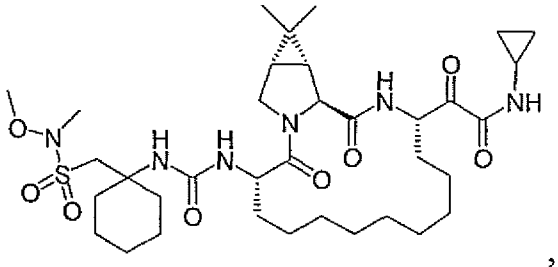
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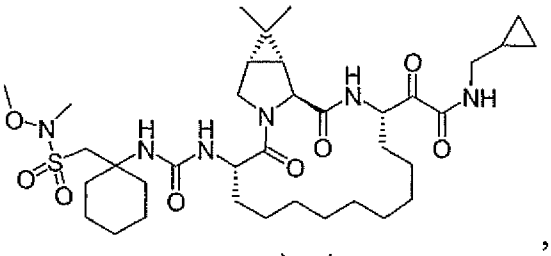
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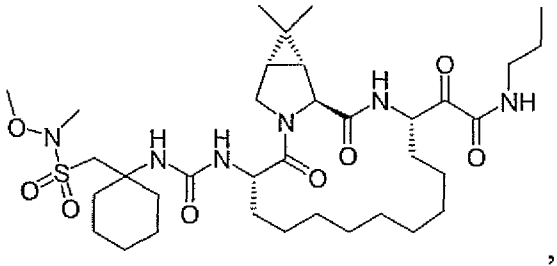
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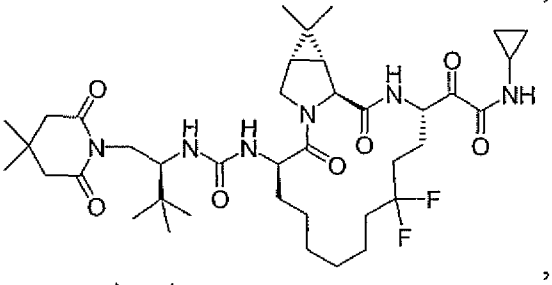
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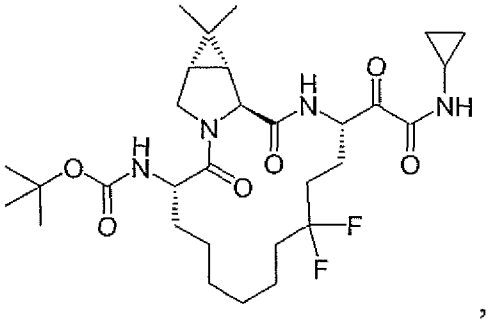
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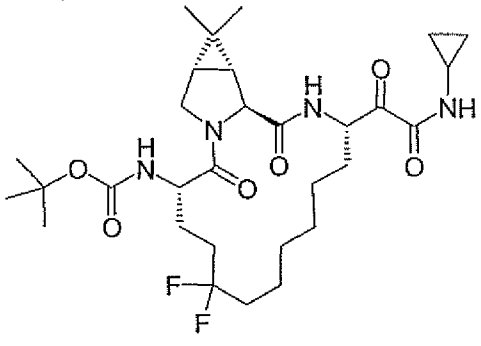
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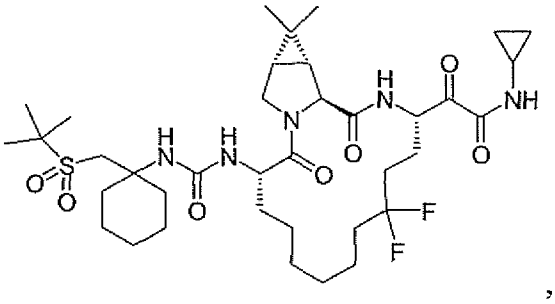
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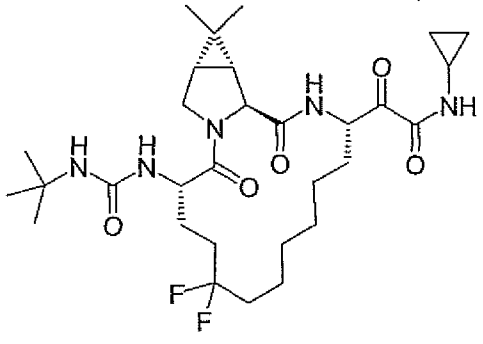
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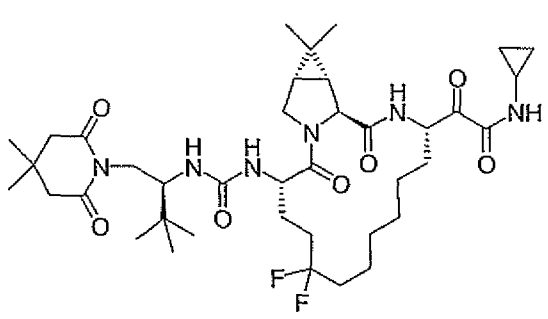
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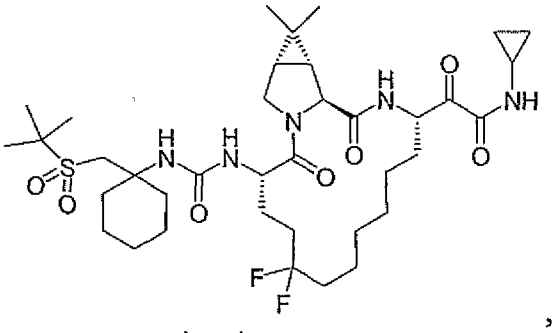
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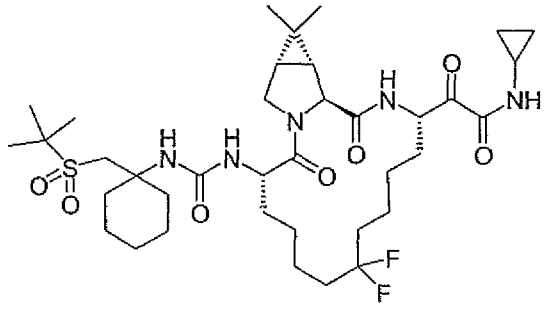
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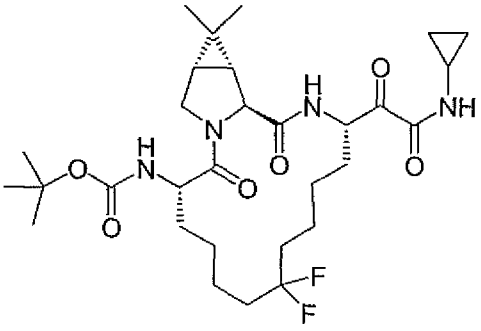
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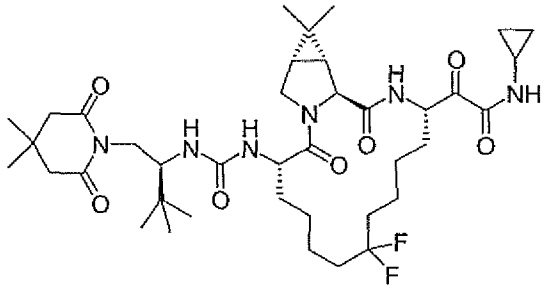
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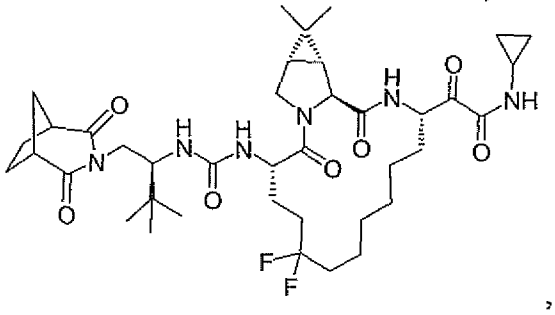
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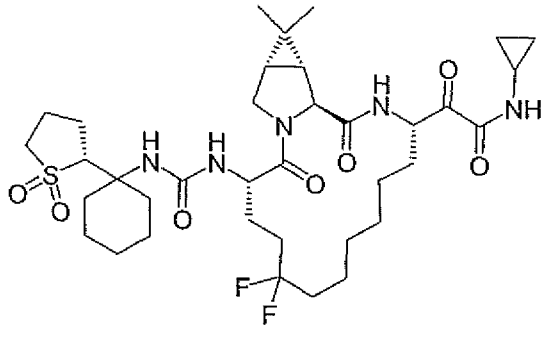
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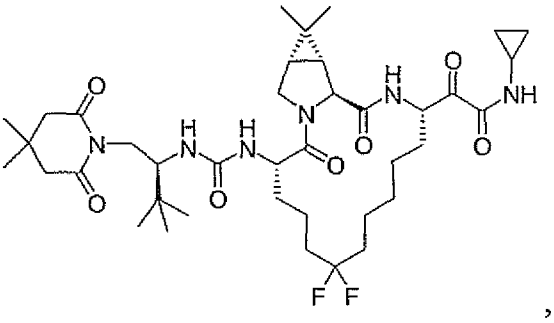
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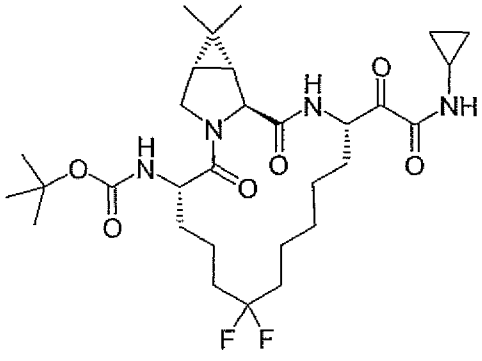
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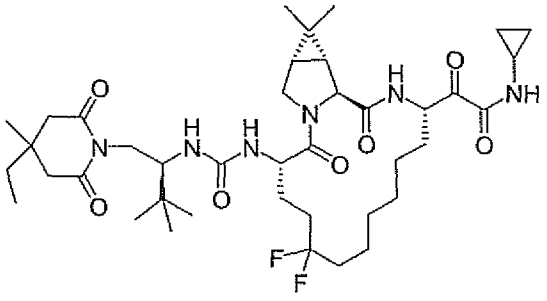
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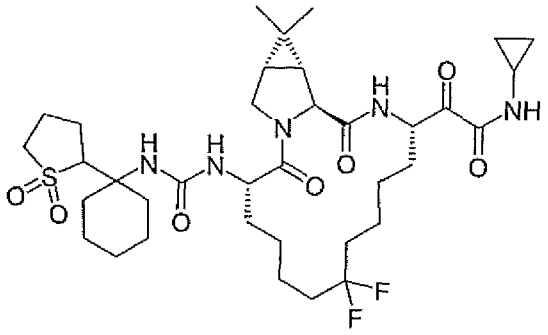
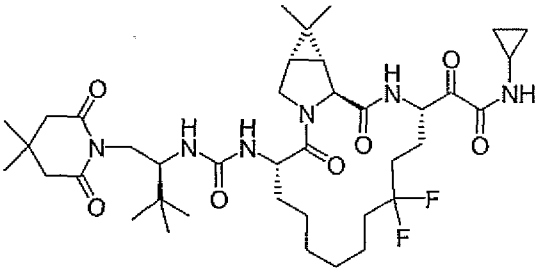
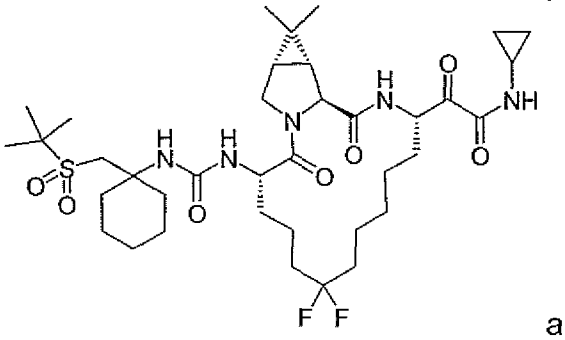
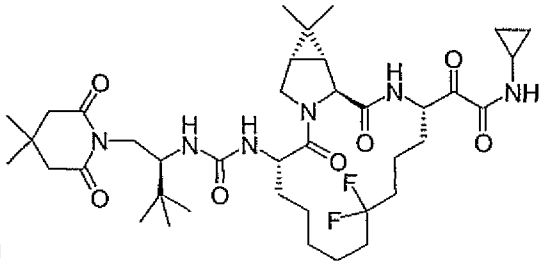

and

2. A pharmaceutical composition comprising as an active ingredient at least one compound of claim 1.

3. The pharmaceutical composition of claim 2 for use in treating disorders associated with HCV.

4. The pharmaceutical composition of claim 2 additionally comprising at least one pharmaceutically acceptable carrier.

5. The pharmaceutical composition of claim 4, additionally containing at least one antiviral agent.

6. The pharmaceutical composition of claim 5, still additionally containing at least one interferon.

7. The pharmaceutical composition of claim 6, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

8. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

9. The method of claim 8, wherein said administration is oral or subcutaneous.

10. A compound of claim 1 in purified form.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/081575

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K5/06 A61P31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/030796 A (SCHERING CORP [US]; VENKATRAMAN SRIKANTH [US]; NJOROGE F GEORGE [US];) 7 April 2005 (2005-04-07) cited in the application whole document, in particular examples.	1-10

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2009	26/01/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Schleifenbaum, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/081575

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