Macrocyclic NS3-Serine Protease Inhibitors of Hepatitis C Virus Comprising N-Cyclic P2 Moieties

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 specifically 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 and European Patent Application Publication No. EP 381 216). 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.

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.

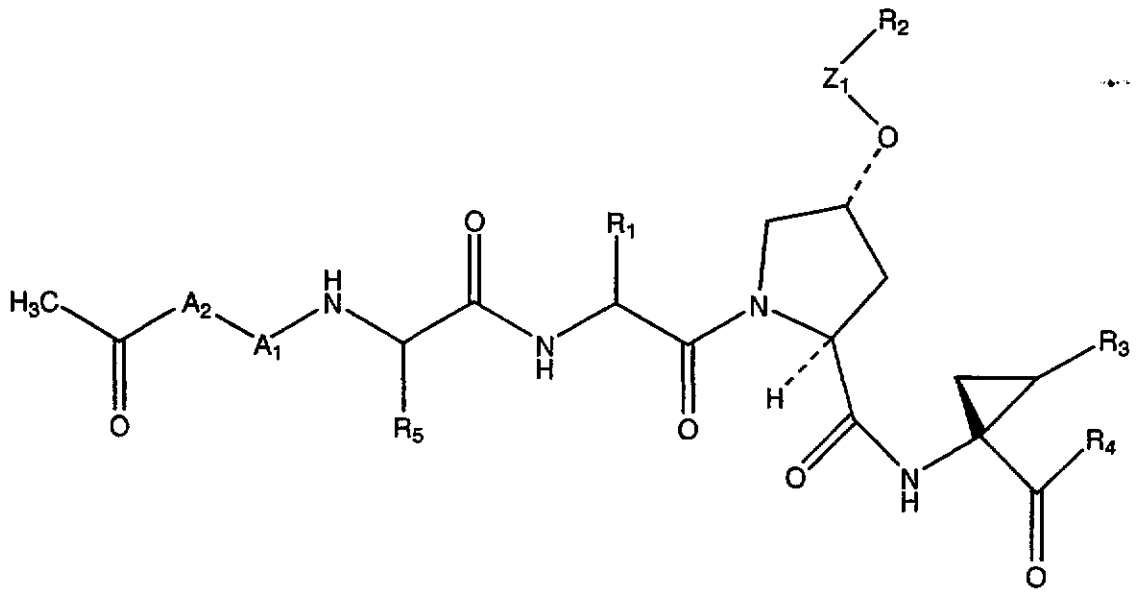
Inhibitors of HCV protease that have been reported include antioxidants (see, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (see, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella 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)).

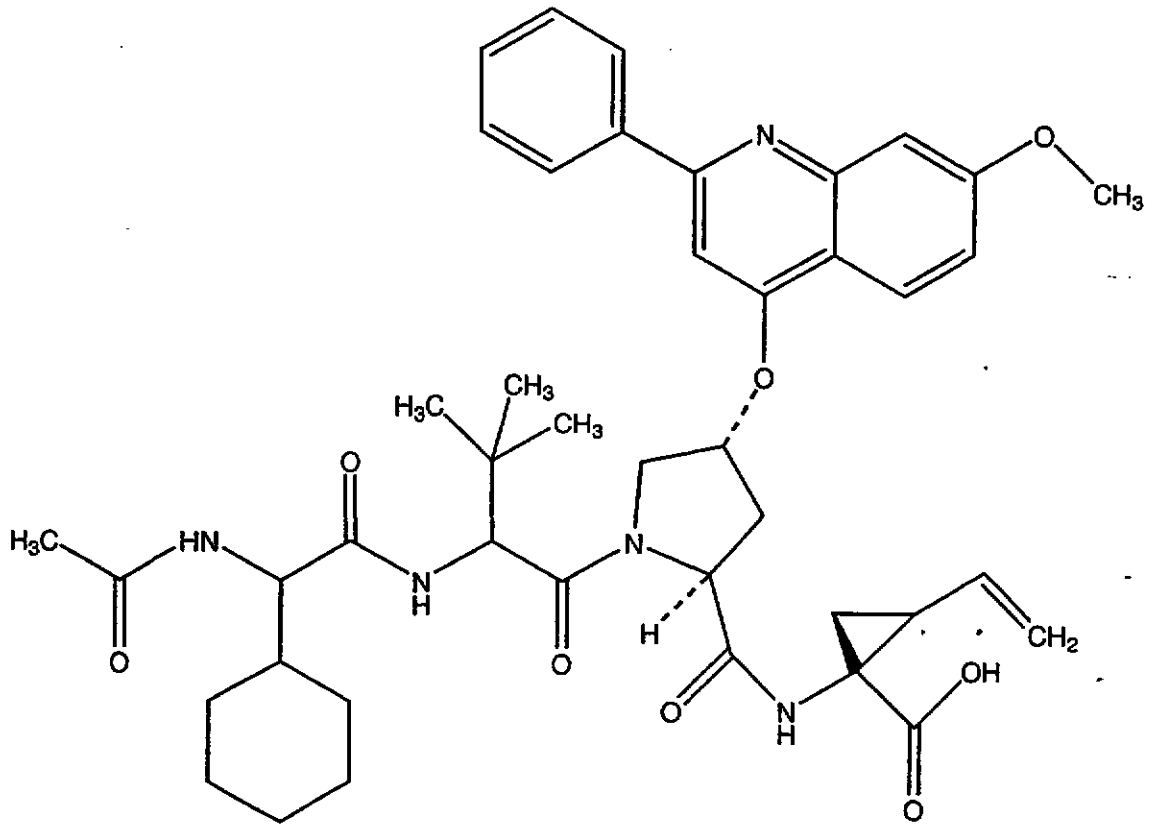
Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

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%.

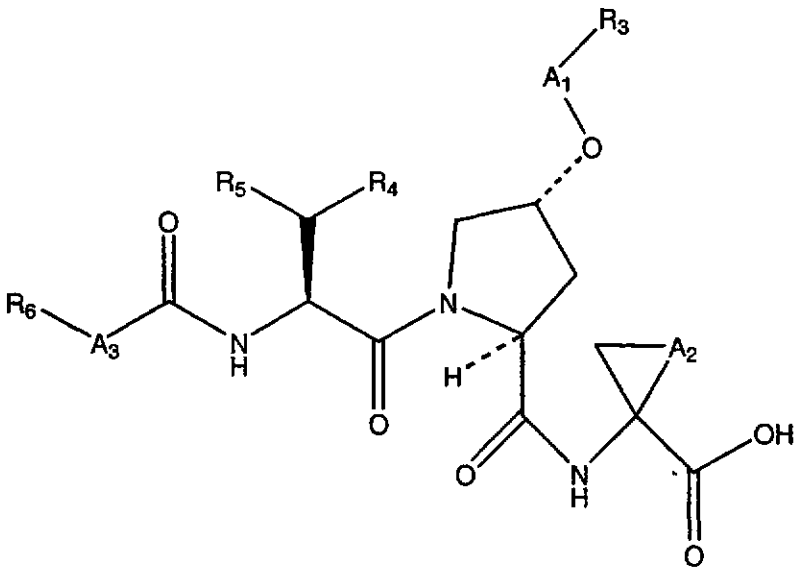
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



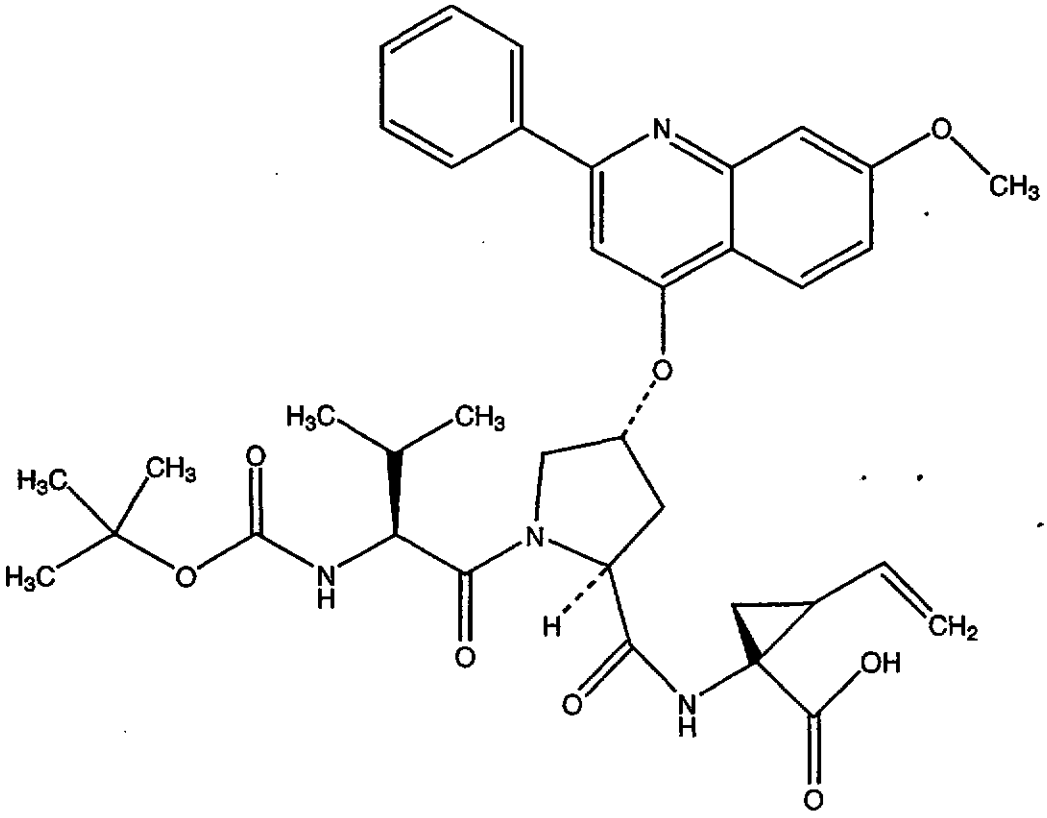
where the various elements are defined therein. An illustrative compound of that series is:



Reference is also made to WO 00/09543 (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.

There is a need for new treatments and therapies for HCV infection. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis C.

It is a further object herein to provide methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

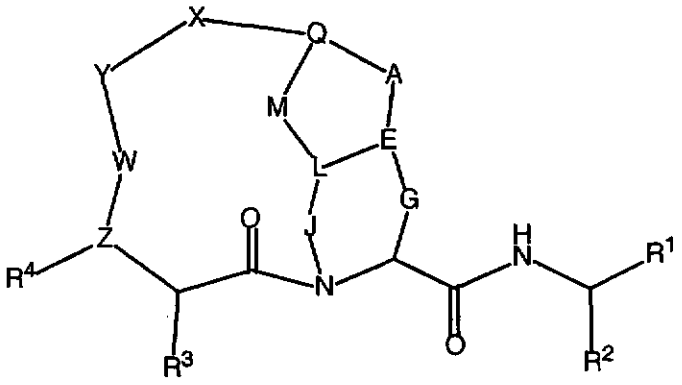
A still further object of the present invention is to provide methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

Another object herein is to provide methods of modulating the processing of the HCV polypeptide using the compounds provided herein.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of macrocyclic inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration or one or more of the symptoms of hepatitis C. Also provided are methods of modulating the interaction of an HCV polypeptide with HCV protease. Among the compounds provided herein, compounds that inhibit HCV NS3/NS4a serine protease activity are preferred. The presently disclosed compounds generally contain about three or more amino acid residues and less than about twelve amino acid residues.

In its principal embodiment, the present invention provides a macrocyclic compound of Formula I:



Formula I

wherein:

X and Y are independently selected from the moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl sulfide, alkyl-aryl sulfide, aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, aryl sulfone, alkyl-alkyl sulfoxide, alkyl-aryl sulfoxide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl urea, alkyl-aryl urea, aryl urea, alkyl carbamate, alkyl-aryl carbamate, aryl carbamate, alkyl -hydrazide, alkyl-aryl hydrazide, alkyl hydroxamide, alkyl-aryl hydroxamide, alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof, with the proviso that X and Y may optionally be additionally substituted with moieties selected from the group consisting of aromatic, alkyl, alkyl-aryl, heteroalkyl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, alkyl sulfide, alkyl-aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, alkyl amide, alkyl-aryl amide, alkyl sulfonamide, , alkyl amines, alkyl-aryl amines, alkyl-aryl sulfonamide, alkyl urea, alkyl-aryl urea, alkyl carbamate and alkyl-aryl carbamate;

$R^1 = COR^5$ or $B(OR)_2$, wherein R^5 = H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, COR^7 wherein R^7 = H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10}, wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})\ CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, or CH;

W may be present or absent, and if W is present, W is selected from C=O, C=S, or SO_2;

Q maybe present or absent, and when Q is present, Q is CH, N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M is also absent, and A is directly linked to X;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_2 or a bond;

E is CH, N or CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$,; and when G is absent, J is present and E is directly connected to the carbon atom where G was connected to;

J maybe absent or present, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, SO_2, NH, NR or O; and when J is absent, G is present and E is directly linked to N;

L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be absent or present, and if

M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; oxygen, nitrogen, sulfur, or phosphorus atoms with said oxygen, nitrogen, sulfur, or phosphorus atoms numbering zero to six;

(cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Thus, for example, the term alkyl (including the alkyl portions of alkoxy) refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single atom having from 1 to 8 carbon atoms, preferably from 1 to 6;

aryl – represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic

carbon atoms of the carbocyclic group being intended as possible points of attachment. Preferred aryl groups include phenyl, 1-naphthyl, 2-naphthyl and indanyl, and especially phenyl and substituted phenyl;

aralkyl – represents a moiety containing an aryl group linked vial a lower alkyl;

alkylaryl – represents a moiety containing a lower alkyl linked via an aryl group;

cycloalkyl – represents a saturated carbocyclic ring having from 3 to 8 carbon atoms, preferably 5 or 6, optionally substituted.

heterocyclic – represents, in addition to the heteroaryl groups defined below, saturated and unsaturated cyclic organic groups having at least one O, S and/or N atom interrupting a carbocyclic ring structure that consists of one ring or two fused rings, wherein each ring is 3 to 9-membered and may or may not have double bonds that lack delocalized pi electrons, which ring structure has from 2 to 8, preferably from 3 to 6 carbon atoms, e.g., 2- or 3-piperidinyl, 2- or 3-piperazinyl, 2- or 3-morpholinyl, or 2- or 3-thiomorpholinyl;

halogen – represents fluorine, chlorine, bromine and iodine;

heteroaryl – represents a cyclic organic group having at least one O, S and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or 4-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, etc. Preferred heteroaryl groups are 2-, 3- and 4-pyridyl; Such heteroaryl groups may also be optionally substituted.

Also included in the invention are tautomers, enantiomers and other optical isomers of compounds of Formula I, as well as pharmaceutically acceptable salts and solvates thereof.

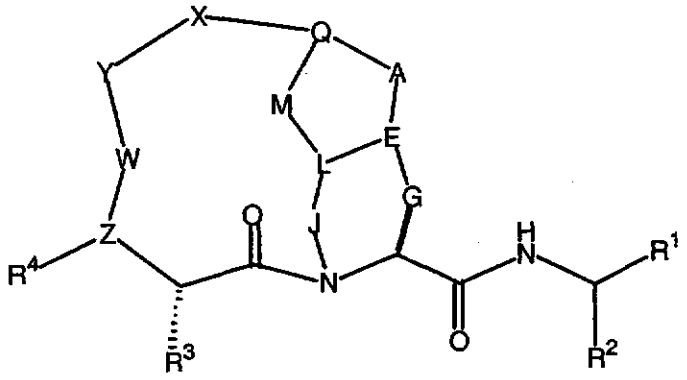
A further feature of the invention is pharmaceutical compositions containing as active ingredient a compound of Formula I (or its salt, solvate or isomers) together with a pharmaceutically acceptable carrier or excipient.

The invention also provides methods for preparing compounds of Formula I, as well as methods for treating diseases such as, for example, HCV and related disorders. The methods for treating comprise administering to a patient suffering from said disease or diseases a therapeutically effective amount of a compound of Formula I, or pharmaceutical compositions comprising a compound of Formula I.

Also disclosed is the use of a compound of Formula I for the manufacture of a medicament for treating HCV and related disorders.

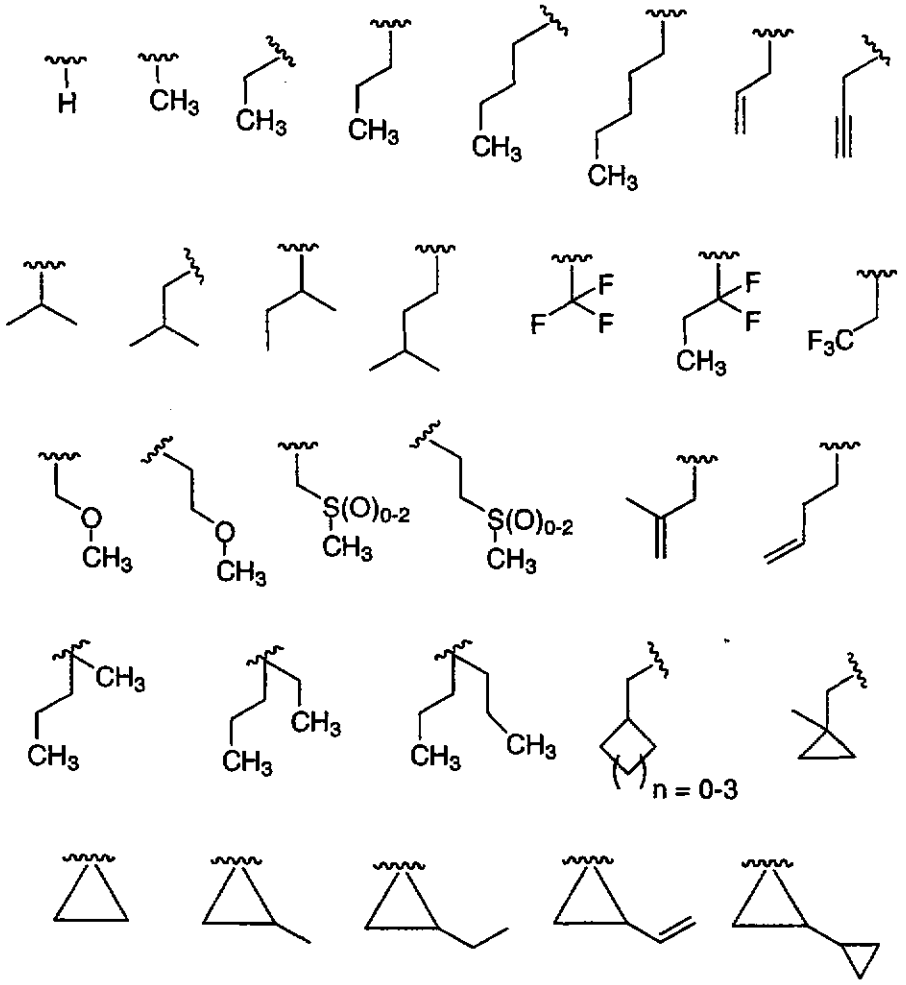
Detailed Description of Preferred Embodiments

In one embodiment, the present invention discloses compounds of Formula I as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease. Among the compounds encompassed by Formula I, preferred compounds are those which have the Formula II:

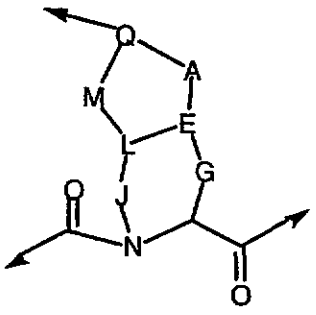


Formula II

or a pharmaceutically acceptable derivative thereof, where the various definitions are given above. Some of the preferred embodiments include, but are not limited to, the following definitions of the various functionalities in the above-noted general formulas I and II. Thus, for example, R^2 in formula I may be selected from the following moieties:

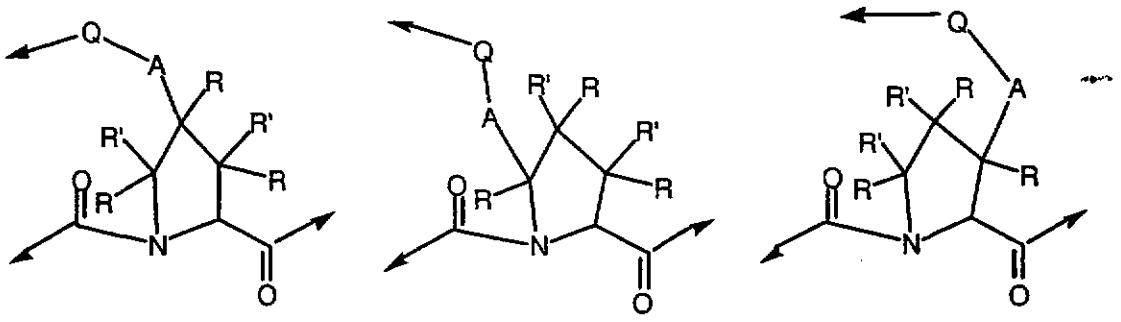


Some preferred representations for the moiety



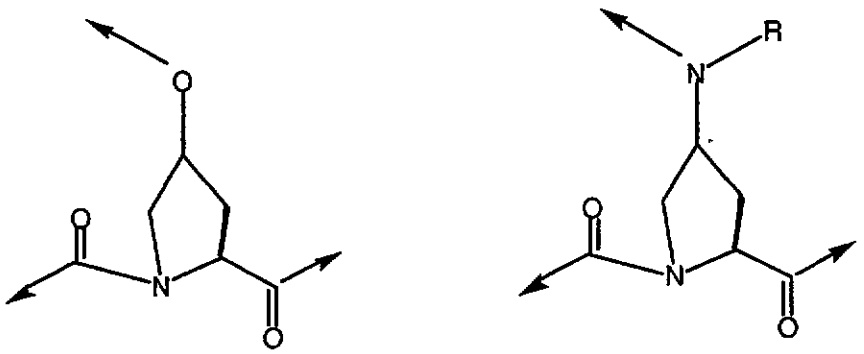
are, for example, the following structures a, b, or c:

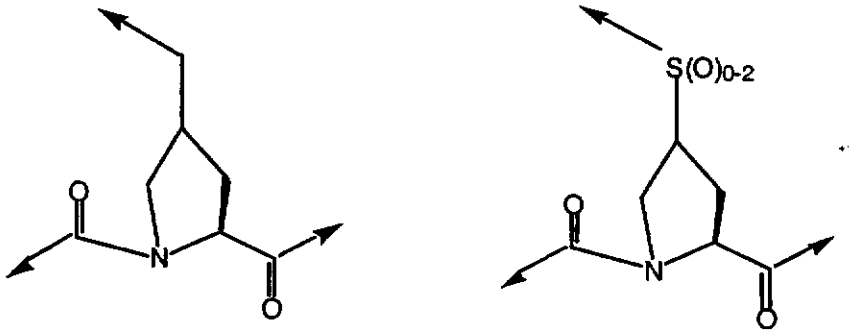
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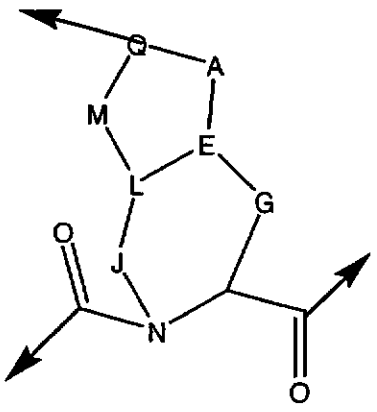
a b c

The structure a may be selected from the following non-limiting types of structures:

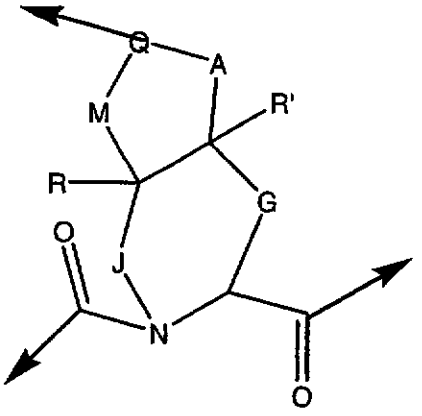




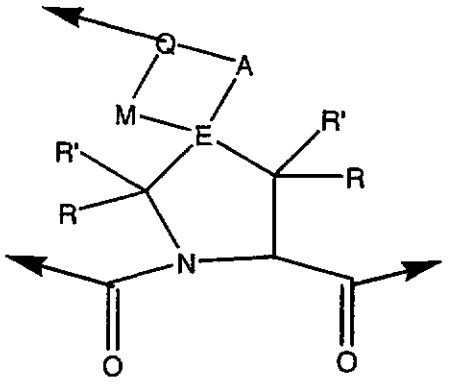
Other additional preferred embodiments are, for example, where the moiety:



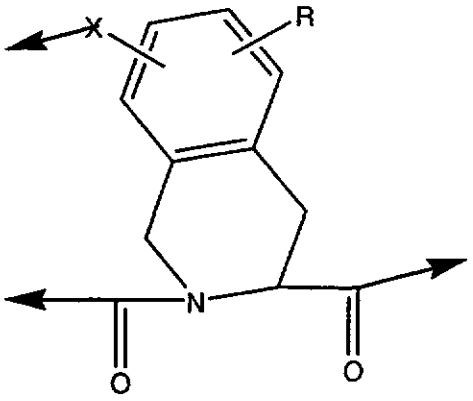
is sometimes the following structures, where the definitions for the various positions are exemplified in the structures of compounds shown later in this section:



,

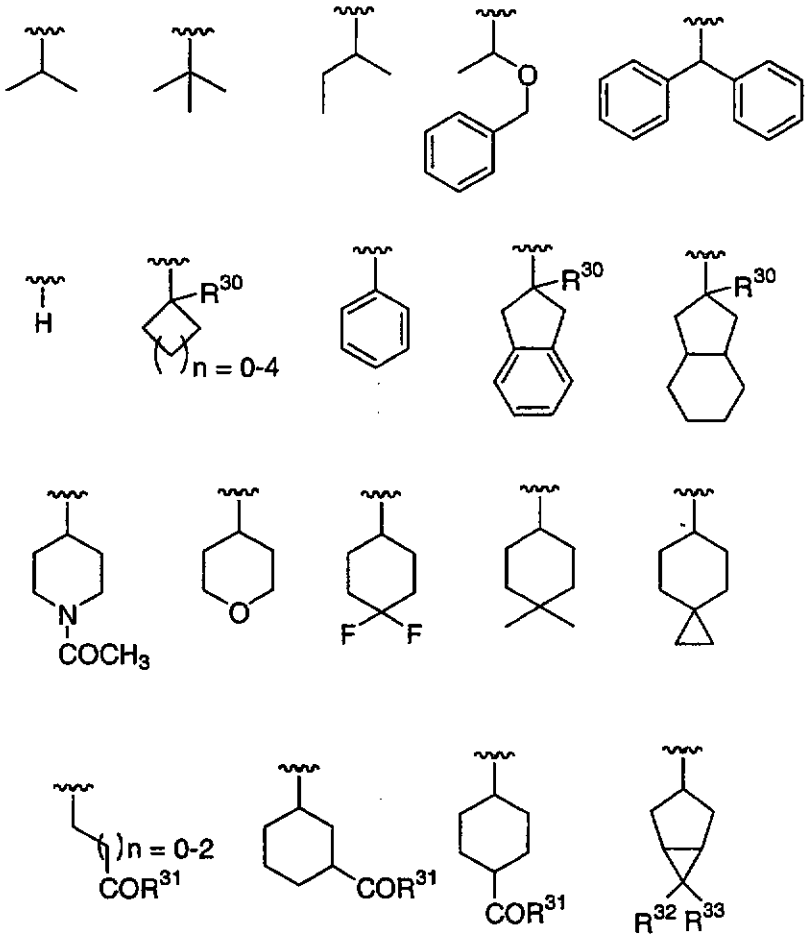


or



In some more preferred compounds, the moieties G and J are independently selected from $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$, and the moiety A-E-L-M-Q is an aromatic ring consisting of two to eight carbon atoms, zero to six hetero atoms with X and J being *ortho*, *para* or *meta* with respect to each other.

In other preferred embodiments, R^3 in formula I is selected from the following structures:

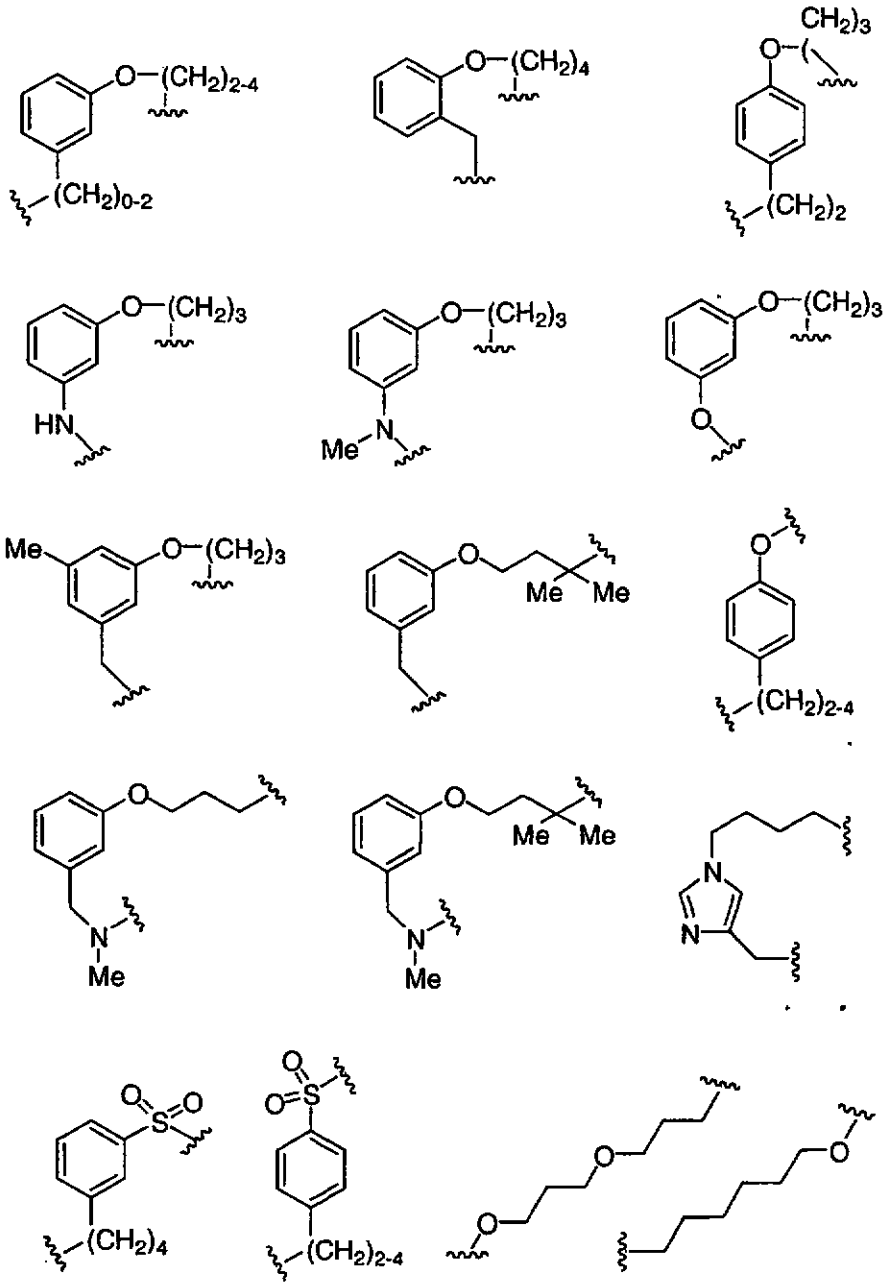


wherein R^{30} = H, CH_3 or other alkyl groups;

R^{31} = OH, O-alkyl, NH_2 or N-alkyl;

R^{32} and R^{33} may be the same or different and are independently selected from H, F, Cl, Br and CH_3;

and the moiety X-Y is selected from the following structures:



Several additional and further refinements of the above-noted various definitions for the compounds represented by Formula I are noted in the **Claims** section of this application. They are also represented by the various compounds listed in the specification and claims. Such refinements, definitions and limitations are to be considered as representing the entire invention of this application.

Representative compounds of the invention which exhibit excellent HCV protease inhibitory activity are listed below along with their activity (ranges of K_i values in nanomolar, nM). The Example numbers refer to the numbers for the various structures in the EXAMPLES section found in the later parts of this application.

Table 1: HCV protease continuous assay results

Example Number	Ki* (nM)
1A	a
1B	b
2	b
3	b
4A	a
4B	b
5	b
6	b
7A	a
7B	b
8	a
9	b
10A	a
10B	b
11	a
12A	a
12B	b
13A	a
13B	b
14	b
15	b
16	b
17	b
18	b
19	b

20A	a
20B	b
21	a
22	b
23	a
24	a
25	a
26A	a
26B	a
27A	a
27B	b
28A	a
28B	b
29A	a
29B	b
30	b
31	b
37A	a
37B	a
38A	a
38B	a
39	a
40	a
41	a
42	a
43	b
44A	a
44B	a
46	a
53A	a
53B	a
56A	a
56B	a
57A	a
57B	b
58	a
59A	b
59B	b
60	a
61	a
62	a
63	a
64	a

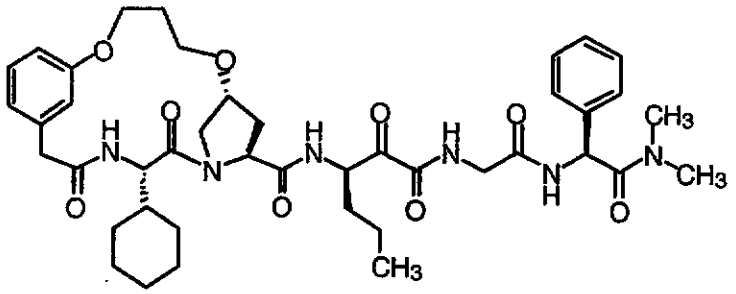
65	b
66A	a
66B	b
67A	a
67B	b
68	b
69A	a
69B	b
70A	a
70B	b
71	b
72	b
73	a
74A	a
74B	b
75A	a
75B	b
76	b
77	a
78	a
79	a
80	b
81	a
82	a
83	b
84	a
85	a
86	a
87	a
88	a
89	a
90	a
91	a
92	b
93	a
94	a
95	b
96	a
97	a
98	b
99	a
100	a
101	b

102	a
103	a
104	a
105	a
106	a
107	a
108	a
109	a
110	b
111	b

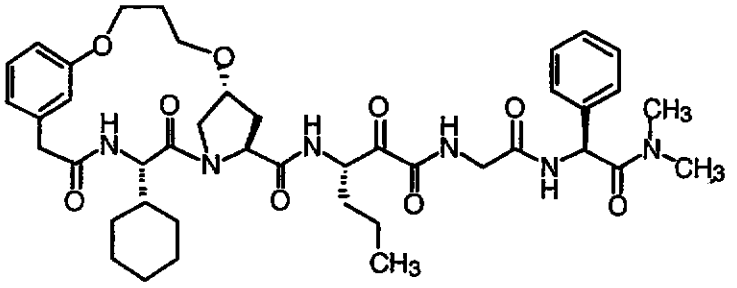
HCV continuous assay Ki* range:

Category b = 1-100 nM; Category a = 101 nM-100 μM

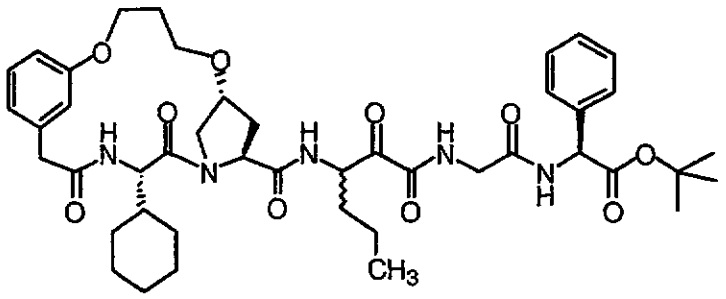
Some of the inventive compounds and the methods of synthesizing the various types of the inventive compounds are listed below, then schematically described, followed by the illustrative Examples.



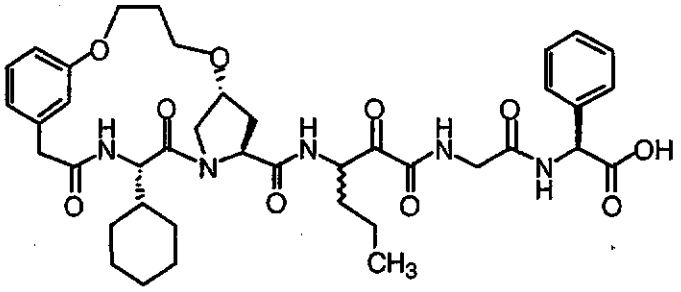
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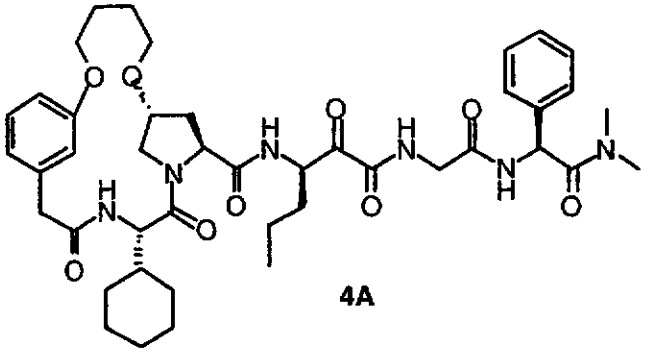
1B



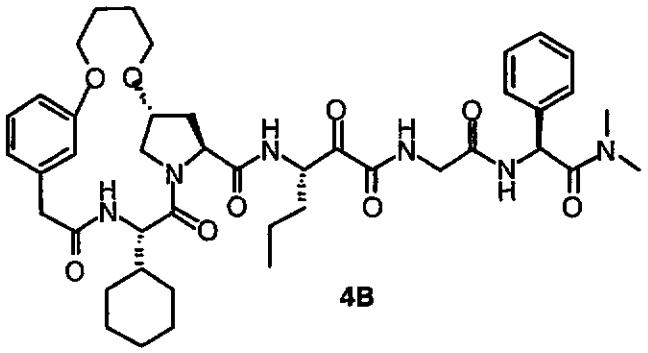
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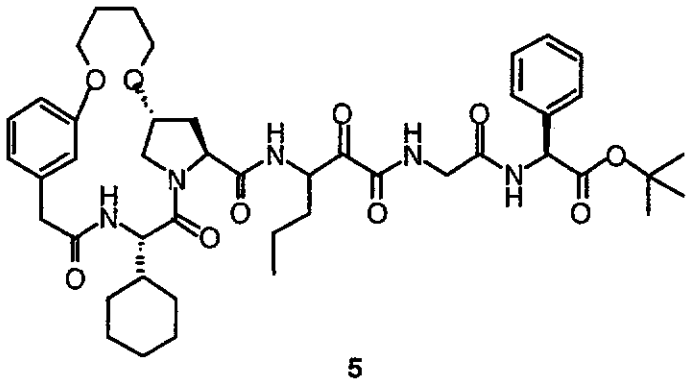


4A

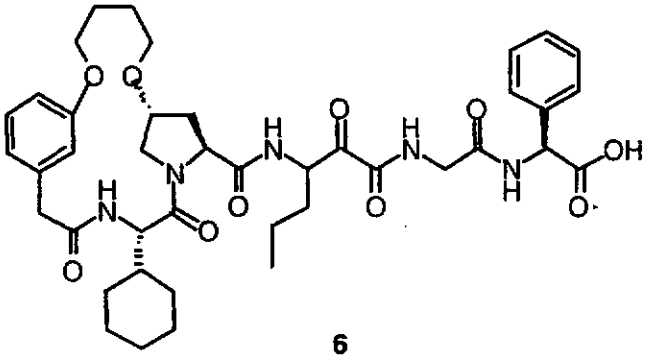


4B

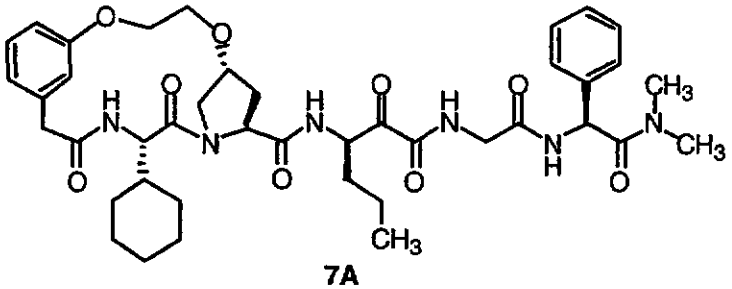
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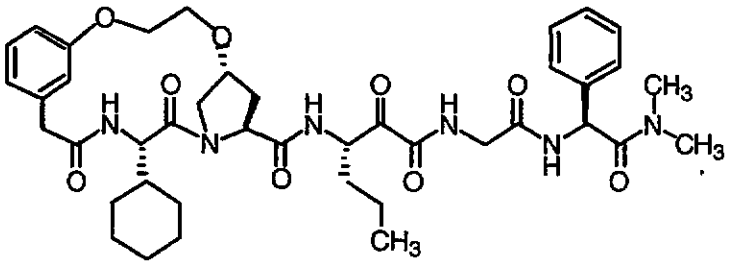
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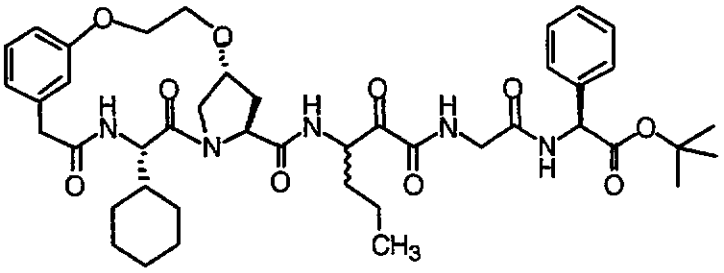


7A

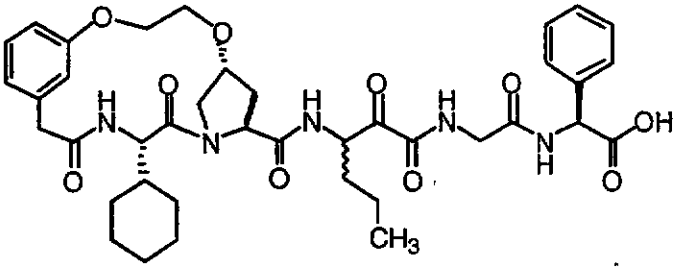


7B

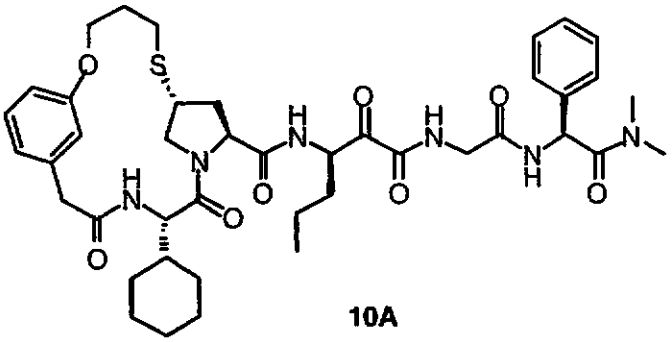
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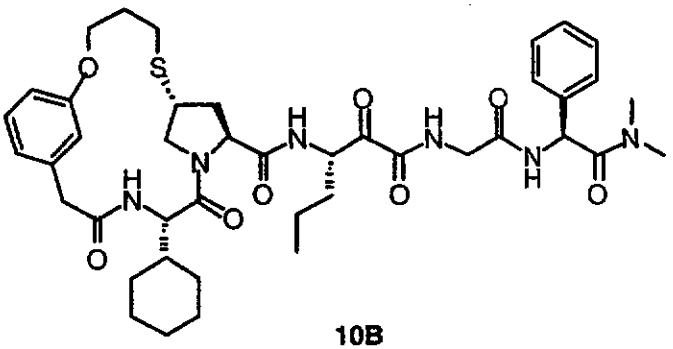
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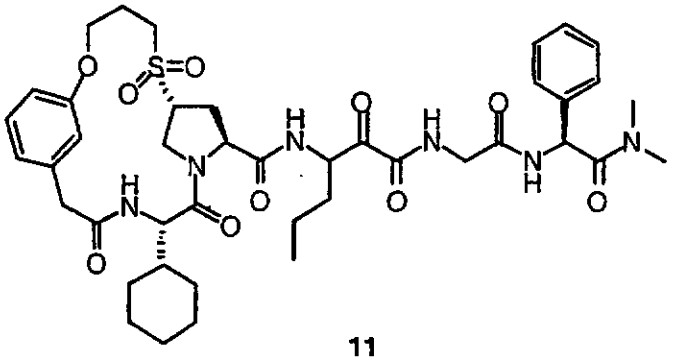
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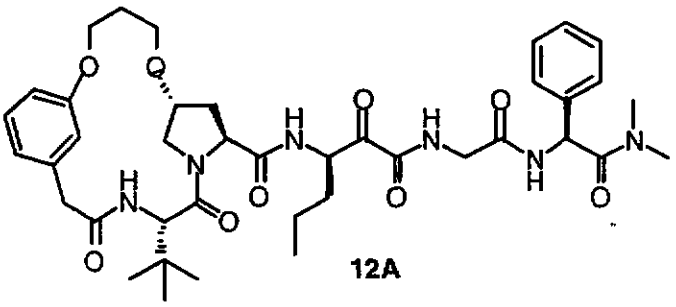
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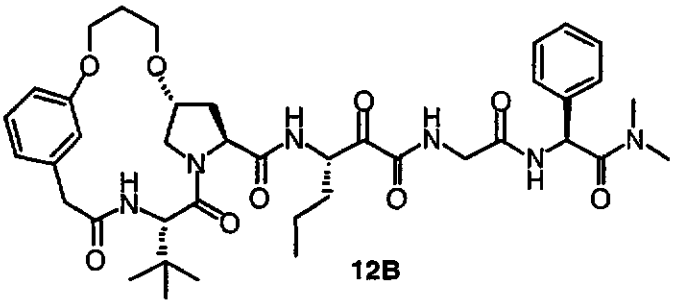
10B



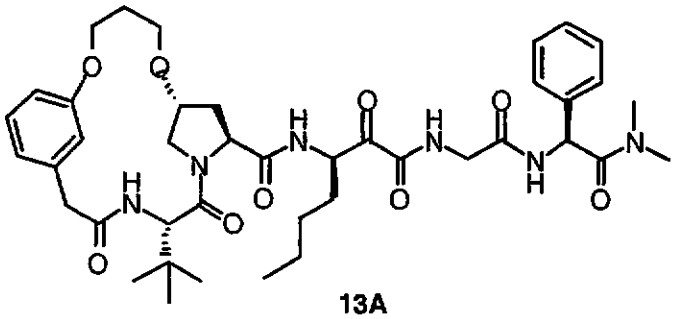
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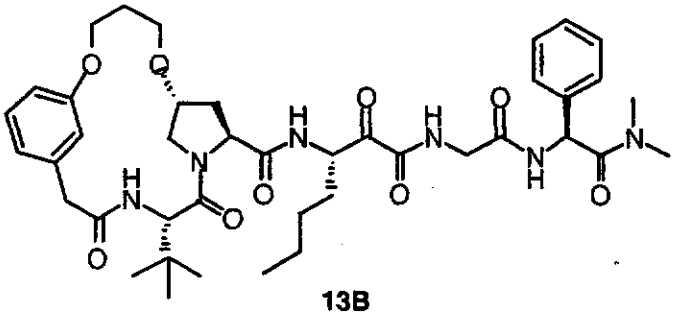
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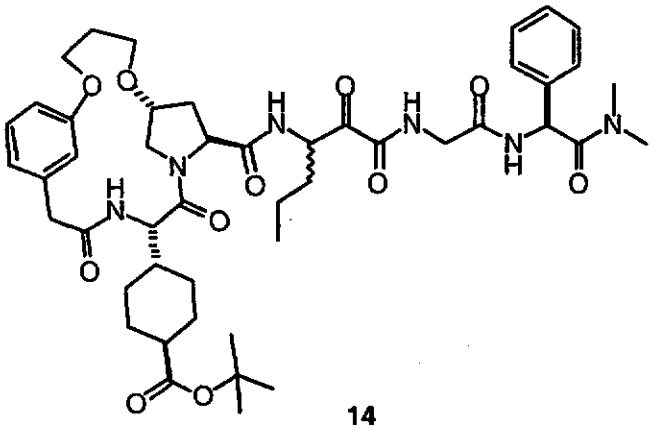
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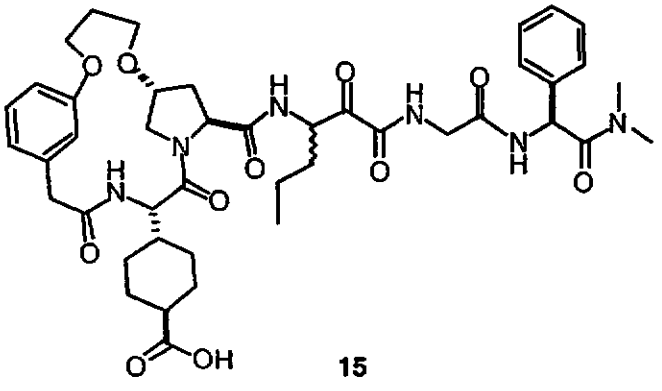
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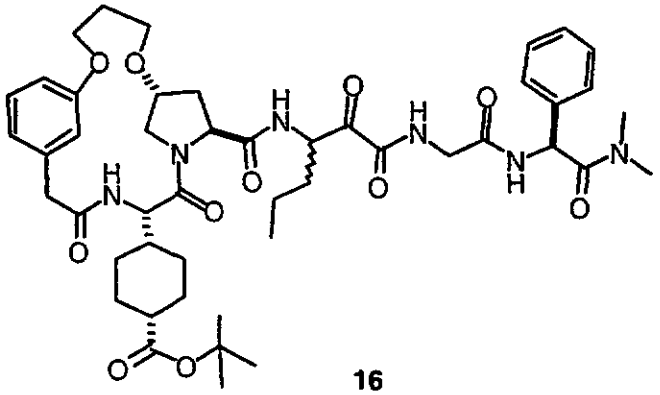
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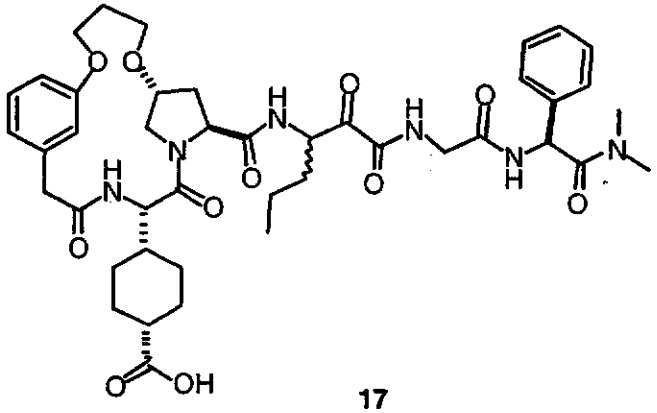
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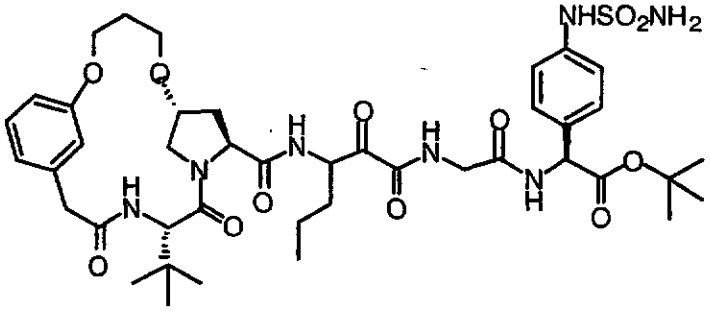
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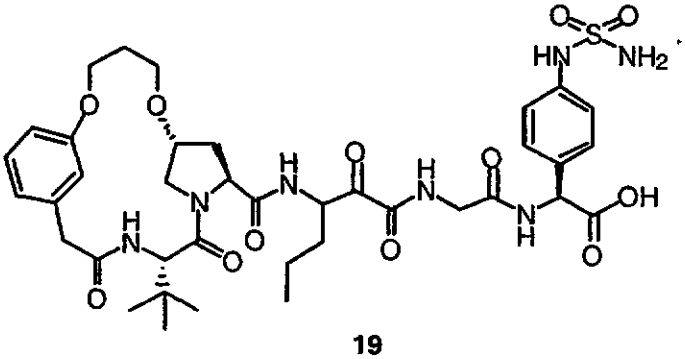
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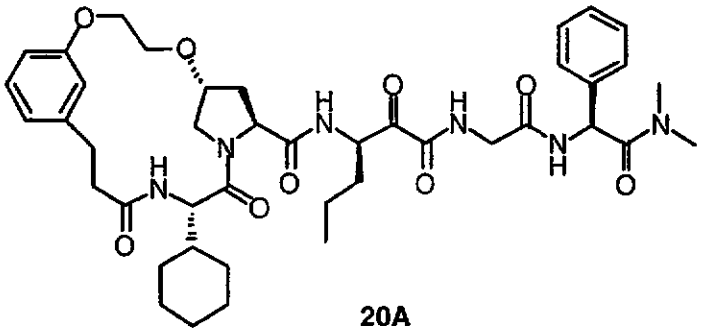
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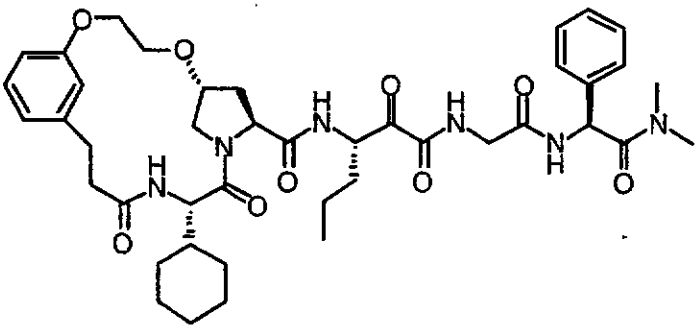
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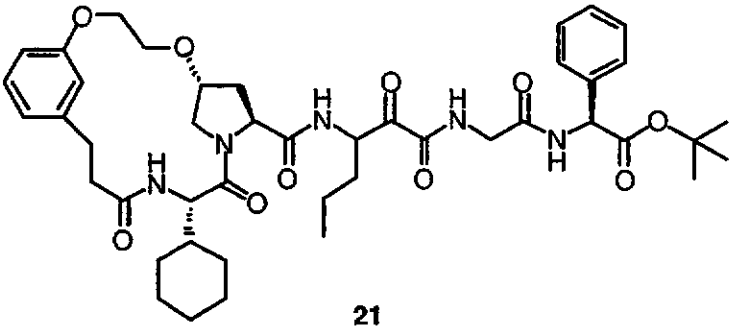
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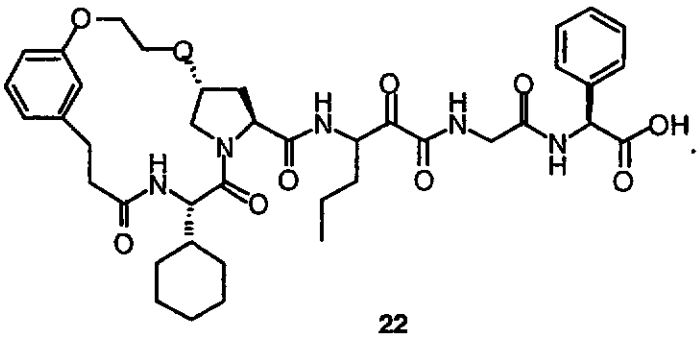
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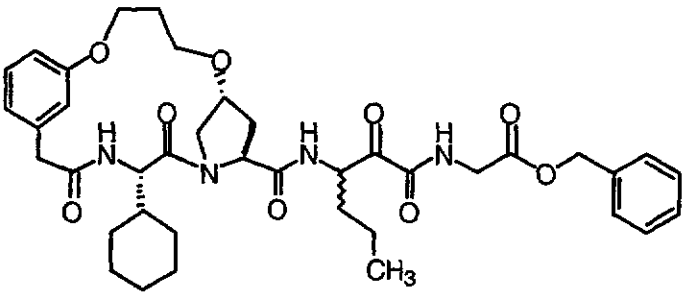
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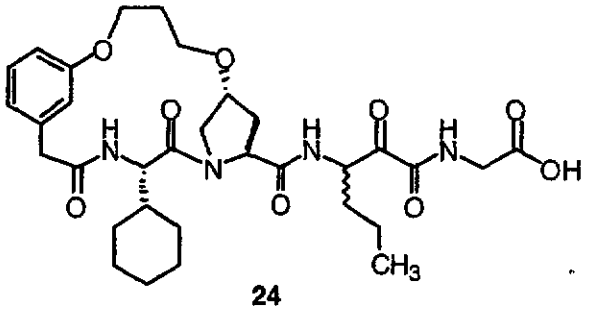
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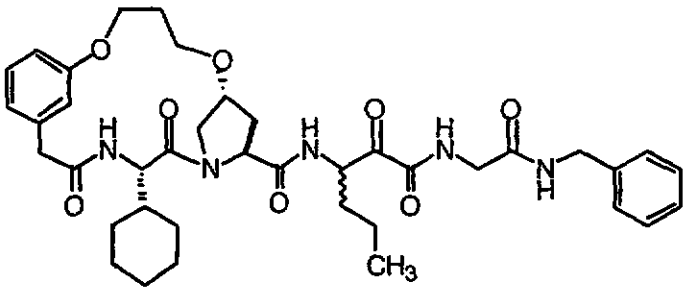
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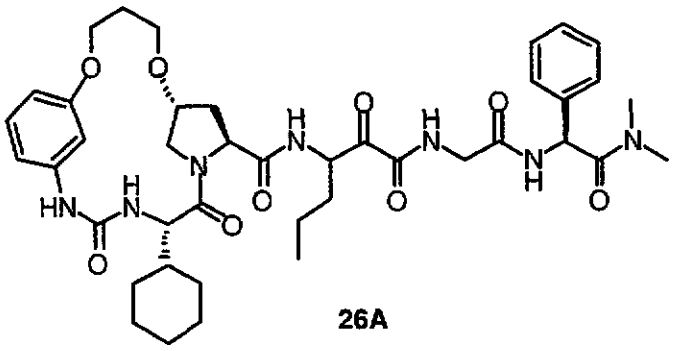


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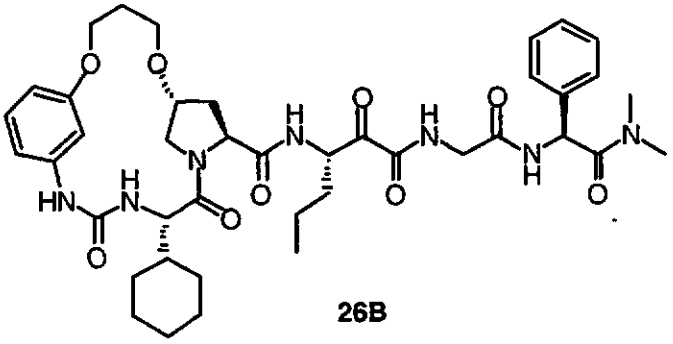


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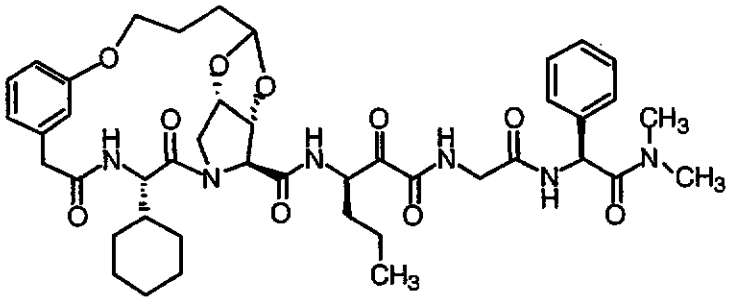
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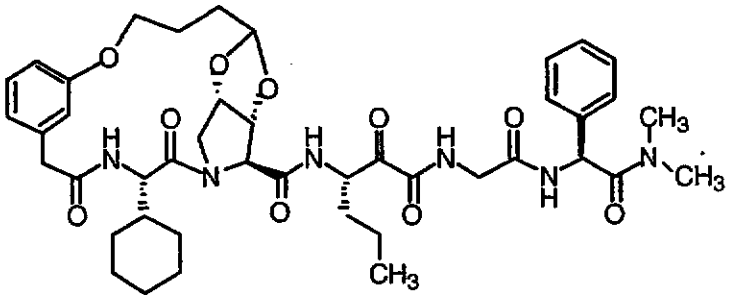
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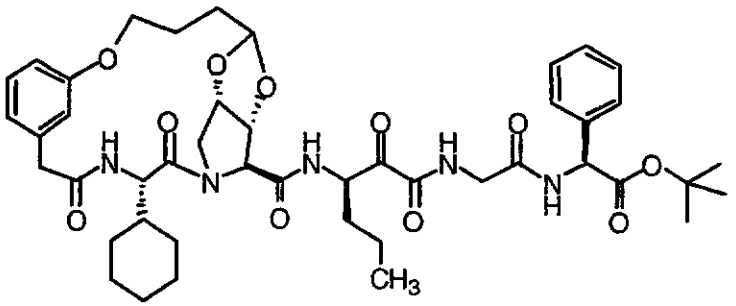
26B



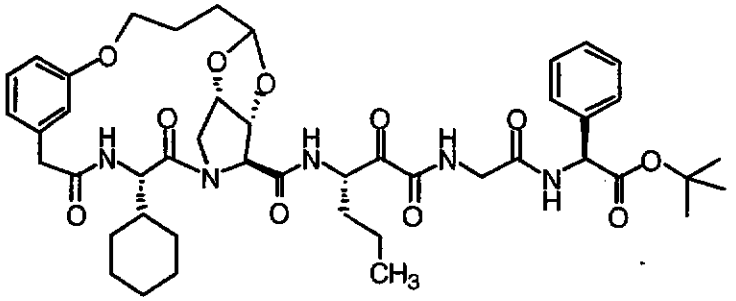
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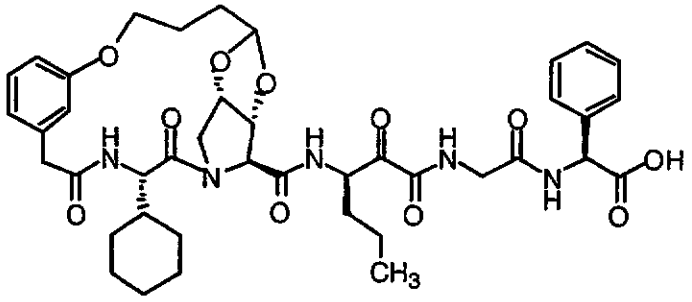
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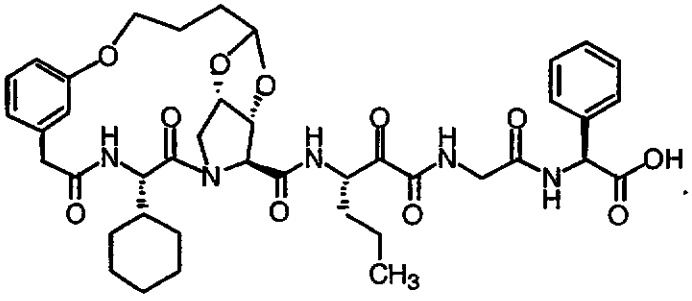
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28B

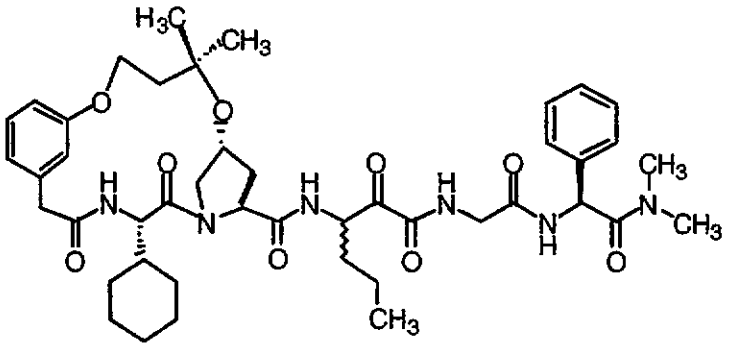


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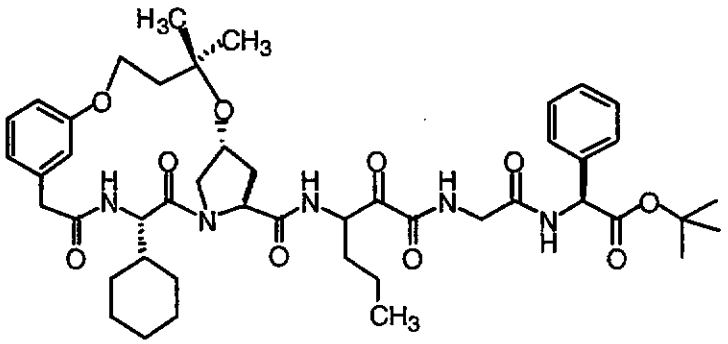


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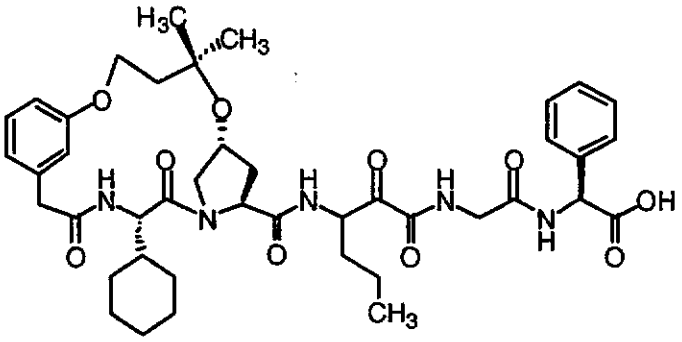
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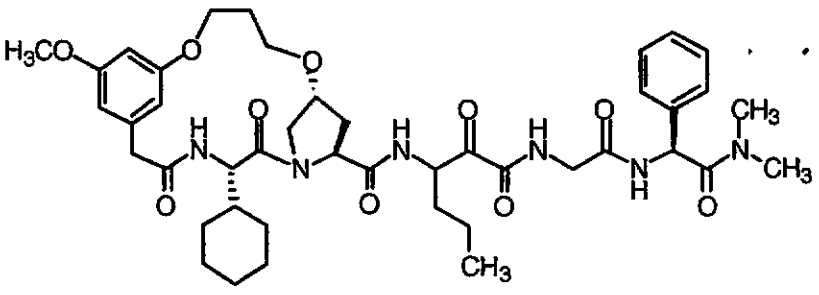
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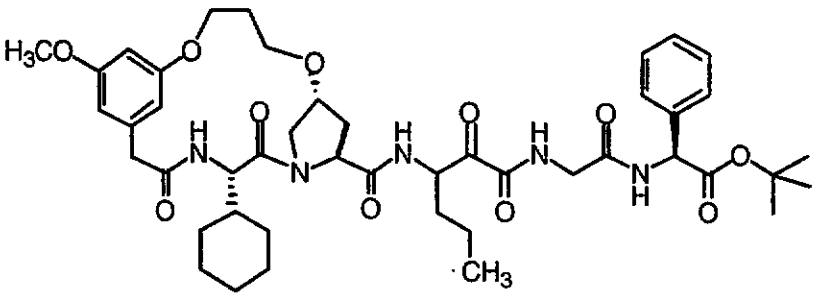
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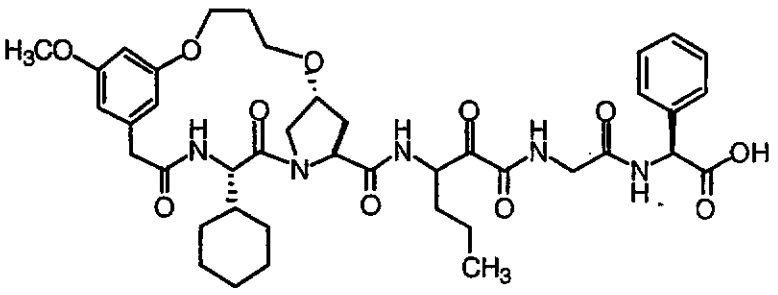
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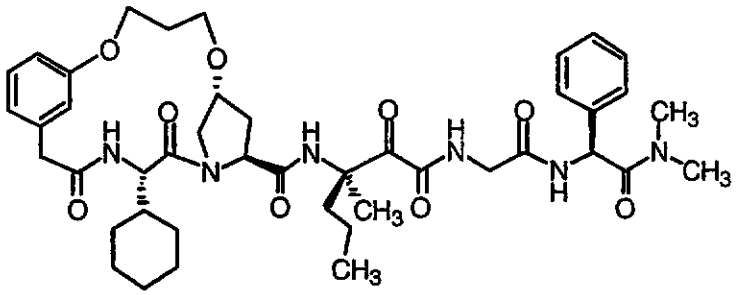
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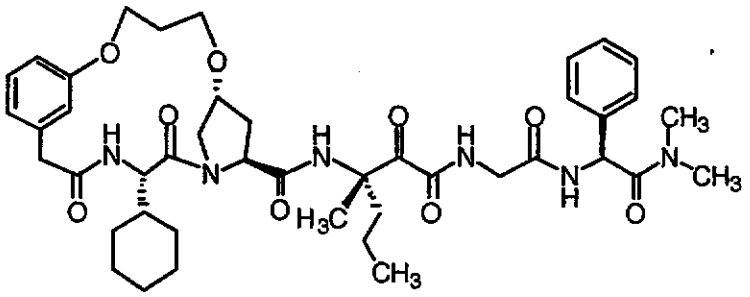
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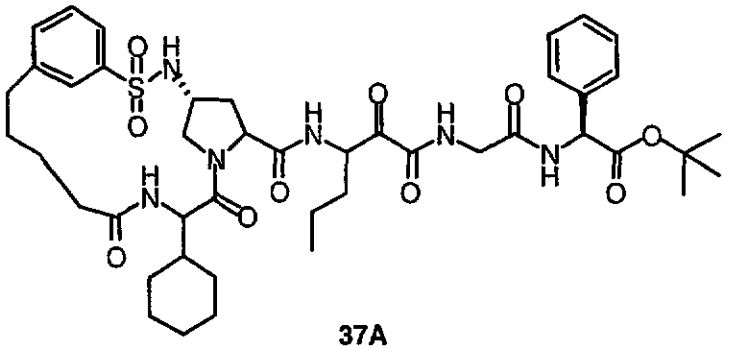
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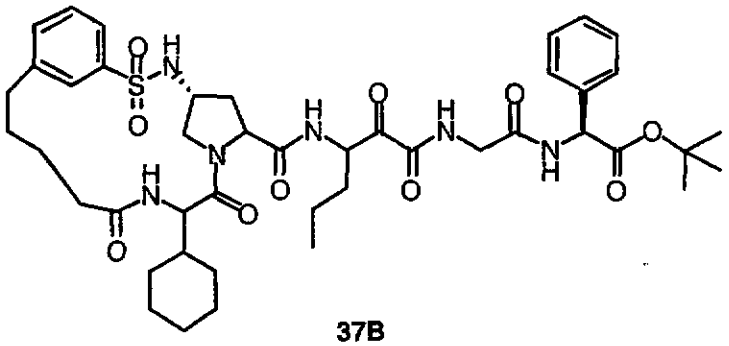
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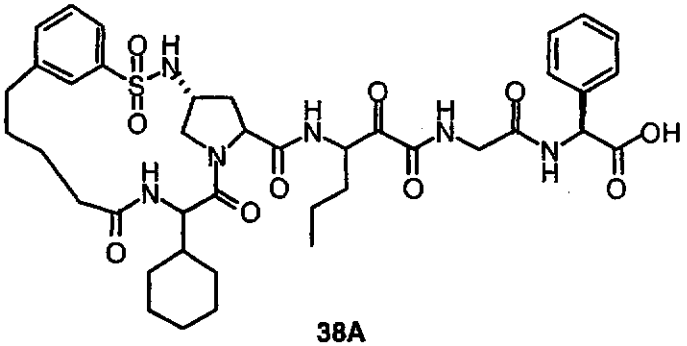
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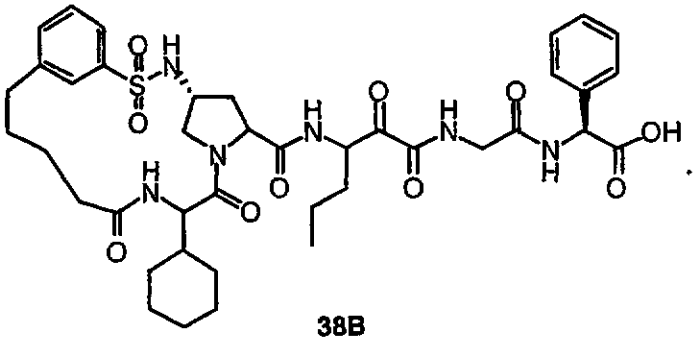
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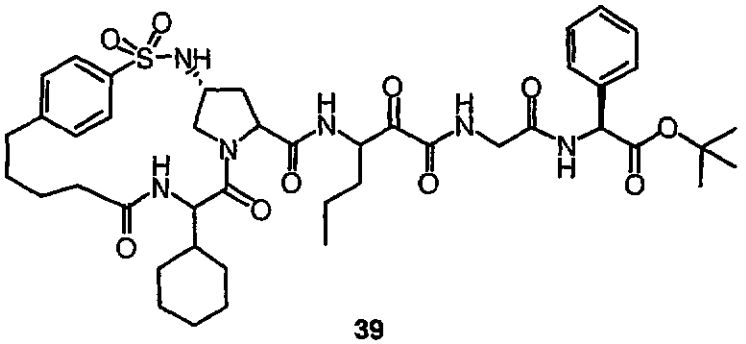
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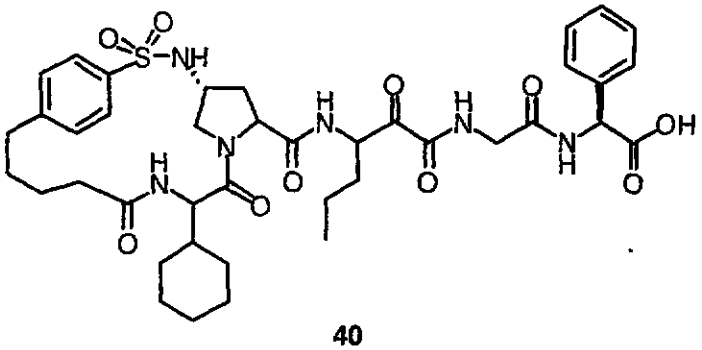
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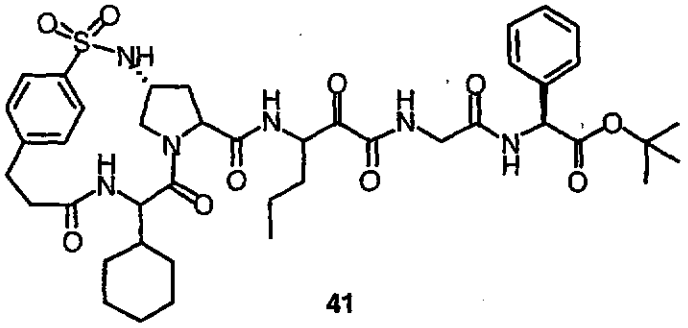
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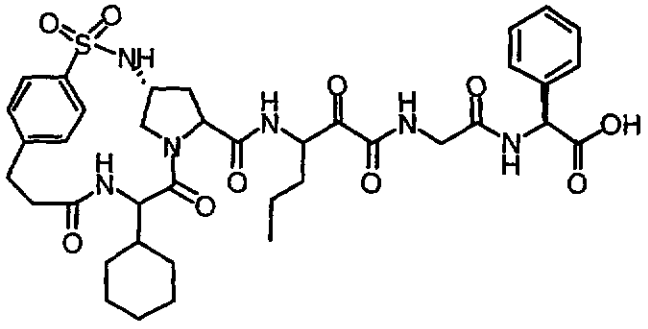
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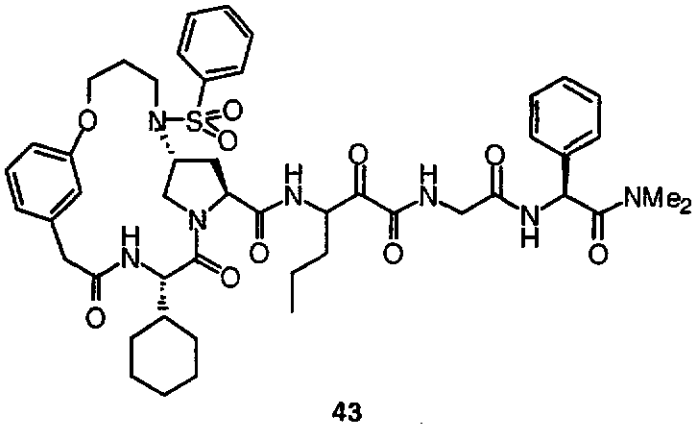
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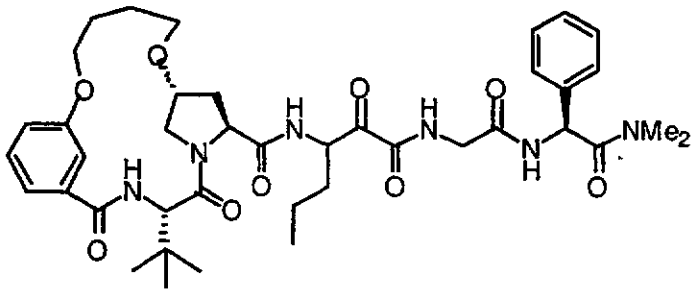
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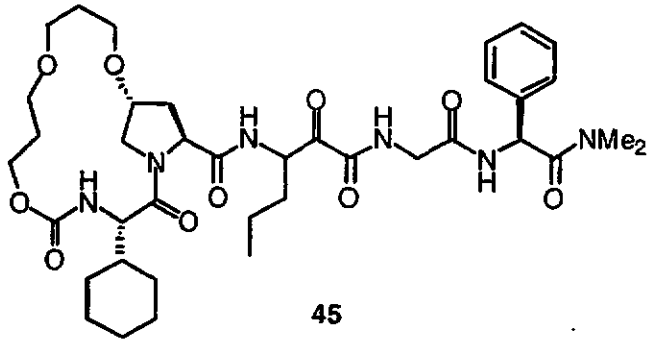
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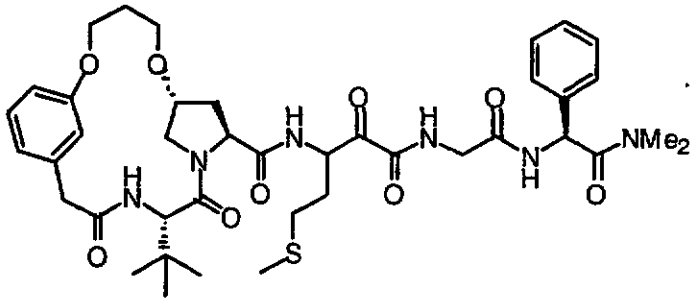
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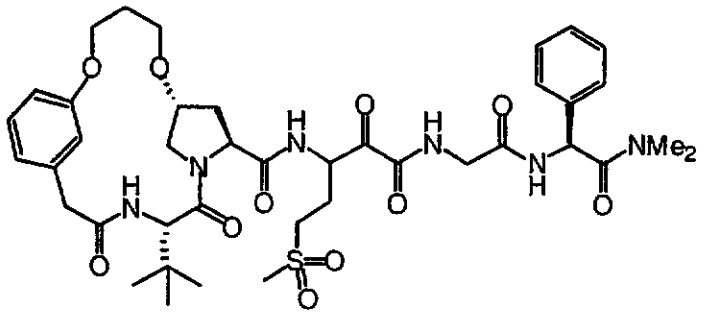
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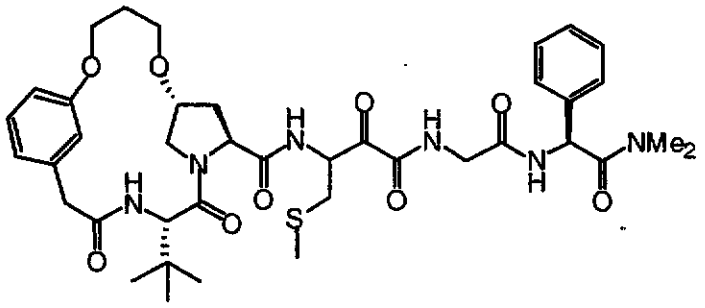
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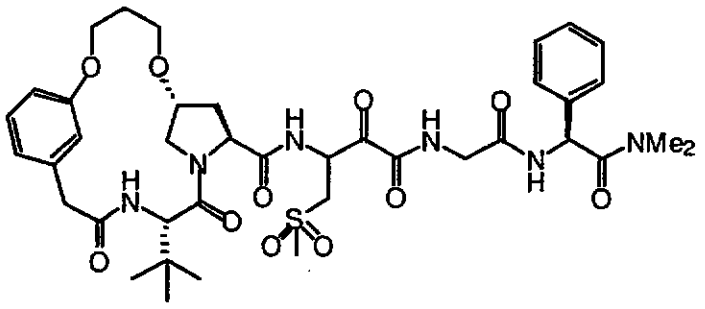
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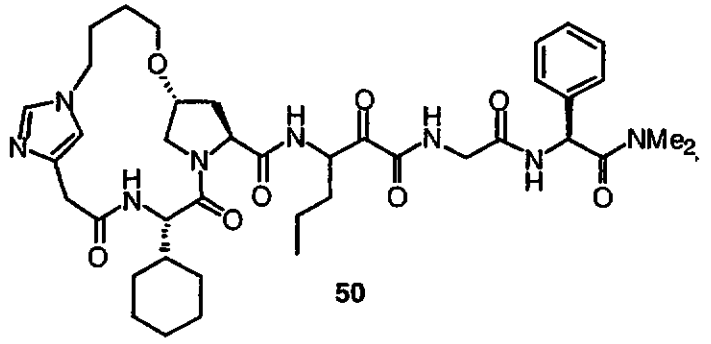
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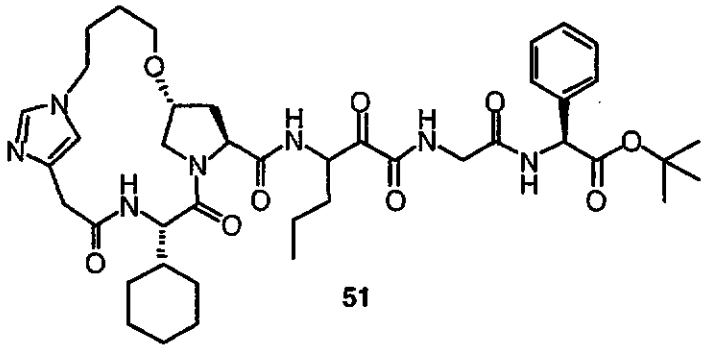
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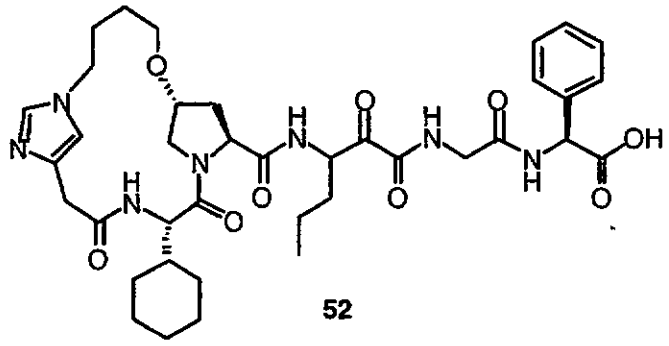
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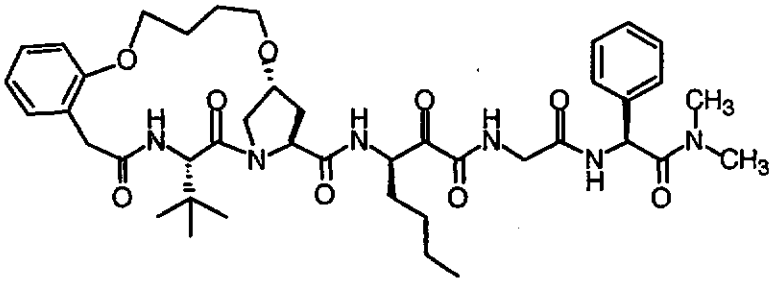


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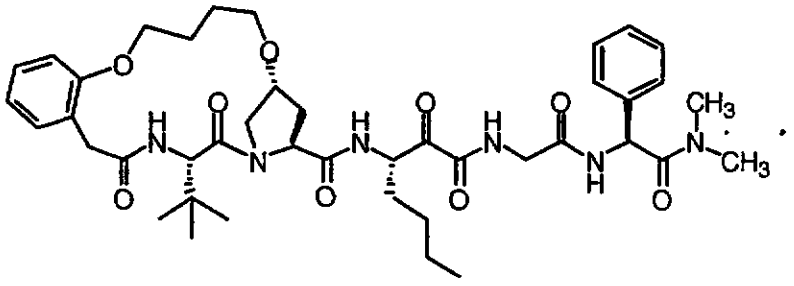


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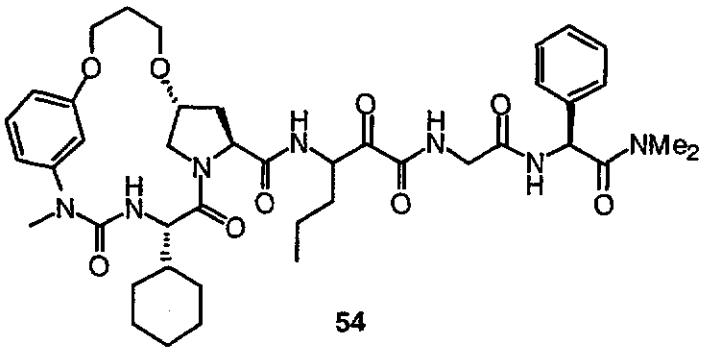
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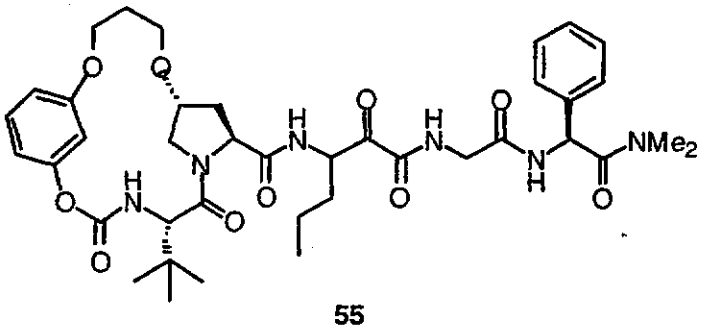
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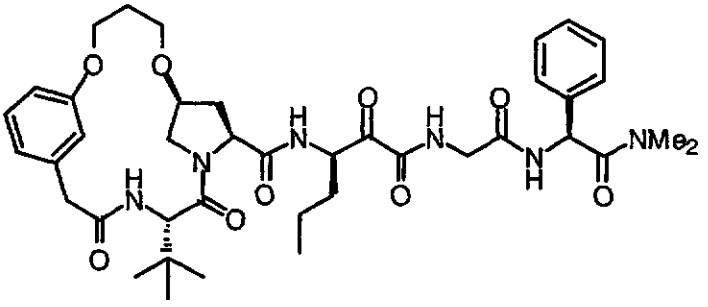
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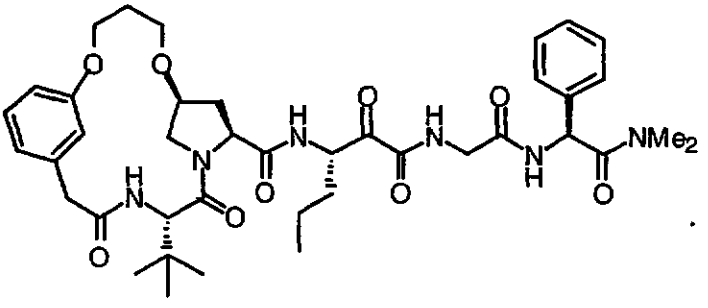
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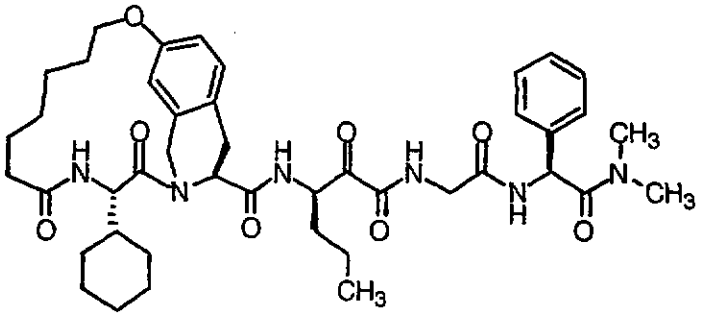


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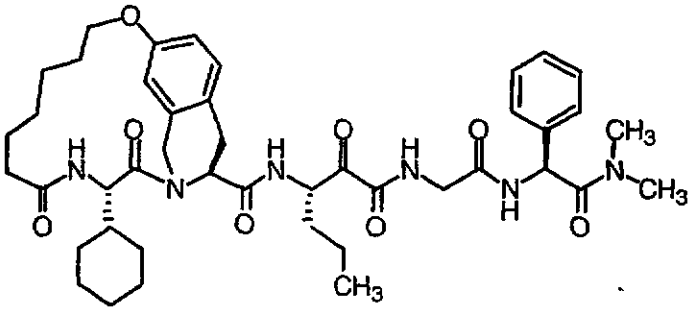


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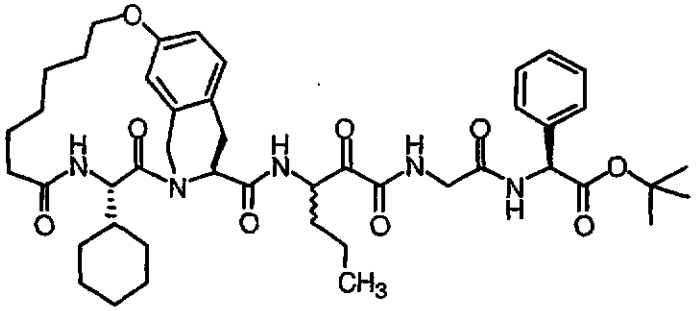
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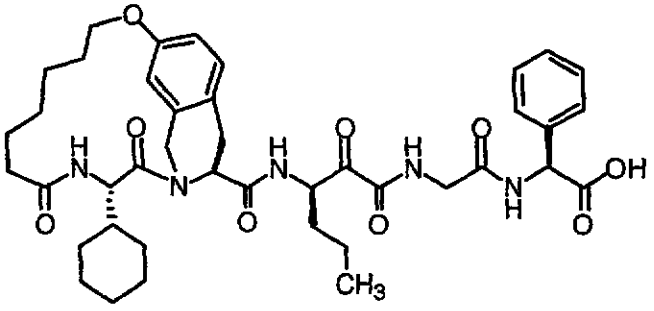


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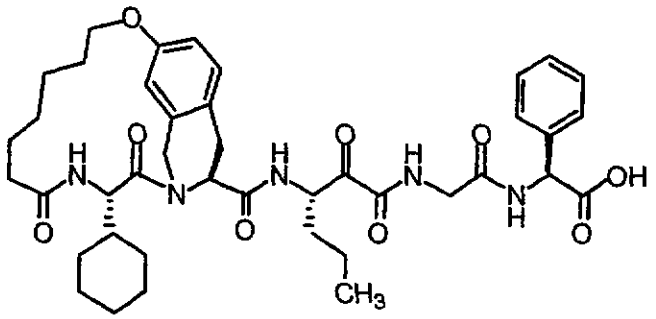
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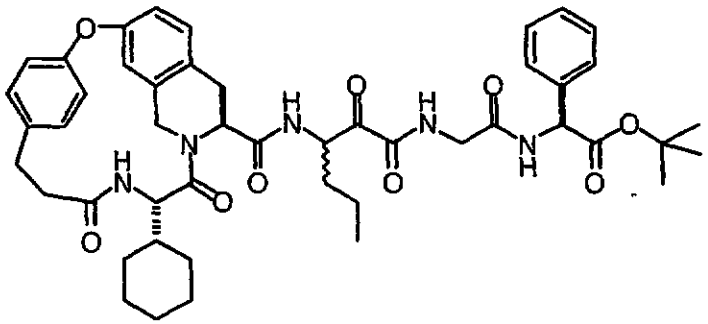


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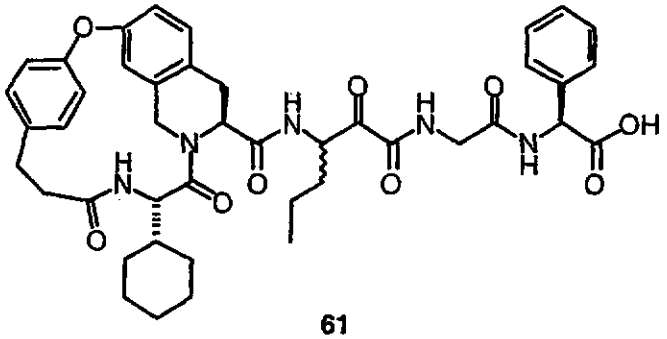


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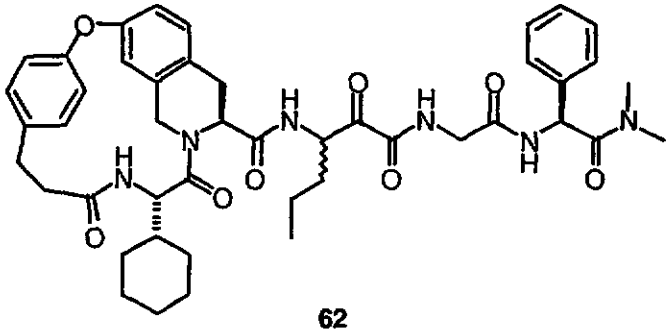


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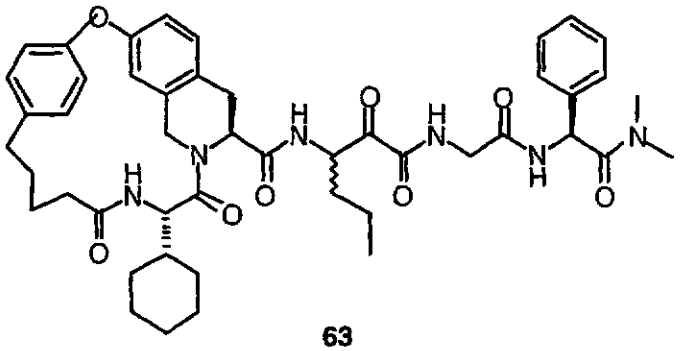


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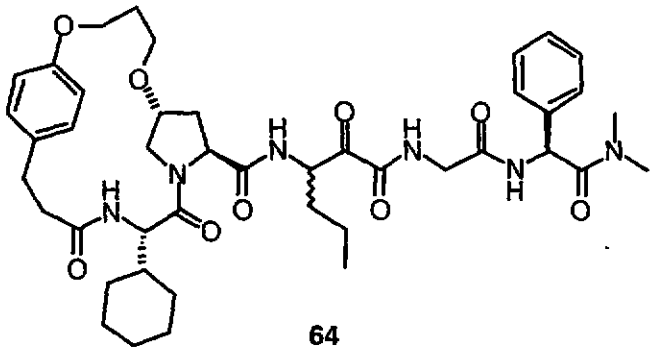


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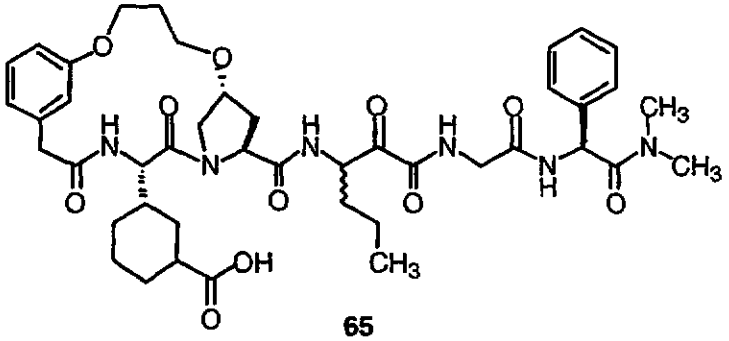
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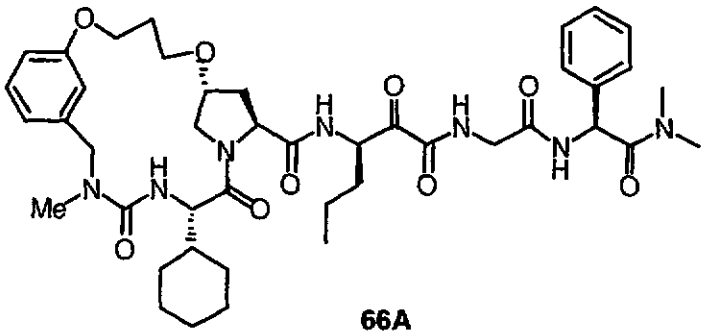


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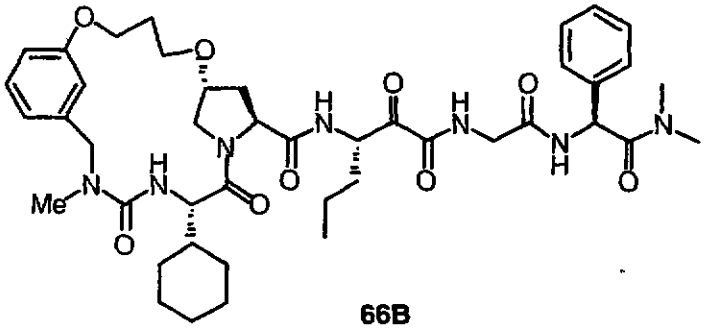


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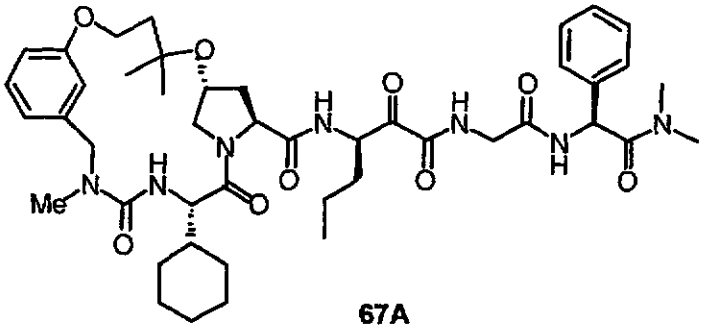
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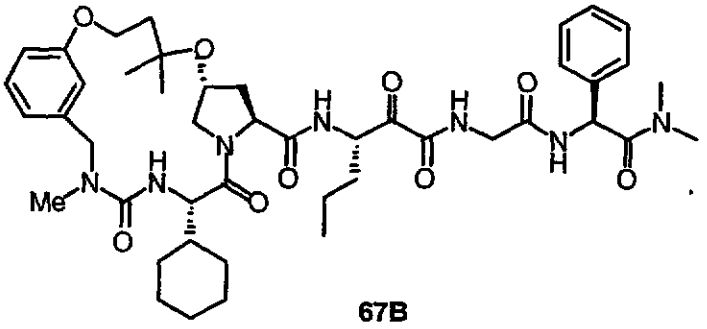
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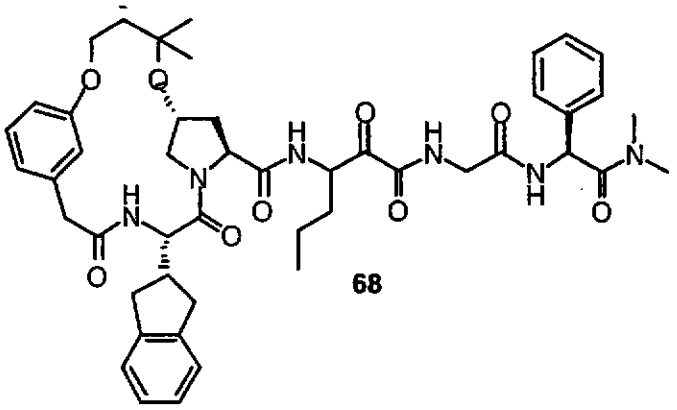
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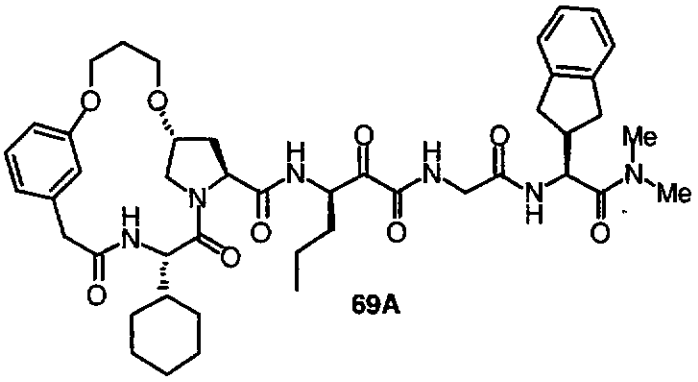
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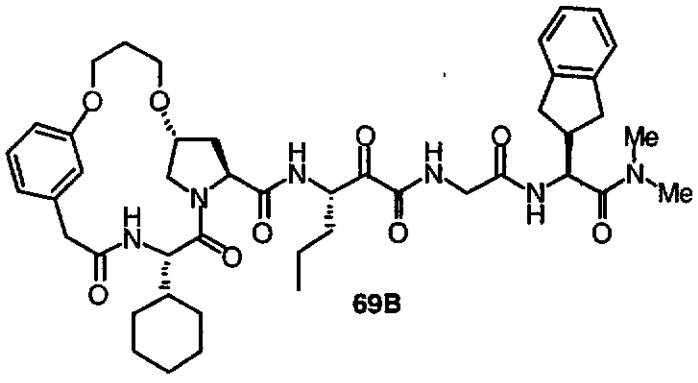
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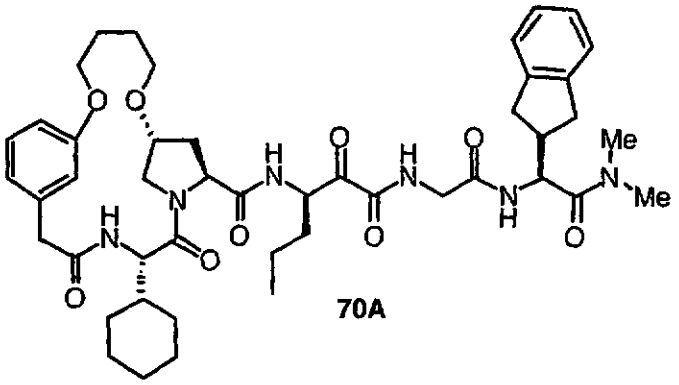
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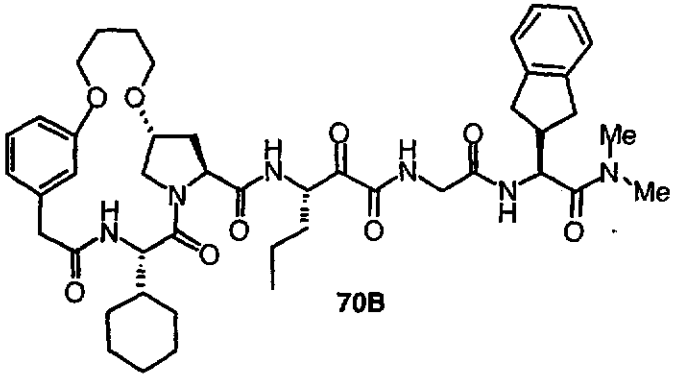
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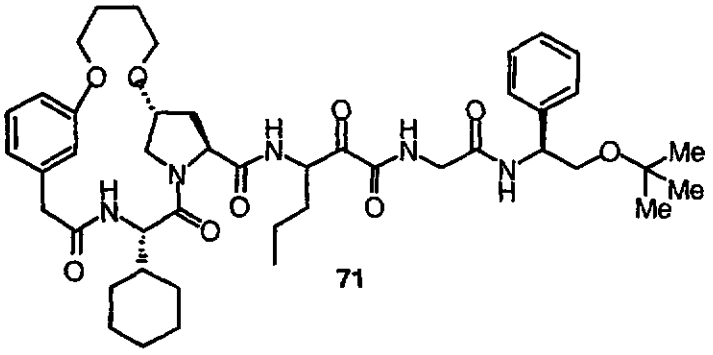
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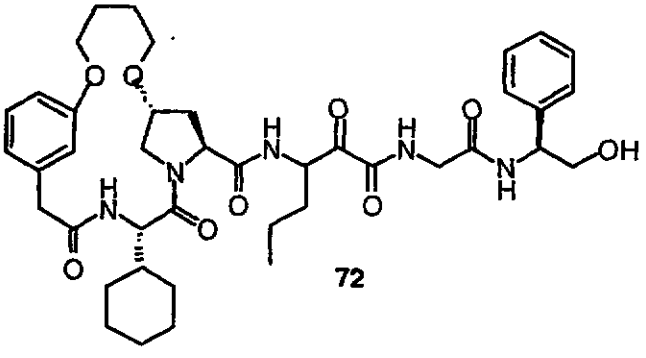
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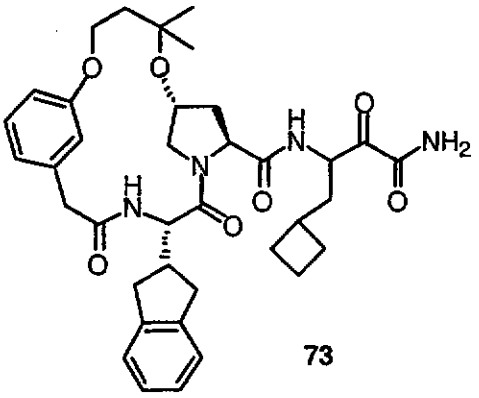


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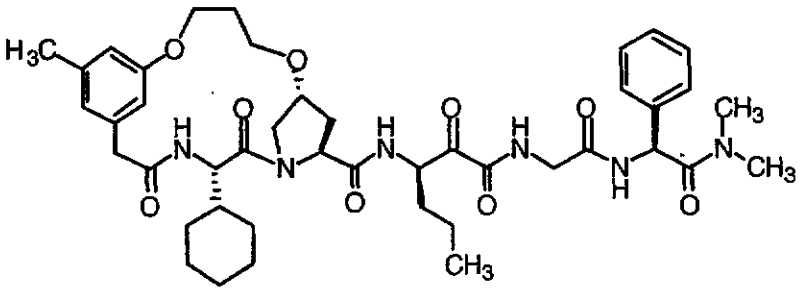


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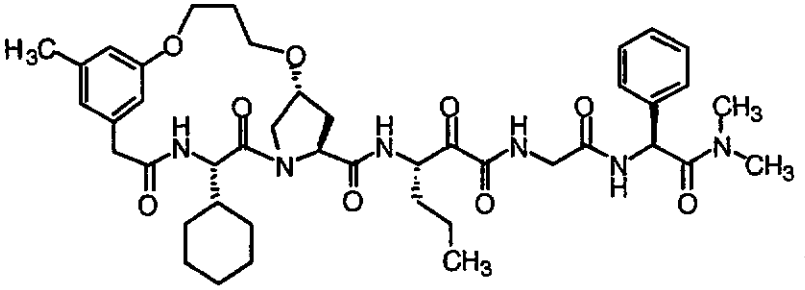
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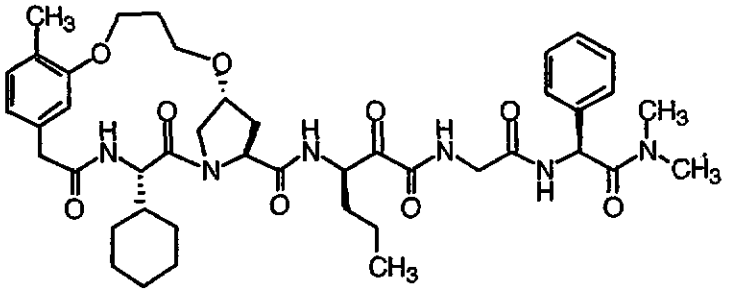
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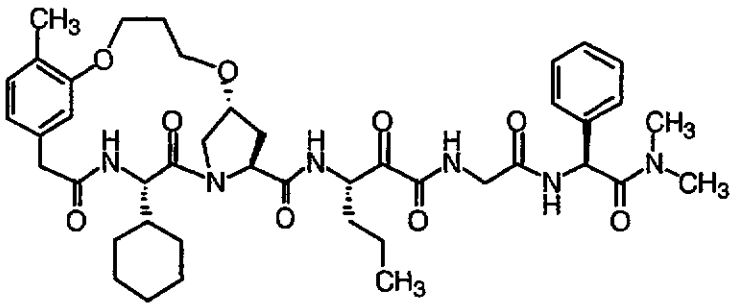


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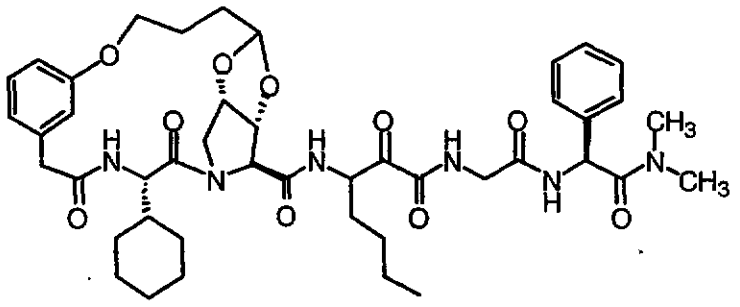


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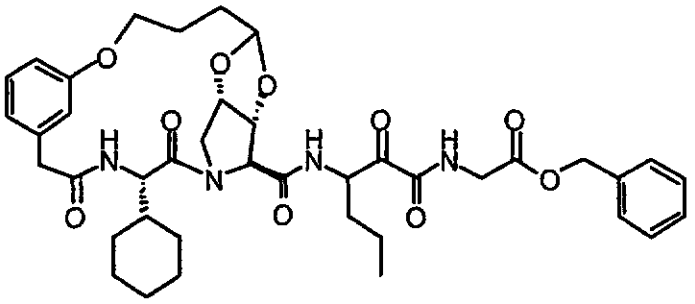
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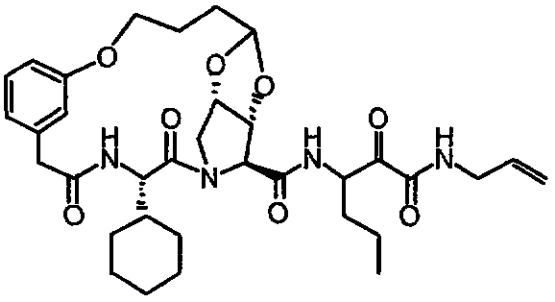
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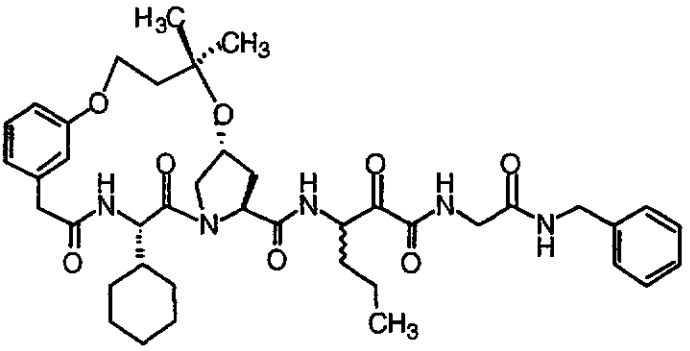
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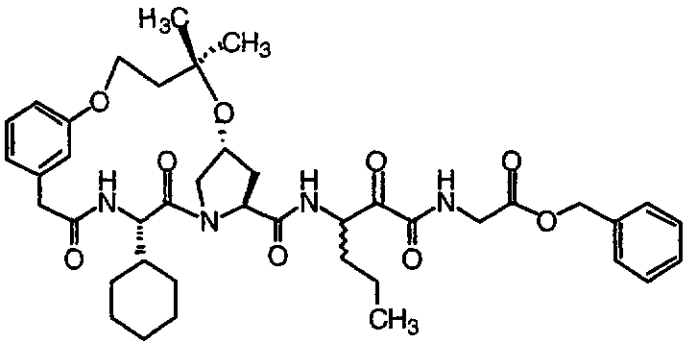
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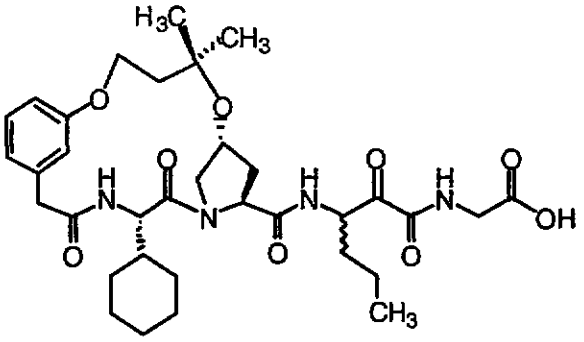
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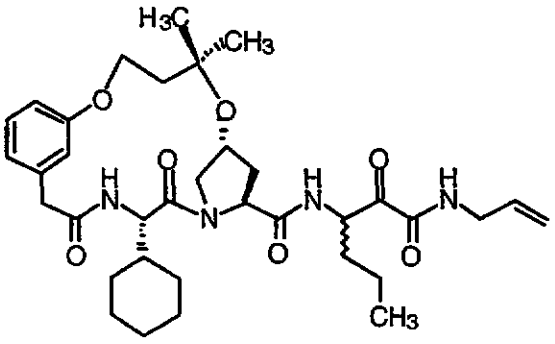
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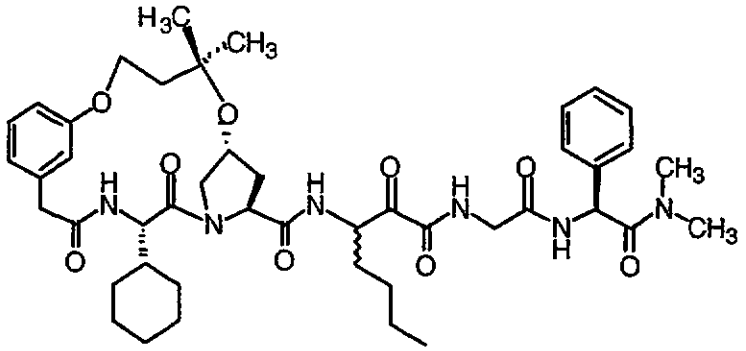
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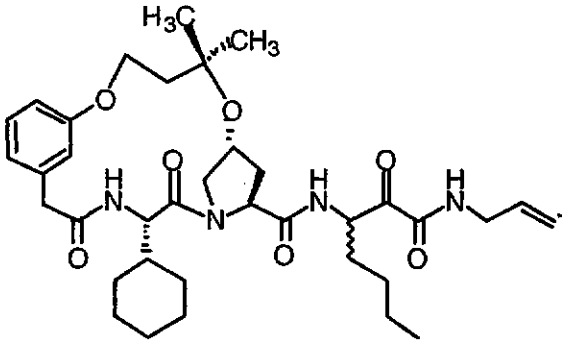
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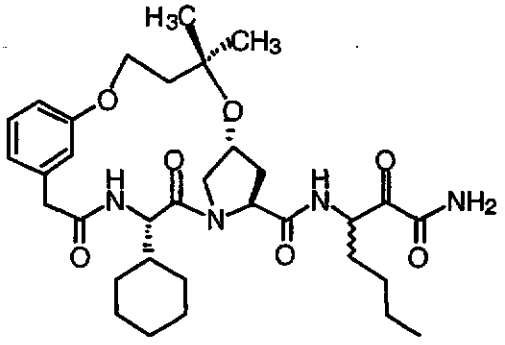
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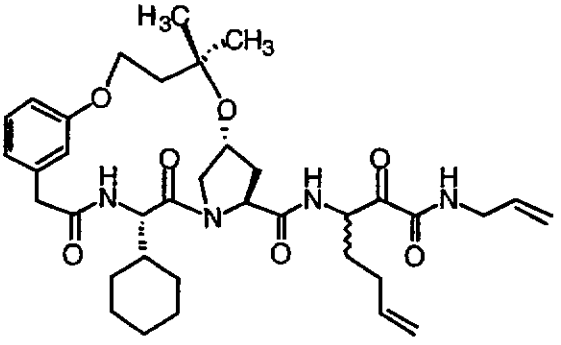
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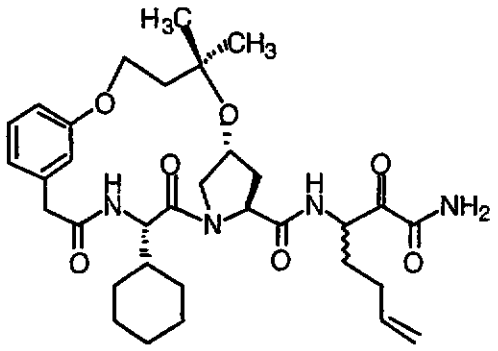
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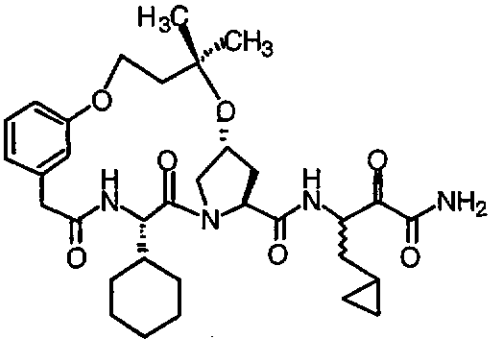
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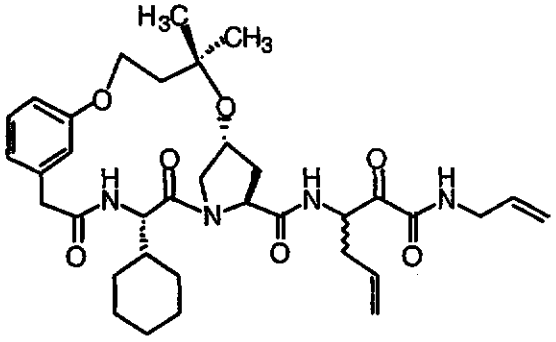
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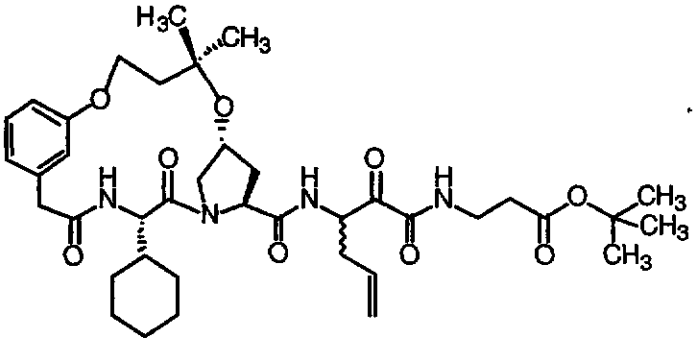
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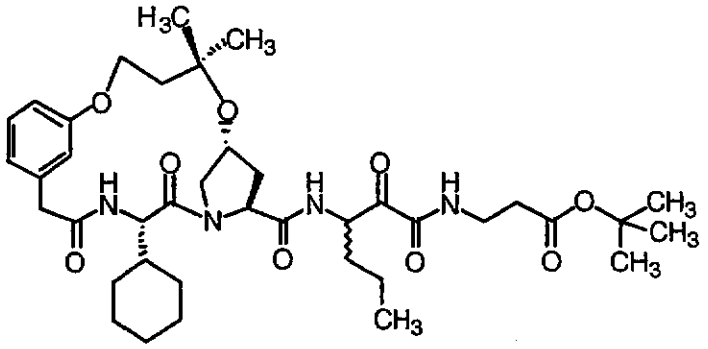


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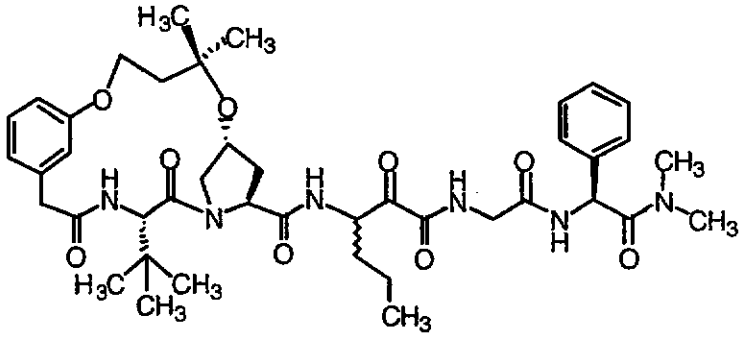


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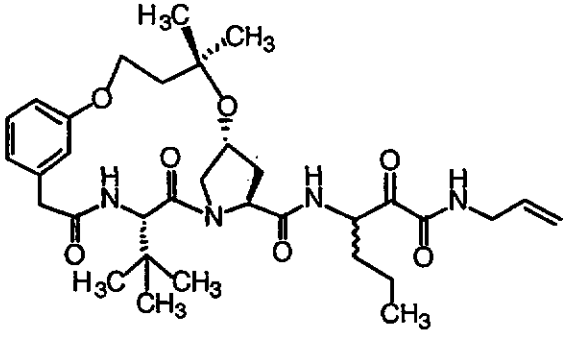
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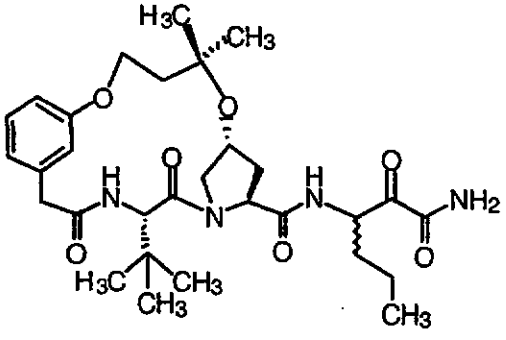
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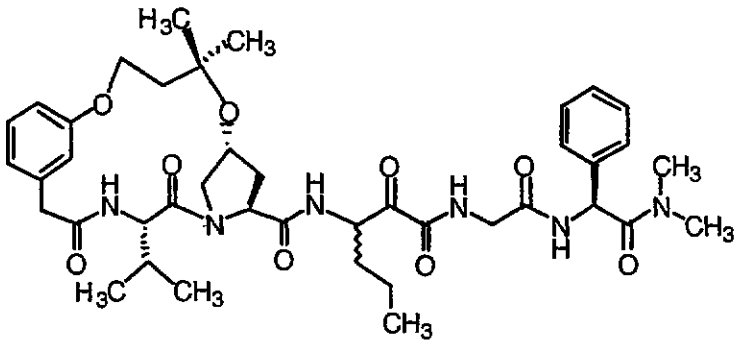
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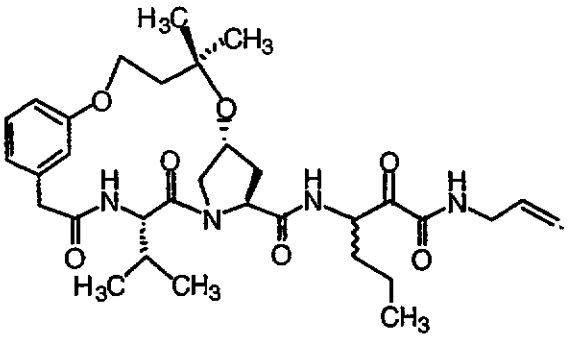
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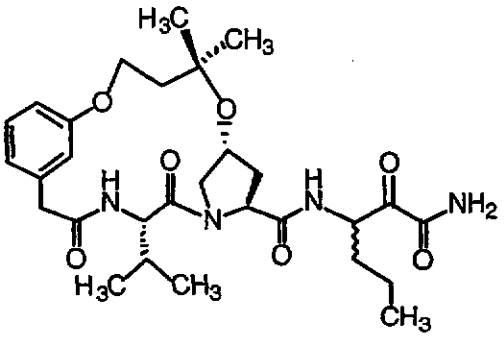
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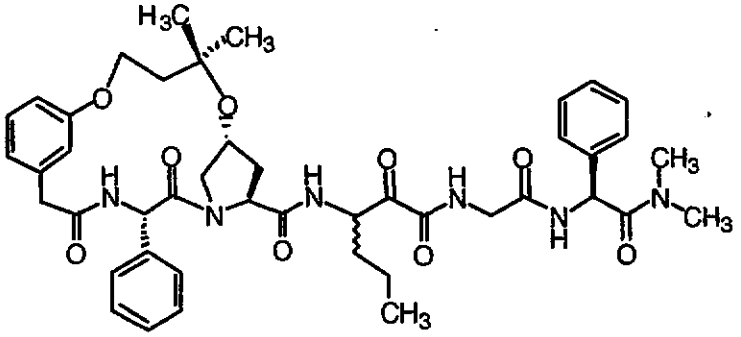
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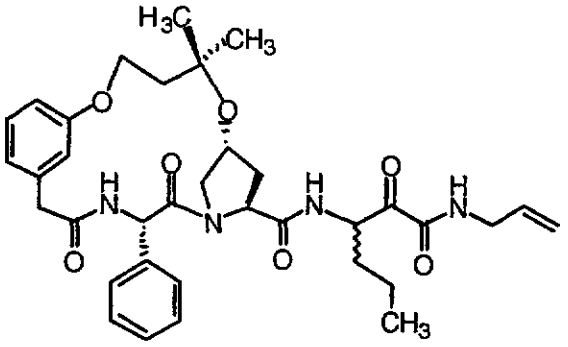
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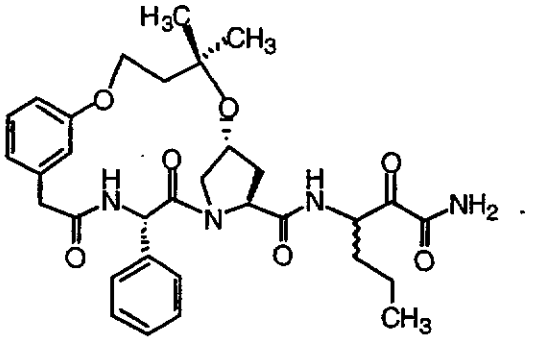
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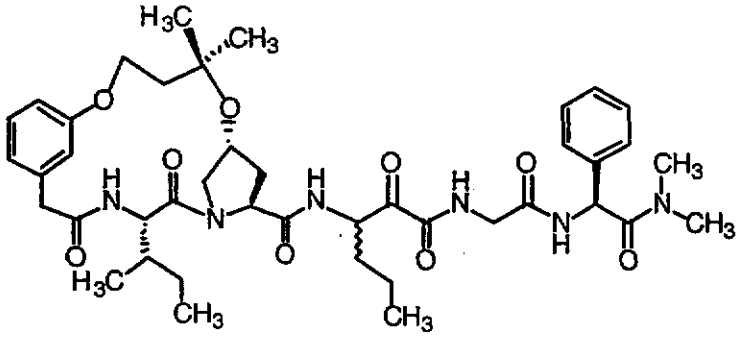
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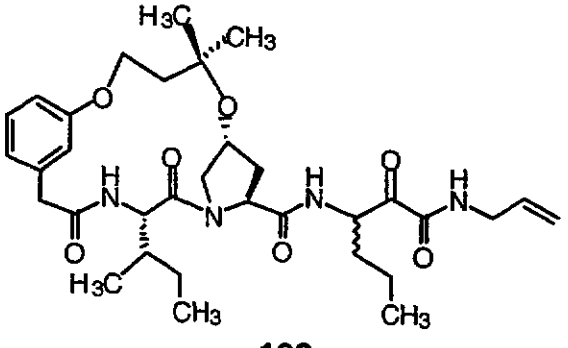
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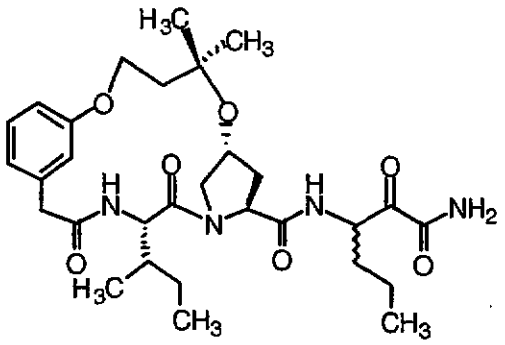
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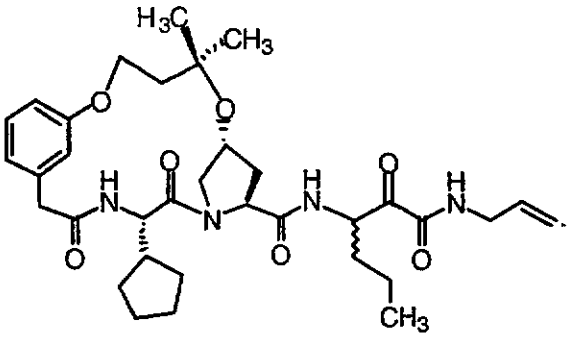
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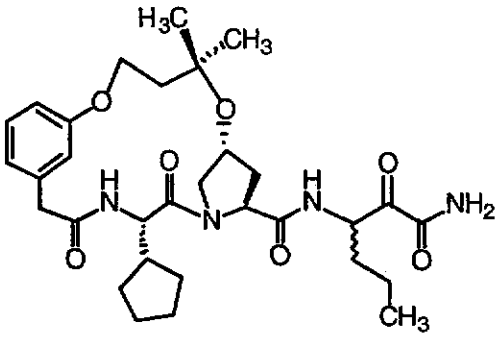
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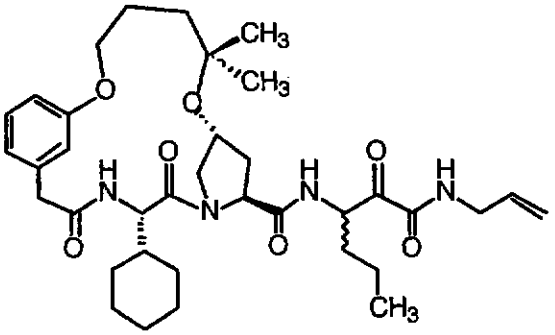
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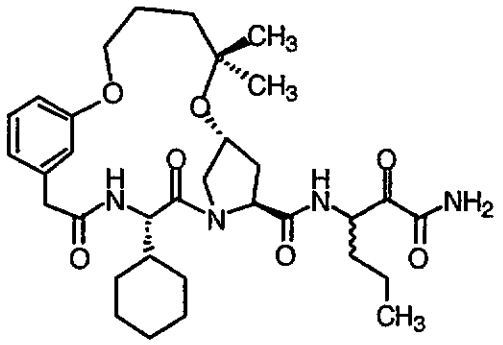
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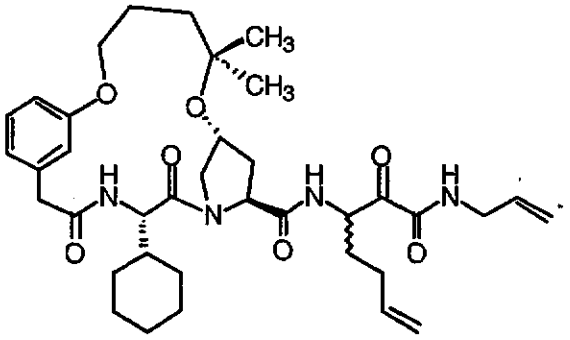
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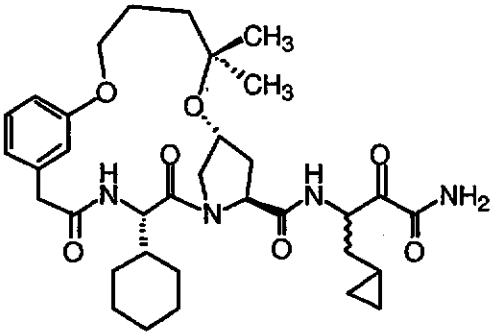
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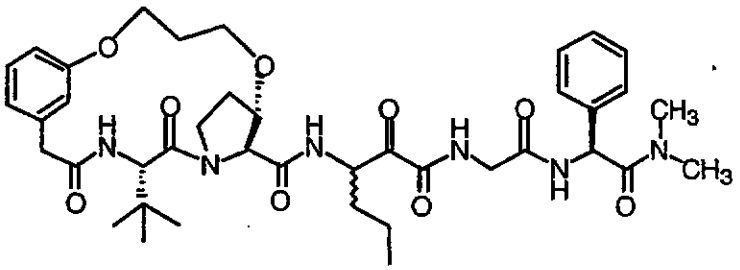
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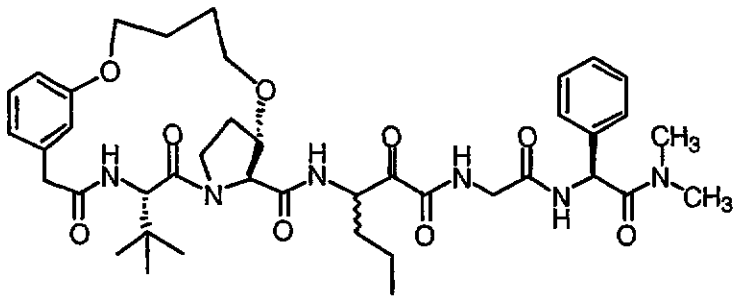
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Depending upon the structure, the compounds of the invention may form pharmaceutically acceptable salts with organic or inorganic acids, or organic or inorganic bases. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. For formation of salts with bases, suitable bases are, for example, NaOH, KOH, NH_4OH, tetraalkylammonium hydroxide, and the like.

In another embodiment, this invention provides pharmaceutical compositions comprising the above-described inventive macrocycles 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.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive macrocycle 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.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is 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 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.

As stated earlier, the invention includes tautomers, enantiomers and other stereoisomers of the compounds also. Thus, as one skilled in the art knows, some of the inventive compounds may exist in 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 macrocyclic 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. It is to be understood that while the following illustrative schemes describe the preparation of macrocycles predominately derived from 4-*cis*-hydroxyproline ("*cis*-HYP") or 7-

hydroxytetrahydroisoquinoline-3-carboxylic acid ("TIC"), suitable substitution of any of both the natural and unnatural amino acids will result in the formation of the desired macrocycles based on such substitution.

Abbreviations which are used in the descriptions of the schemes, preparations and the examples that follow are:

THF: Tetrahydrofuran

DMF: *N,N*-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: *N*-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et_2O: Diethyl ether

Bn: Benzyl

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

PyBrOP: Tris(pyrolidino)bromophosphonium hexafluorophosphate

DMSO: Dimethyl sulfoxide

TFA: Trifluoroacetic acid

HOBt: Hydroxybezotriazole

Hünigs base: Diisoprpylethyl amine

BOP: Benzotrizaol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

LDA: Lithium diisopropyl amide

Ph_3P: Triphenyl phosophine

LAH: Lithium Aluminum Hydride

DMAP: 4-Dimethyl aminopyridine

DCC: Dicyclohexylcarbodiimide

MCPBA: meta-Chloroperbenzoic acid

BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphtol

MeCN: acetonitrile

Pr: Propyl

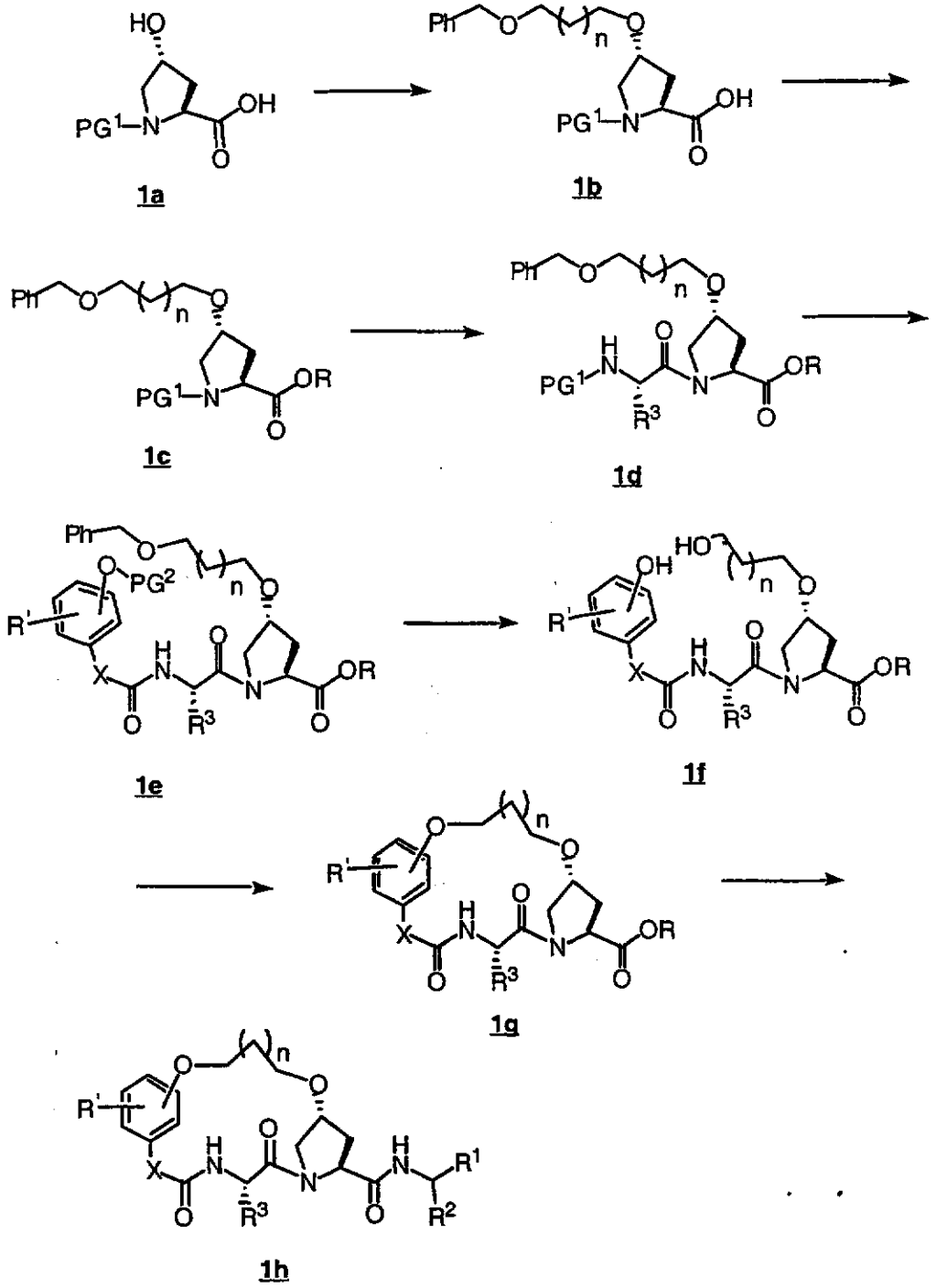
Ac: Acetyl

Ph: Phenyl

General Preparative Schemes:

The preparation of the compound of formula **1h**, wherein R^1, R^2, R^3 are defined above, R' is alkyl, heteroalkyl (OR", SR"', NR"R"' wherein R" and R"' are alkyl groups), halo substituent at *ortho, meta*, or *para* -position to oxygen atom; R is alkyl, aryl, or alkylaryl groups; n is from zero to five; X is $(CH_2)_m$ where m is one to five, oxygen atom, NY where Y is hydrogen atom, alkyl, aryl group; and PG^1 and PG^2 are appropriate protecting groups (PG^1 = t-boc, cbz and PG^2 = H, Bn etc) is outlined in **Scheme** 1. The protected 4-hydroxyproline acid (**1a**) is alkylated at the 4-position by an alkyl bromide in the presence of sodium hydride. The product **1b** is then converted to an ester either with an alcohol under acidic conditions, or with trimethylsilyldiazamethane. After deprotection, the resulting amine is coupled to a Boc-protected amino acid in the presence of HOOBt, EDCI·HCl and NMM. After removal of the Boc group from product **1d**, the dipeptide is reacted with a substituted hydroxyphenyl acetic acid using the same coupling conditions. Catalytic hydrogenation of the benzyl ether gives the precursor for the macrocyclization. The macrocyclization is achieved under Mitsunobu conditions by using triphenylphosphine and ADDP. (The *Mitsunobu* reaction is reviewed by D. L. Hughes, *Org. Reactions*, 42 (1992) 335, John Wiley & Sons, New York, L. Paquette, ed.) After the ester is hydrolyzed to an acid with lithium hydroxide, it is coupled to an amine intermediate to afford **1h**.

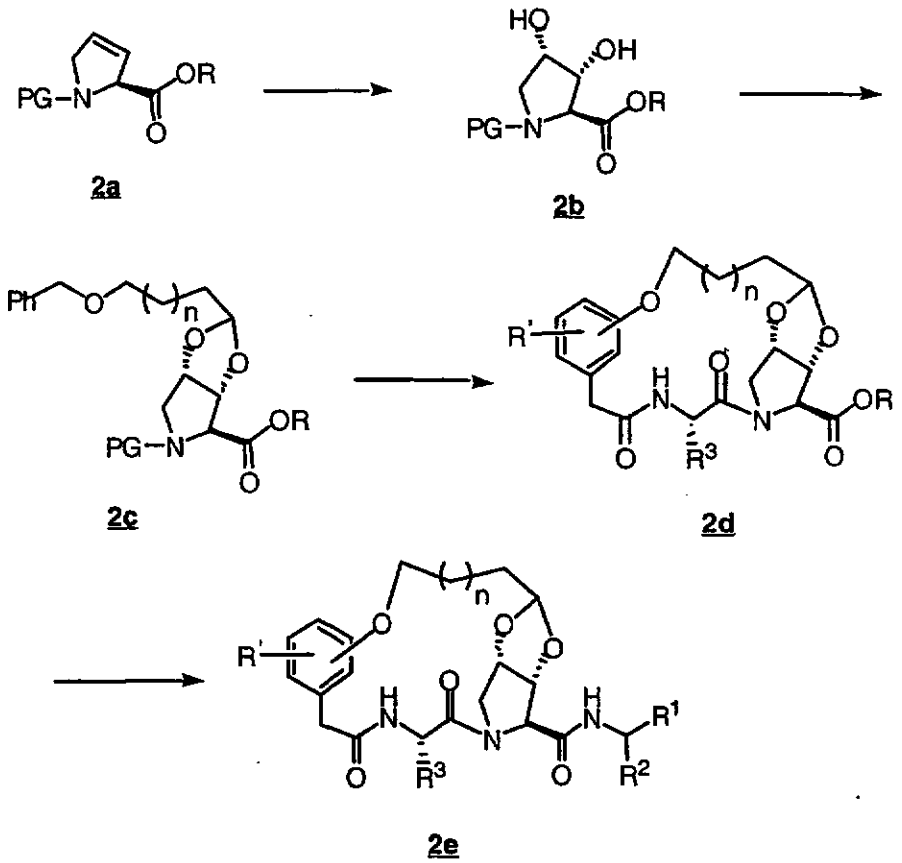
Scheme 1



The preparation of the compound of Formula **2e**, wherein R^1, R^2, R^3, R and R' are defined above, is outlined in **Scheme 2**. The protected 3,4-dehydroproline **2a** is diastereoselectively dihydroxylated to afford *cis*-diol **2b**. The acetal formation between **2b** and an aldehyde can be accomplished in the

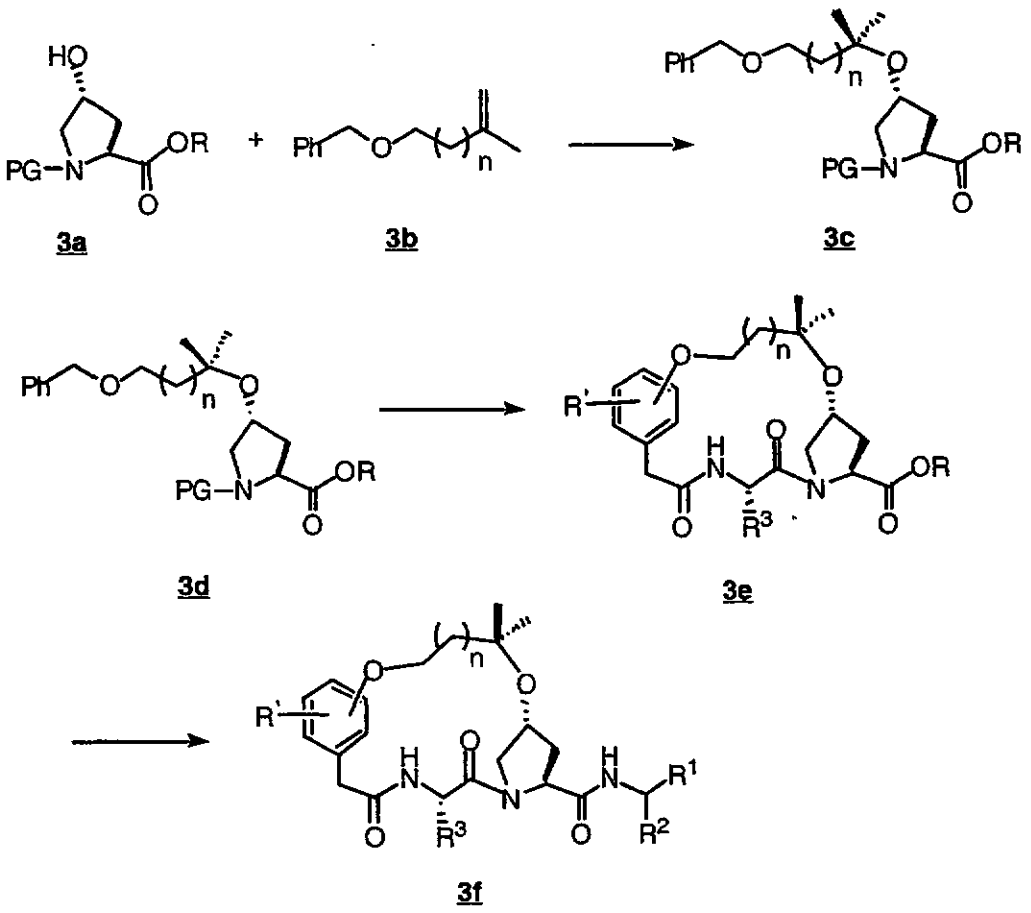
presence of catalytic amount of *p*-toluenesulfonic acid. The bicyclic proline derivative **2c** is converted to the macrocyclic ester **2d** and subsequently to HCV inhibitor **2e** according to the sequence outlined in **Scheme 1**.

Scheme 2



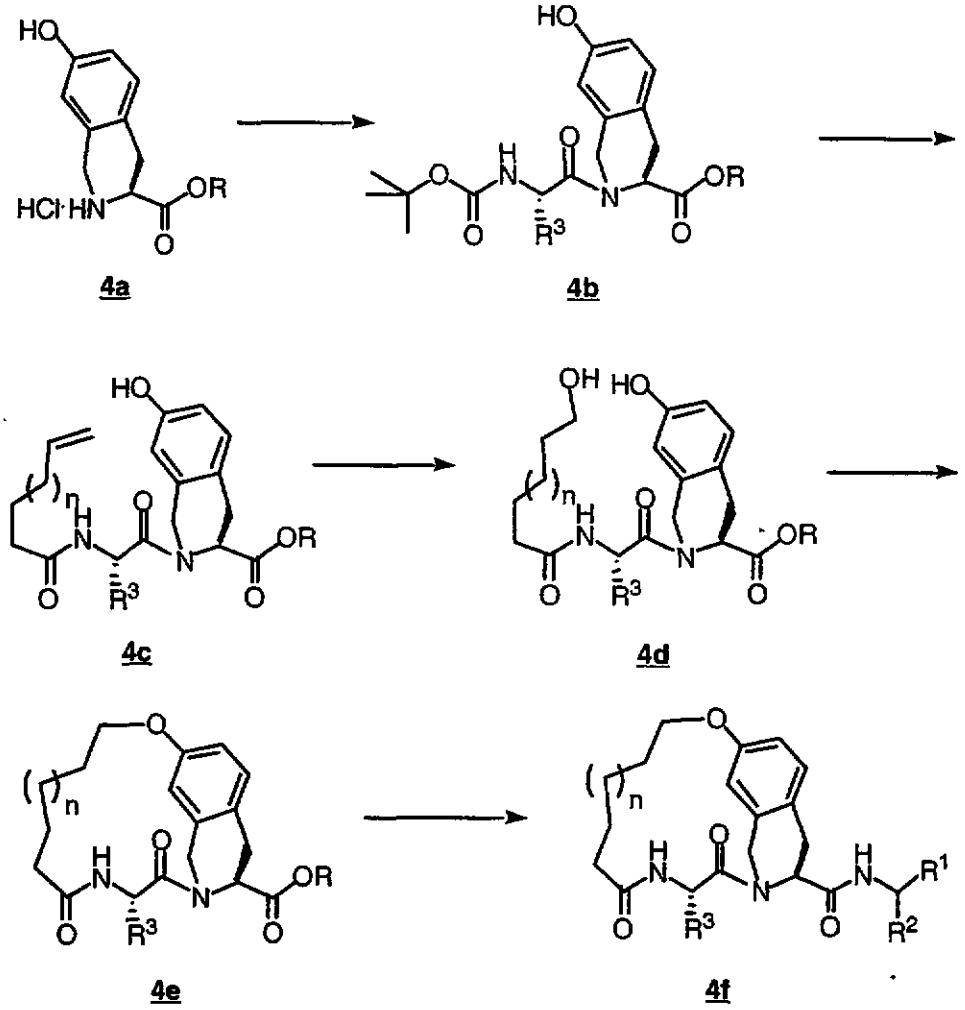
The preparation of the compound of Formula **3f**, wherein R^1, R^2, R^3, R, R' and n are defined above, is outlined in **Scheme 3**. When treated with trifluoroboron diethyletherate, the protected 4-hydroxyproline **3a** and alkene **3b** are converted to proline ether **3c**, which undergoes the same sequence of transformations outlined in **Scheme 1** to give the macrocyclic ester **3e** and subsequently, to the desired final product **3f**.

Scheme 3



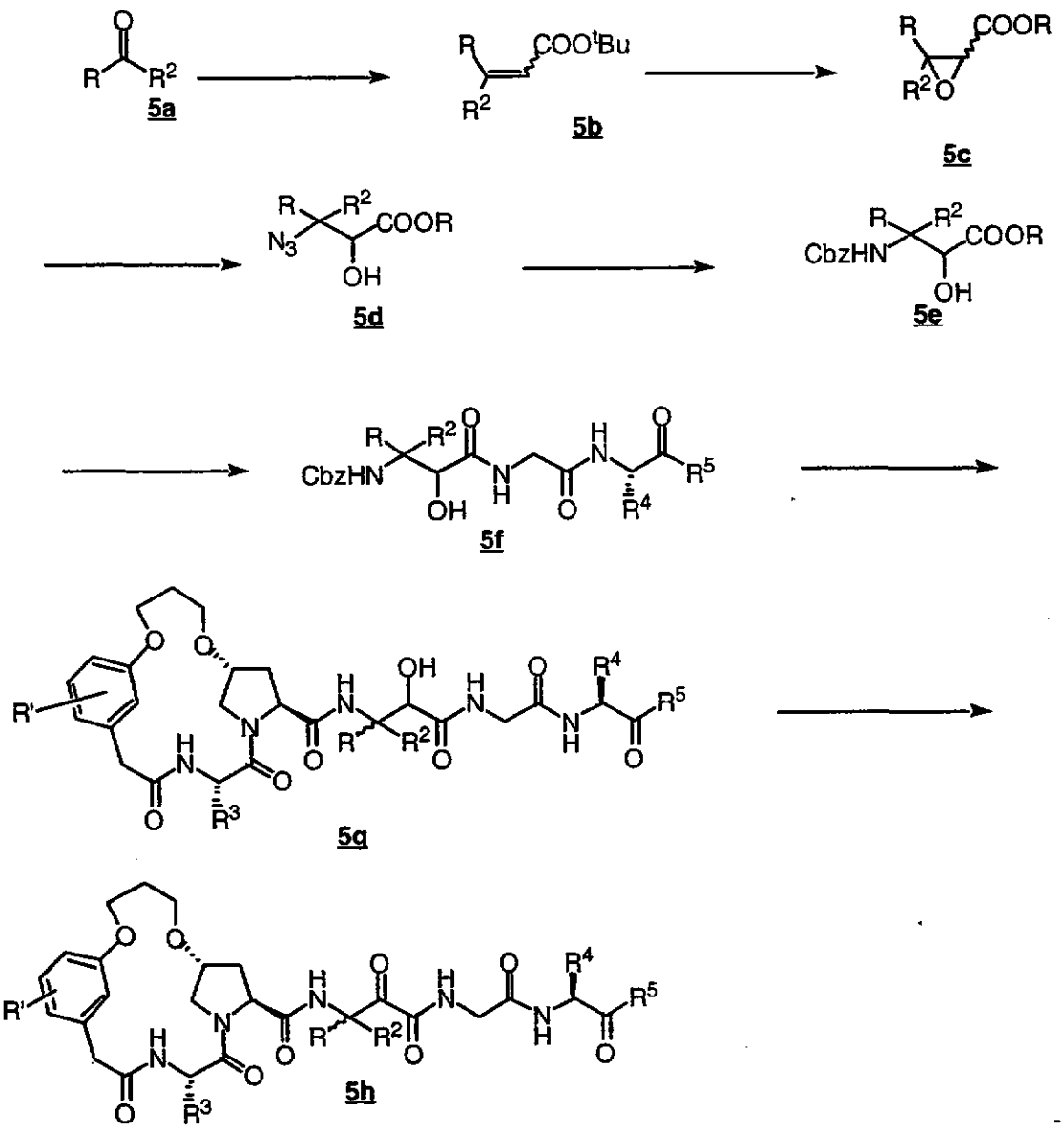
The preparation of the compound of Formula **4f**, wherein R^1, R^2, R^3, R, and n are defined above, is outlined in **Scheme 4**. The coupling between amino ester **4a** and a Boc-protected amino acid was realized in the presence of NMM, HOOBt, and EDCI·HCl. After removal of the Boc group from **4b**, the dipeptide is coupled to a terminal alkene carboxylic acid to give **4c**. The double bond was then converted to an alcohol through hydroboration. The macrocyclization of the phenol alcohol is accomplished under Mitsunobu conditions by using triphenylphosphine and ADDP. After the resulting ester **4e** is hydrolyzed to an acid with lithium hydroxide, the acid is coupled to an amine intermediate to afford **4f**.

Scheme 4



The preparation of the compound of Formula **5h** in **Scheme 5** where in R, R^2, R^3, R' are defined in **Scheme 1**, R^4 being alkyl, cycloalkyl, aryl, heteroaryl, and heteroalkyl and R^5 is OR, NR_2, or OH. The compound **5b** was obtained by a Wittig reaction of **5a** with *tert*-butyl phosphonoacetate and NaH. The compound **5b** was converted to **5c** by the treatment of MCPBA. The epoxide **5c** was further opened with NaN_3 to give compound **5d** which was reduced with Pd/C/ H_2 to the amine and Cbz protected using Cbz-Cl, Et_3N to obtain compound of the formula **5e.** The compound **5e** was deprotected with TFA and further elaborated to **5f.** The Cbz group of **5f** was hydrogenolyzed and then coupled with compound of formula **1g** using EDCI, HOOBt, NMM to obtain **5g**. The compound of the type **5g** is oxidized with Dess-Martin reagent to generate compounds of formula **5h**.

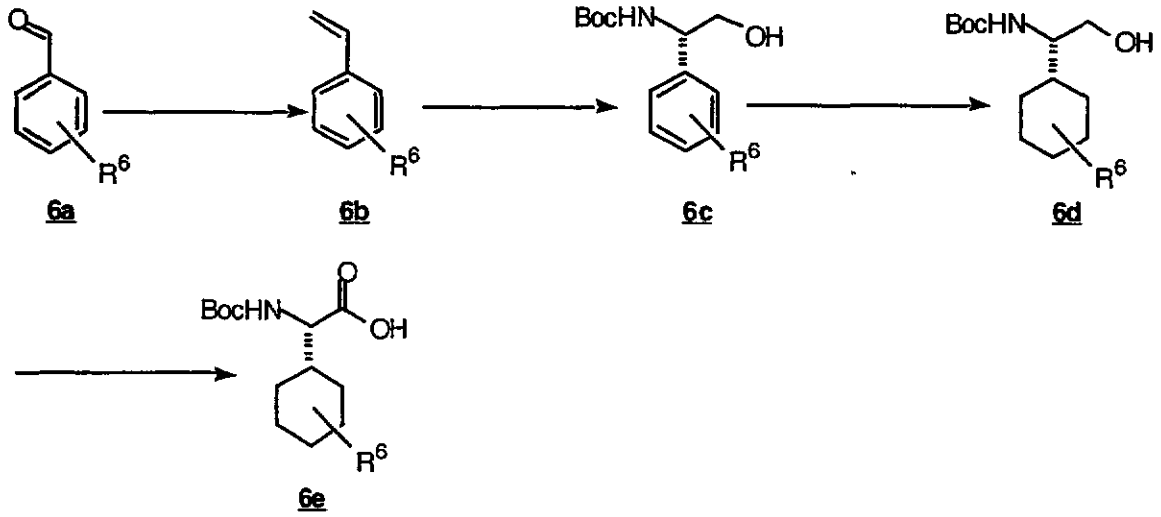
Scheme 5:

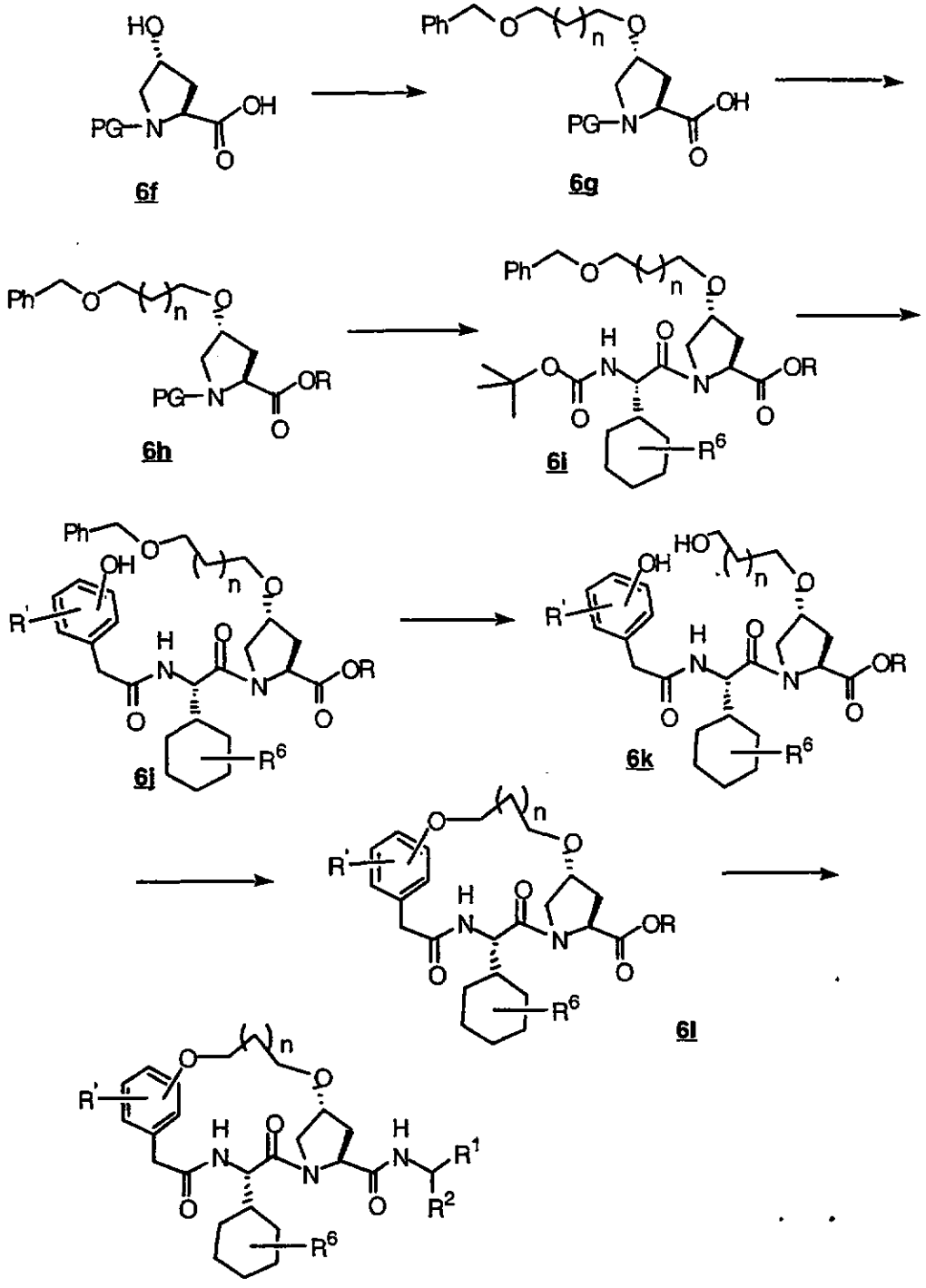


The compound of formula **6m** is synthesized as outlined in **Scheme 6** wherein R^1, R^2, R' and n are defined in **Scheme 1** and R^5 being alkyl, aryl, ester, carboxylic acid and carboxylamides. The compound of type **6b** is synthesized from **6a** by a Wittig olefination using Ph_3PCH_3I and BuLi. The compound **6b** is further aminohydroxylated to synthesize compound of the type **6c**, which was reduced using Rh/C, and H_2 to afford compound of type **6d**. The compound **6d** was oxidized to compound of type **6e** using $RuCl_3$ and H_5IO_6. The compound **6e**

was elaborated to compound **6i** by coupling it with deprotected **6h** using NMM, EDCI, and HOOBt. Extension of compound **6i** to **6j** was again achieved by coupling deprotected **6i** and appropriately substituted phenyl acetic acid using EDCI, HOOBt and NMM. The compound **6k** obtained after hydrogenolysis of benzyl group in **6j** was cyclized to **6l** using the Mitsunobu conditions. **6l** was further elaborated to compounds of type **6m** as outlined in **Scheme 1**.

Scheme 6:



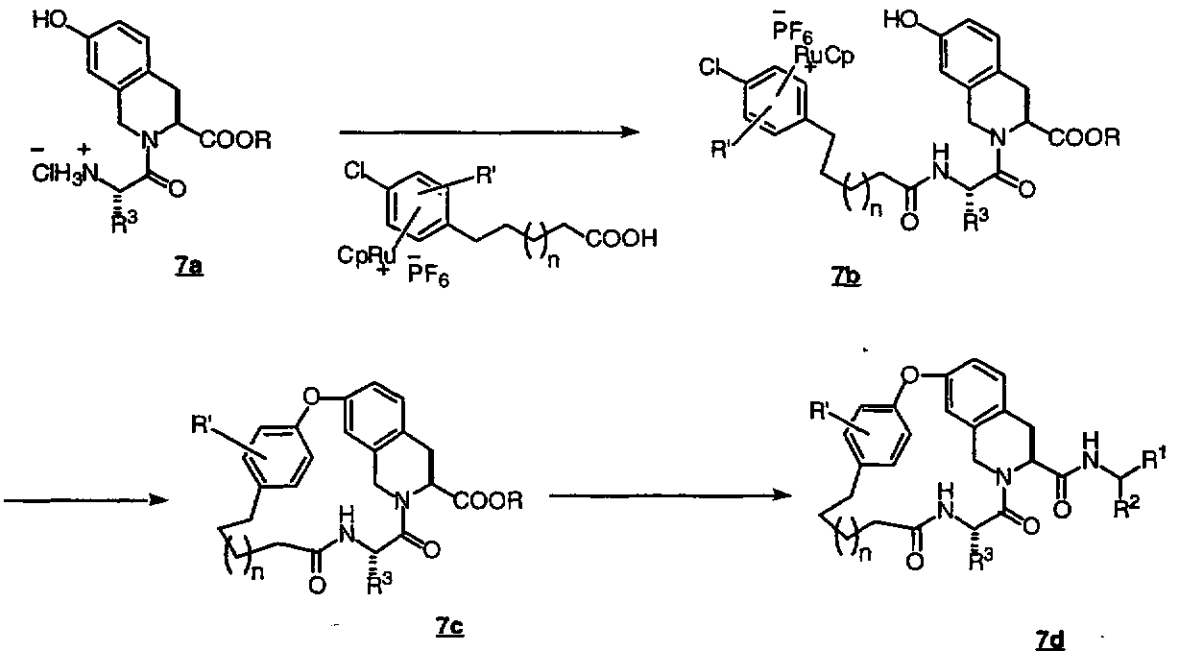


6m

The compounds of type **7d** are synthesized using the arene ruthenium chemistry wherein the substituents R^1, R^2, R^3, R' are defined in **Scheme 1**, and n=0 to 3. The synthesis of the compound of formula **7b** was obtained from compound of type **7a** by an EDCI, HOBt, Hünigs base coupling. The treatment of

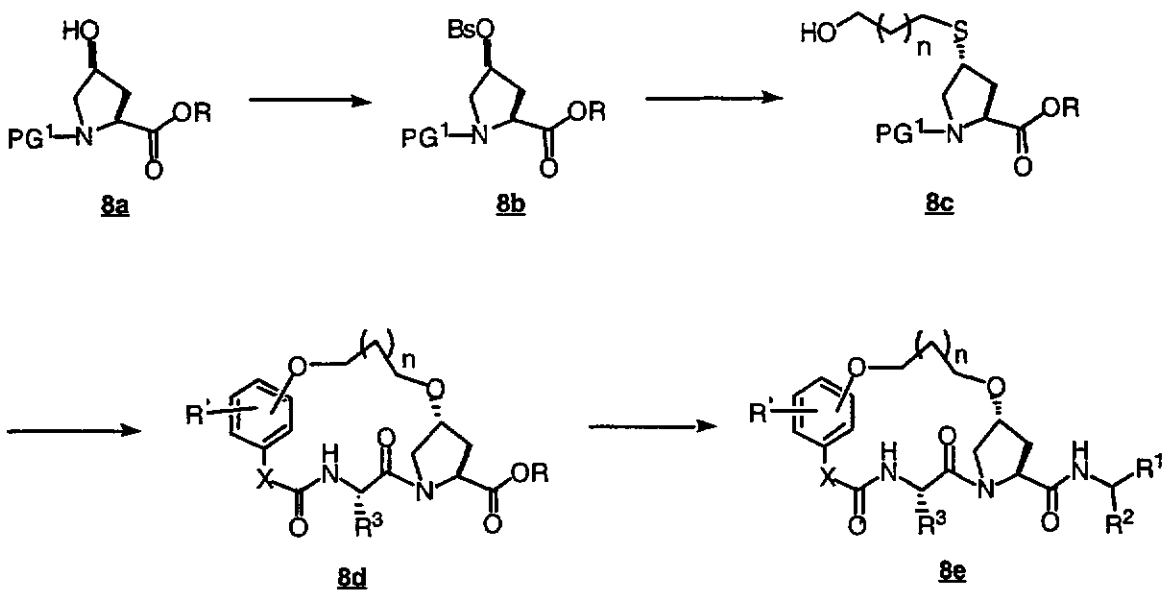
7b with Cs_2CO_3 and photolytic removal of ruthenium converted the compound of type **7b** to type **7c**, which was further elaborated to compounds **7d** as outlined in **Scheme 1.**

Scheme 7



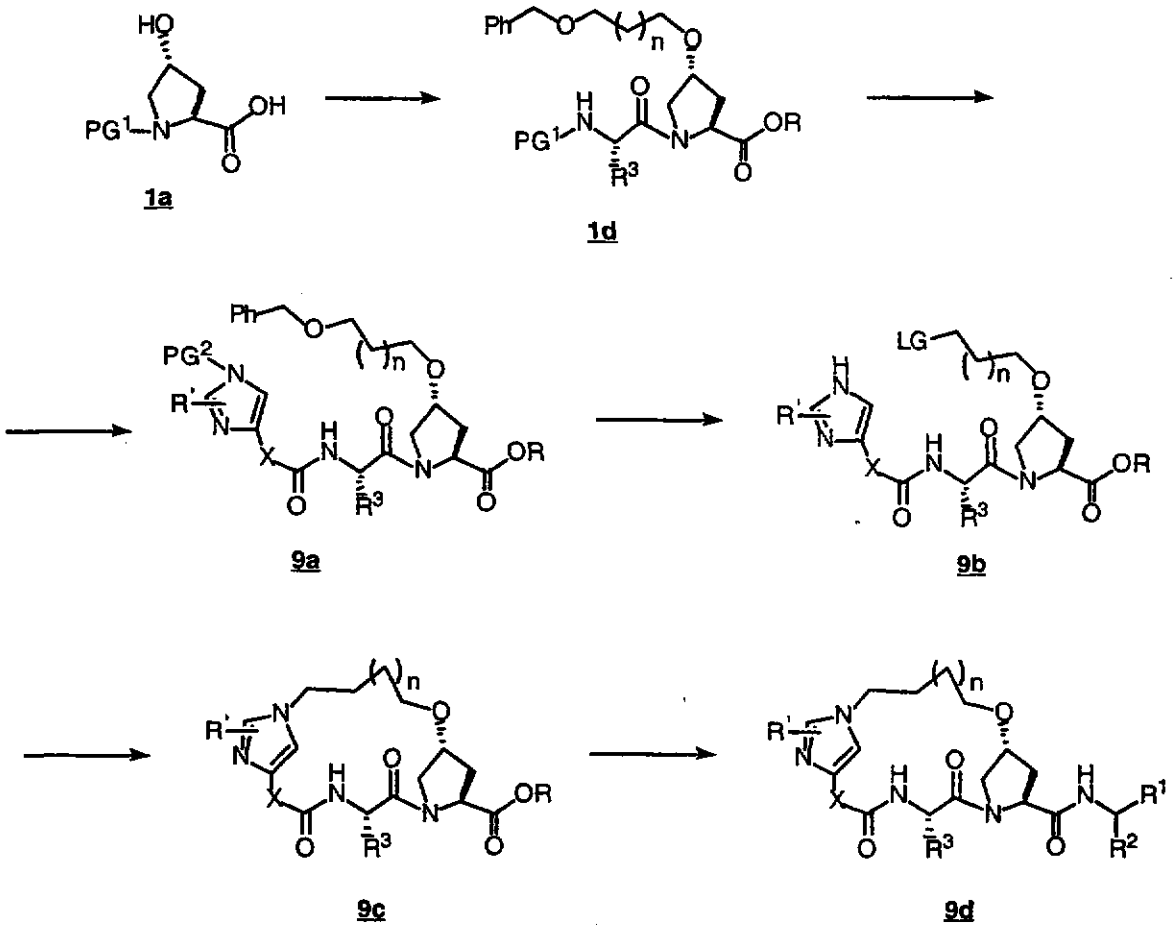
The preparation of the compound of formula **8e**, wherein R^1, R^2, R^3 are defined above, R' is alkyl, heteroalkyl (OR", SR"', NR"R"' wherein R" and R"' are alkyl groups), halo substituent at *ortho*, *meta*, or *para* -position to oxygen atom; R is alkyl, aryl, or alkylaryl groups; n is from zero to five; and X is $(CH_2)_m$ where m is one to five, oxygen atom, NY where Y is hydrogen atom, alkyl, aryl group is outlined in **Scheme 8.** The protected *cis*-4-hydroxyproline derivative **8a** is converted to the brosylate (Bs = 4-bromobenzenesulfonyl) derivative **8b** which was displaced with the appropriate mercaptoalcohol under sodium hydride conditions to give **8c**. Conversion to the macrocyclic ester **8d** and subsequently to the desired target **8e** was accomplished as outlined in **Scheme 1.**

Scheme 8



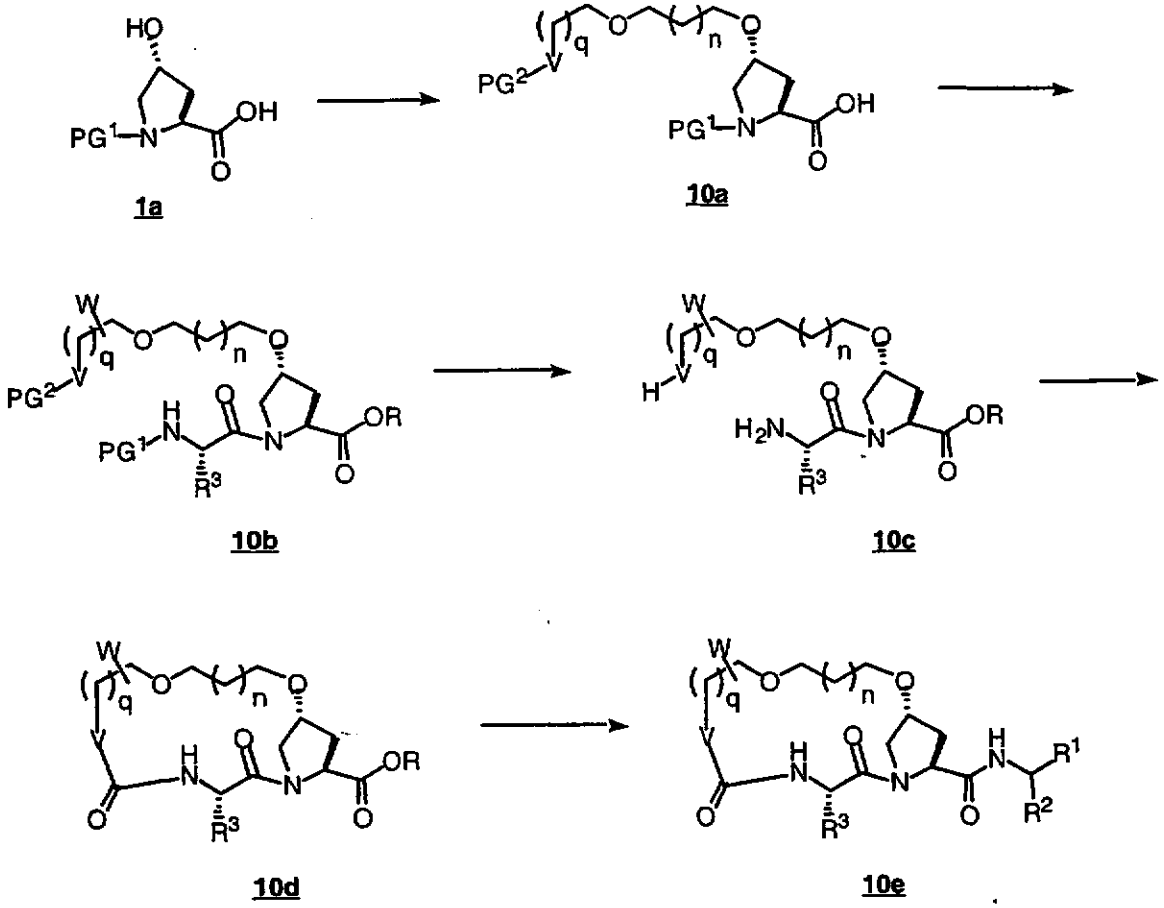
The preparation of the compound of formula **9d**, wherein R^1, R^2, R^3 are defined above, R' is alkyl, heteroalkyl (OR", SR"', NR"R"' wherein R" and R"' are alkyl groups), halo substituent at *ortho*, *meta*, or *para* -position to oxygen atom; R is alkyl, aryl, or alkylaryl groups; n is from zero to five; X is $(CH_2)_m$ where m is one to five, oxygen atom, NY where Y is hydrogen atom, alkyl, aryl group; and LG is leaving group (e.g., OTs, Br) is outlined in **Scheme 9**. The protected 4-hydroxyproline derivative **1a** is converted to **9a** via formation of **1d** (which is described in **Scheme 1**). Removal of the benzyl ether followed by conversion to an appropriate leaving group and unravelling the N protecting group provided **9b**. Conversion to the macrocyclic ester **9c** was carried out by treatment with sodium carbonate/sodium iodide in refluxing acetone. Subsequent processing to the desired target **9d** was accomplished as outlined in **Scheme 1**.

Scheme 9



The preparation of the compound of formula **10e**, wherein R^1, R^2, R^3 are defined above, R' is alkyl, heteroalkyl (OR", SR"', NR"R"' wherein R" and R"' are alkyl groups), halo substituent at *ortho*, *meta*, or *para* -position to oxygen atom; R is alkyl, aryl, or alkylaryl groups; n and q is any combination of zero to five; V is oxygen atom, NY where Y is hydrogen atom, alkyl, aryl group; W is alkyl, aryl, alkylaryl, heteroaryl; PG^1 and PG^2 are appropriate protecting groups (PG^1 = t-boc, cbz and PG^2 = H, Bn, etc) is outlined in **Scheme 10**. The protected 4-hydroxyproline derivative **1a** is converted to **10b** as described in **Scheme 1**. Removal of the protecting group (**10c**) followed by treatment with phosgene equivalent results in the macrocyclic ester **10d**. Conversion to the desired target **10e** was accomplished as outlined in **Scheme 1**.

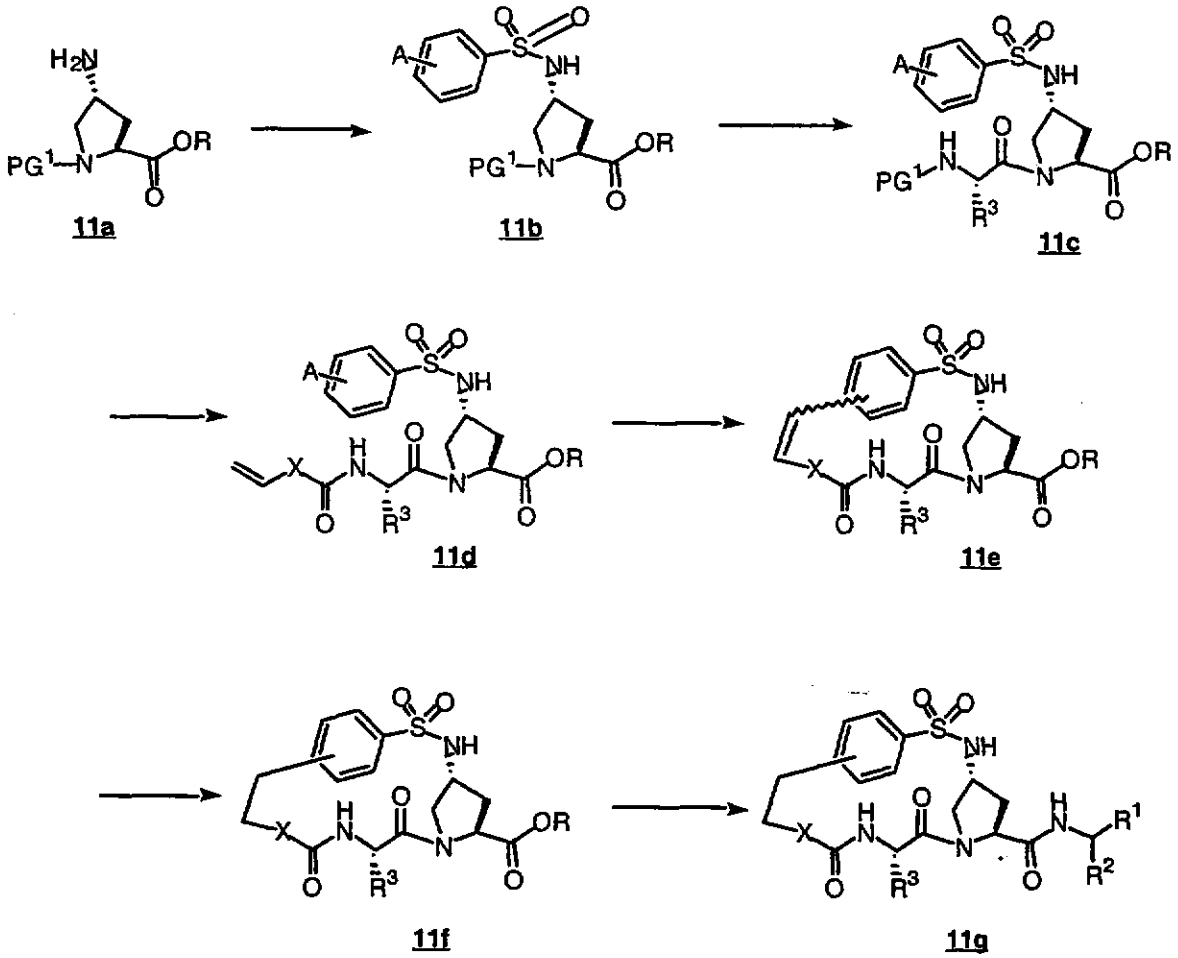
Scheme 10



The preparation of the compound of formula **11g**, wherein R^1, R^2, R^3 are defined above, R is alkyl, aryl, or alkylaryl groups; X is $(CH_2)_m$, $(CH_2)_mO$, $(CH_2)_mNY$ where m is one to five, and Y is hydrogen atom, alkyl, aryl group; A is hydrogen atom or appropriately positioned halogen atom; PG^1 is appropriate protecting groups (PG^1 = t-boc, cbz, etc) is outlined in **Scheme 11**. The protected 4-aminoproline derivative **11a** is converted to **11b** by treatment with suitable benzenesulfonyl chloride and a base. Removal of protecting group and coupling with a protected aminoacid derivative gave **11c**. This was converted to **11d** using similar deprotection, coupling strategy. Palladium(0) catalyzed cyclization afforded **11e** as a mixture of isomers which was hydrogenated to provide

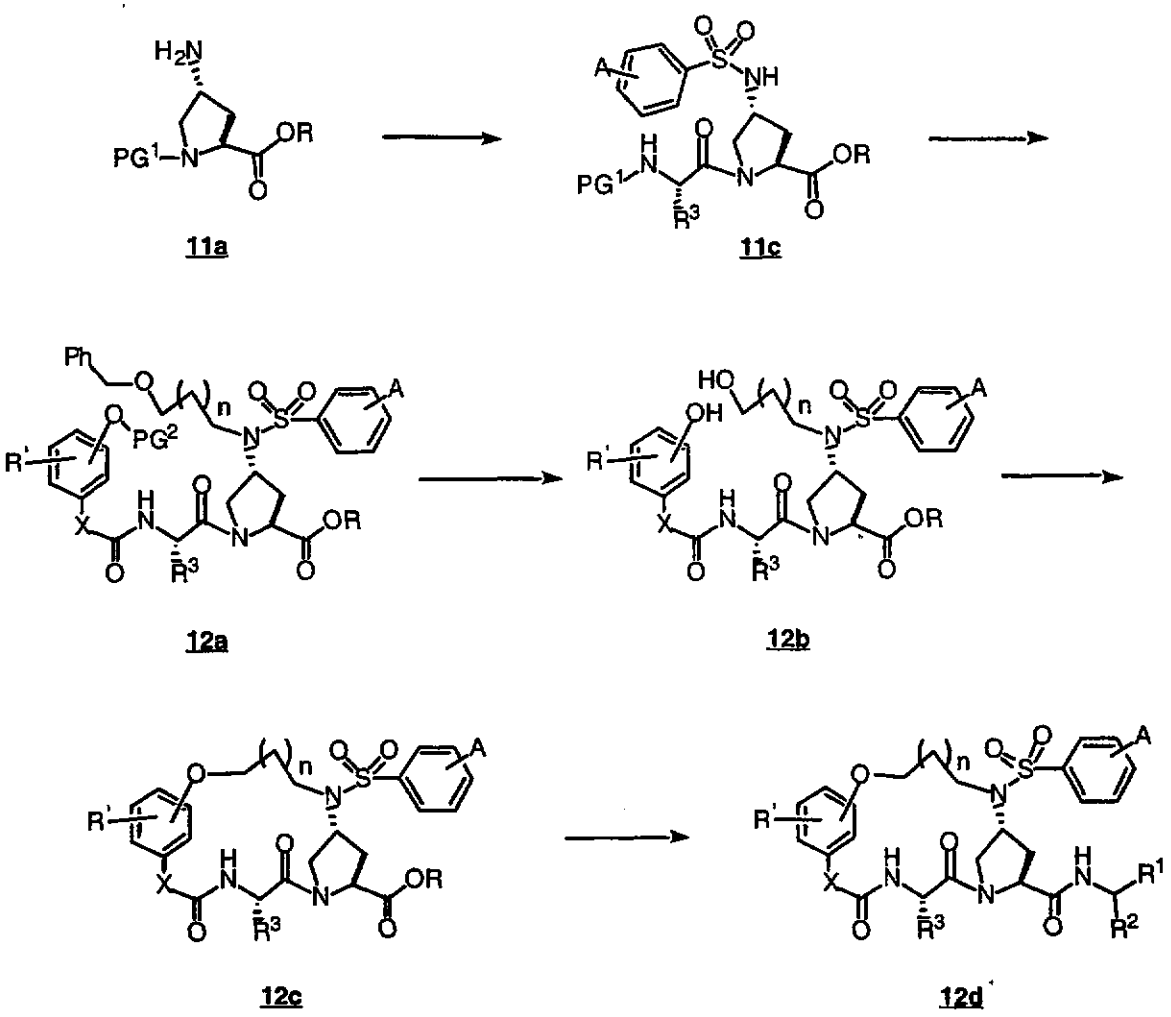
macrocyclic ester **11f**. Subsequent conversion to the desired target **11g** was accomplished as outlined in **Scheme 1**.

Scheme 11



The preparation of the compound of formula **12d**, wherein R^1, R^2, R^3 are defined above, R is alkyl, aryl, or alkylaryl groups; n is from zero to five; X is $(CH_2)_m$ where m is one to five, oxygen atom, NY where Y is hydrogen atom, alkyl, aryl group; A is hydrogen atom or appropriately positioned halogen atom; and PG^1 and PG^2 are appropriate protecting groups (PG^1 = t-boc, cbz and PG^2 = H, Bn etc) is outlined in **Scheme 12**. The protected 4-aminoproline derivative **11a** is converted to **11c** as described in **Scheme 11**. Conversion of **11c** to the macrocyclic ester **12c** and subsequent conversion to the desired target **12d** was accomplished as outlined in **Scheme 1**.

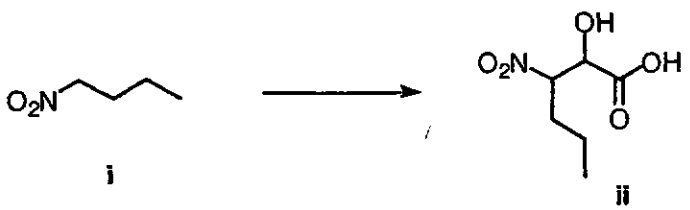
Scheme 12



Preparation of Intermediates:

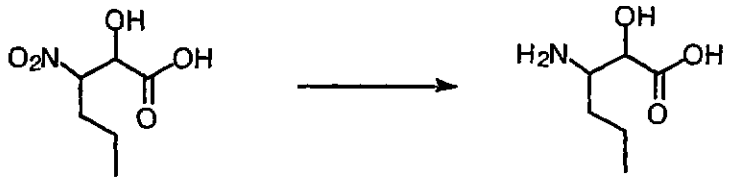
Intermediate A:

Step 1:



To a stirred solution of 1-nitrobutane (16.5 g, 0.16 mol) and glyoxylic acid in H_2O (28.1 g, 0.305 mol) and MeOH (122 mL) at 0°C-5°C, was added dropwise triethyl amine (93 mL, 0.667 mol) over 2 hrs. The solution was warmed to room temperature, stirred overnight and concentrated to dryness to give an oil. The oil was then dissolved in H_2O and acidified to pH =1 with 10% HCl, followed by extraction with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product **ii** (28.1 g, 99% yield)

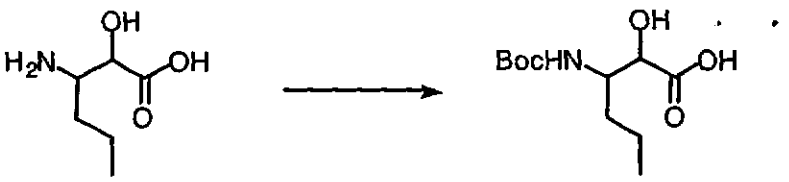
Step 2:



ii **iii**

To a stirred solution of starting material **ii** (240 g, 1.35 mol) in acetic acid (1.25 L) was added 10% Pd/C (37 g). The resulting solution was hydrogenated at 59 psi for 3 hrs and then at 60 psi overnight. The acetic acid was then evaporated and azeotroped 3 times with toluene, then triturated with MeOH and ether. The solution was then filtered and azeotroped twice with toluene to give an off white solid (131 g, 0.891 mol, 66%).

Step 3:

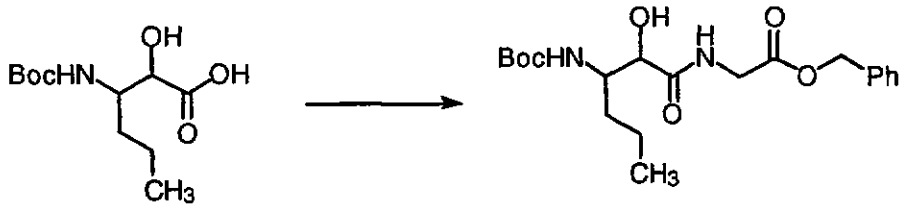


iii **iv**

To a stirred solution of the amino acid **iii** (2.0 g, 13.6 mmol) in dioxane (10 mL) and H_2O (5mL) at 0°C, was added 1N NaOH solution (4.3 mL, 14.0 mmol).

The resulting solution was stirred for 10 minutes, followed by addition of di-*t*-butyldicarbonate (0.110 g, 14.0 mmol) and stirred at 0°C for 15 minutes. The solution was then warmed to room temperature, stirred for 45 minutes and kept at refrigerator overnight and concentrated to dryness to give a crude material. To the solution of this crude material in EtOAc (100 mL) and ice, was added $KHSO_4$ (3.36 g) and H_2O (32 mL) and stirred for 4-6 minutes. The organic layer was then separated and the aqueous layer was extracted twice with EtOAc and the combined organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product as a clear gum (3.0 g, 89% yield).

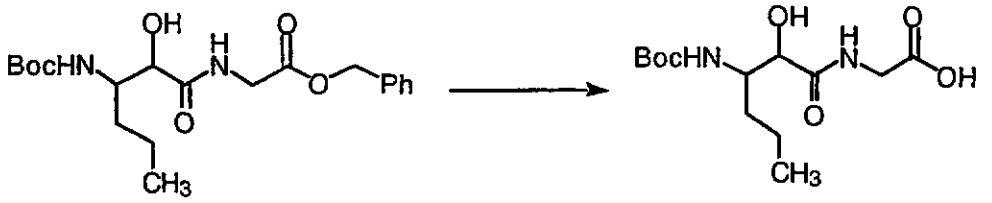
Step 4:



iv v

To a stirred solution of starting material (3.00 g, 12.0 mmol) in DMF (15 mL) and CH_2Cl_2 (15 mL) at -20°C was added HOOBt (1.97 g, 12.0 mmol), *N*-methyl morpholine (4.0 mL, 36.0 mmol) and EDCI (2.79 g, 14.5 mmol) and stirred for 10 minutes, followed by addition of $HCl \cdot H_2N$-Gly-OBn (2.56 g, 13.0 mmol). The resulting solution was stirred at -20°C for 2 hrs, then kept at refrigerator overnight and concentrated to dryness, followed by dilution with EtOAc (150 mL). The EtOAc solution was then washed twice with saturated $NaHCO_3$, H_2O, 5%. H_3PO_4, brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product (4.5 g, 94%). LRMS *m/z* MH^+= 395.1.

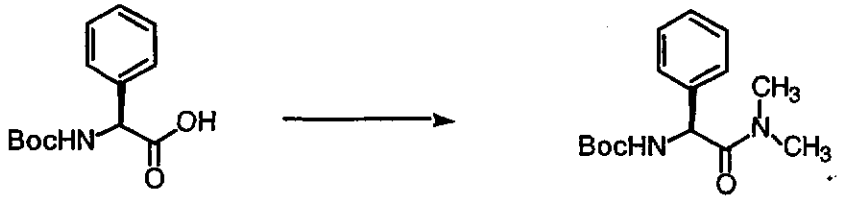
Step 5:



v vi

The solution of starting material **v** (7.00 g, 17.8 mmol) in absolute ethanol (300 mL) was stirred at room temperature under a hydrogen atmosphere in the presence of Pd-C (300 mg, 10%). The reaction progress was monitored by TLC. After 2h, the mixture was filtered through a celite pad and the resulting solution was concentrated in vacuo to give the product **vi** (5.40 g, quantitative). LRMS *m/z* MH^+= 305.1.

Step 6:

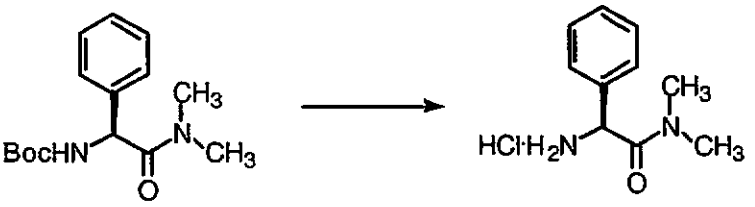


vii viii

To a solution of dimethylamine hydrochloride (1.61 g, 19.7 mmol), *N*-Boc-phenylglycine (4.50 g, 17.9 mmol), HOOBt (3.07 g, 18.8 mmol) and EDCI (4.12-g, 21.5 mmol) in anhydrous DMF (200 mL) and CH_2Cl_2 (150 mL) at -20°C was added NMM (5.90 mL, 53.7 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then allowed to warm to rt., and EtOAc (450 mL), brine (100 mL) and 5% H_3PO_4 (100 mL) were added. After layers were separated, the organic solution was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried ($MgSO_4$), filtered and

concentrated in vacuo to afford crude product **viii** (4.86 g) as a white solid, which was used without further purification.

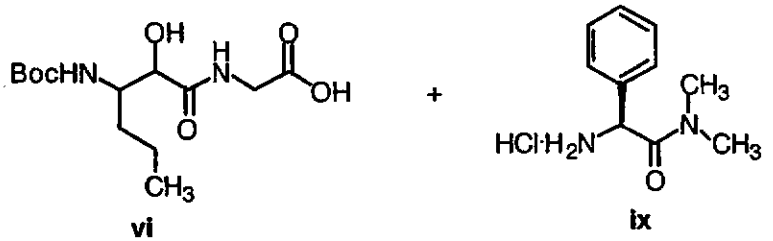
Step 7:



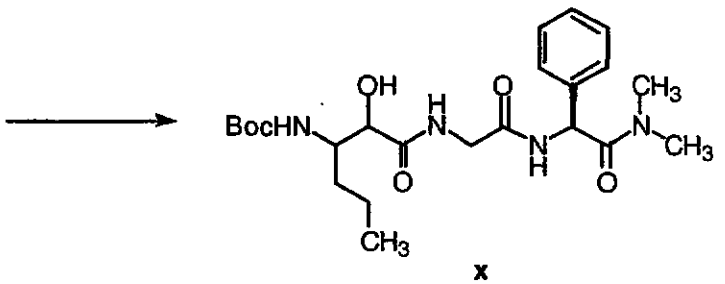
viii **ix**

The *N*-Boc-phenylglycine dimethylamide **viii** (4.70 g, crude) was dissolved in 4 N HCl (60 mL, 240 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 4 h, the solution was concentrated in vacuo to yield a white solid which was used in the next reaction without further purification. LRMS *m/z* MH^+= 179.0.

Step 8:



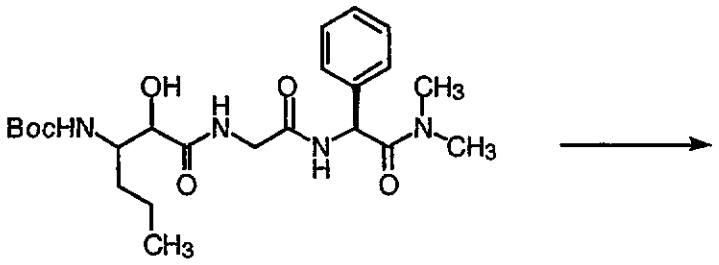
vi **ix**



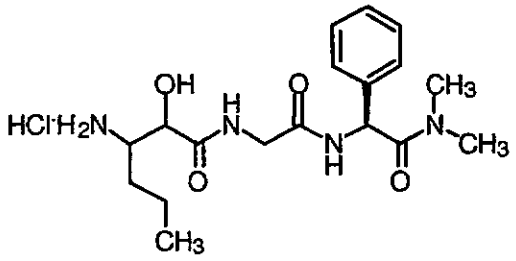
x

The desired compound **x** was prepared according to the coupling procedures described in Step 4. LRMS *m/z* MH^+= 465.1.

Step 9:



x

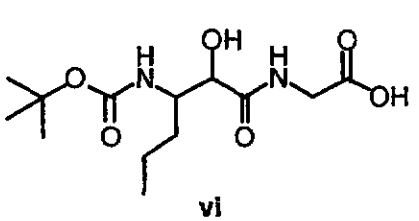


A

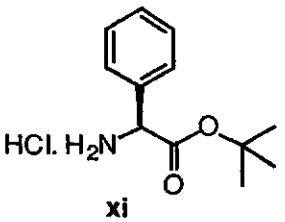
The desired intermediate **A** was prepared from tripeptide **x** according to the procedures described in Step 7. LRMS *m/z* MH^+= 365.1.

Intermediate B:

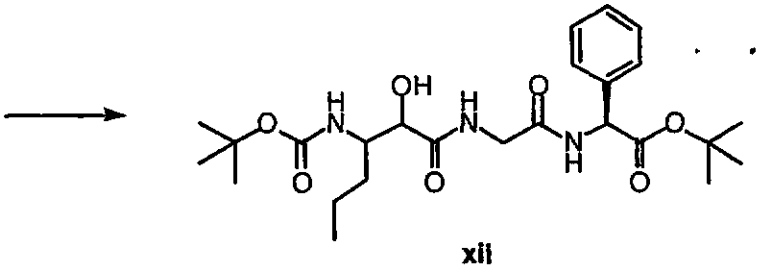
Step 1



vi



xi

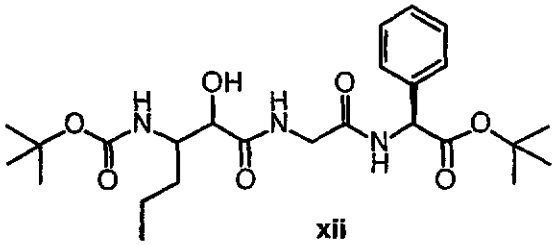


xii

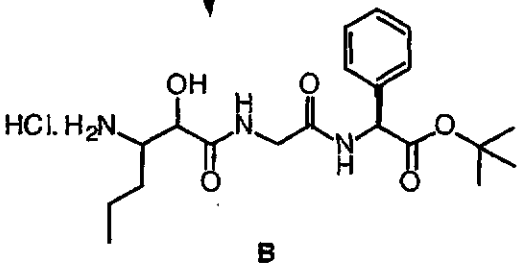
The desired product **xii** was obtained by the procedure described for Intermediate **A**, Step 8 using commercially available **xi** as the coupling partner.

The crude material was sufficiently pure for further studies. A portion of the product was purified by flash chromatography using 97/3 dichloromethane/MeOH. HRMS (FAB) Calcd for $C_{25}H_{40}N_3O_7$: 494.2866 $(M+H)^+$. Found: 494.2863.

Step 2



xii

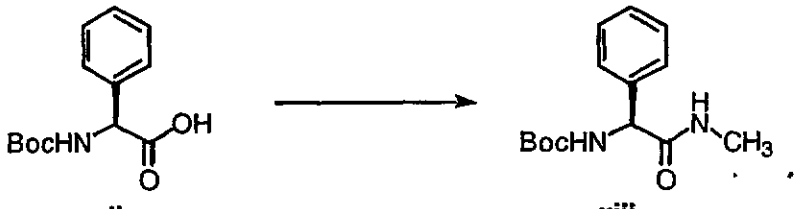


B

The desired product **B** was obtained by the procedure described for Intermediate **A**, Step 7. The crude material was used without further purification.

Intermediate C:

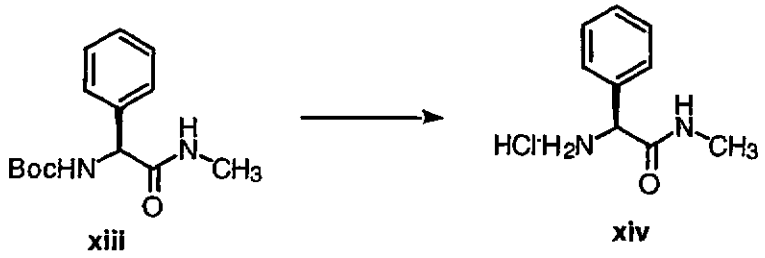
Step 1:



vii xiii

The desired compound **xiii** was prepared similar to the coupling procedures described in Step 6 for intermediate **A** except for substituting methylamine for dimethylamine.

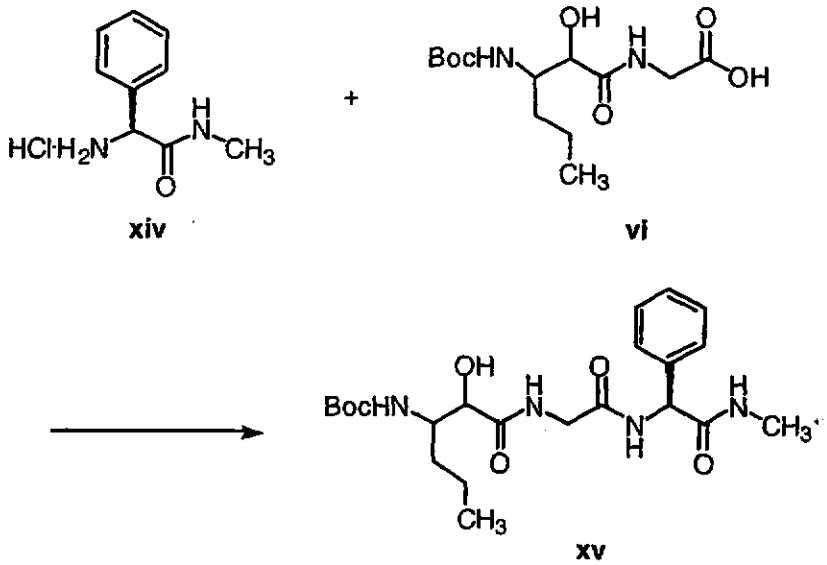
Step 2:



xiii xiv

The desired compound **xiv** was prepared from **xiii** according to the procedures described in Step 7 for intermediate **A**.

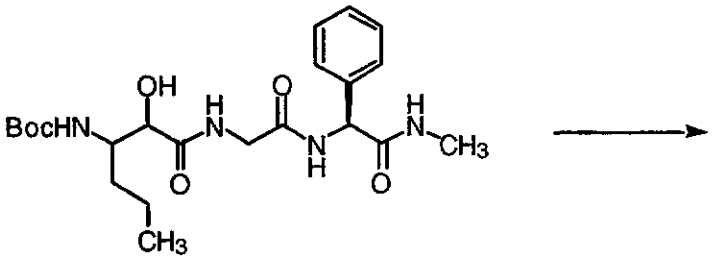
Step 3:



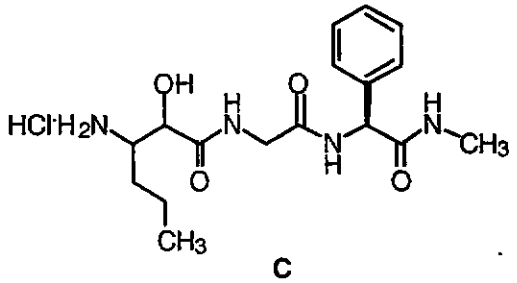
xiv vi xv

The desired compound **xv** was prepared according to the coupling procedures described in Step 6 for intermediate **A**, except for substituting amine **xiv** for amine **ix**. LRMS *m/z* MH^+= 451.1.

Step 4:



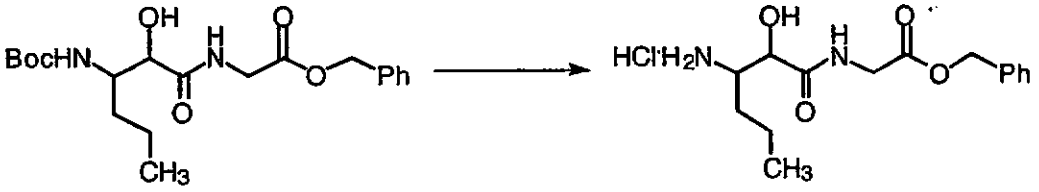
xv



C

The desired intermediate **C** was prepared according to the procedures described in Step 7 for intermediate **A**. LRMS *m/z* MH^+= 351.1. It was used without further purification.

Intermediate D:

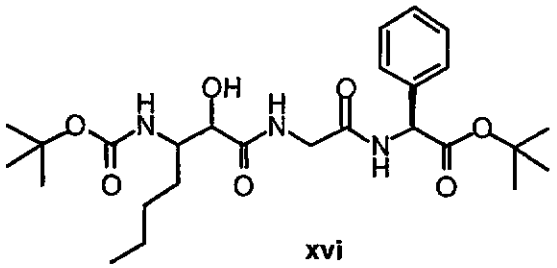


v D

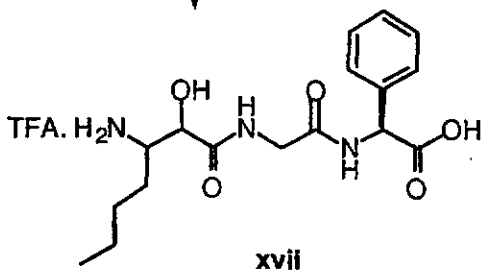
The desired intermediate **D** was prepared from compound **v** according to the procedures described in Step 7 for intermediate **A**. It was used without further purification.

Intermediate E

Step 1



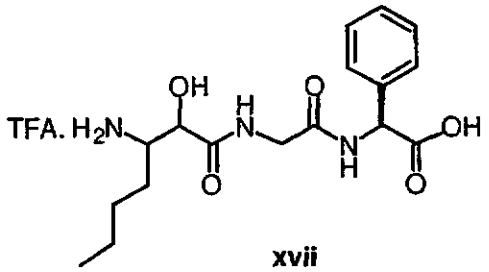
xvi



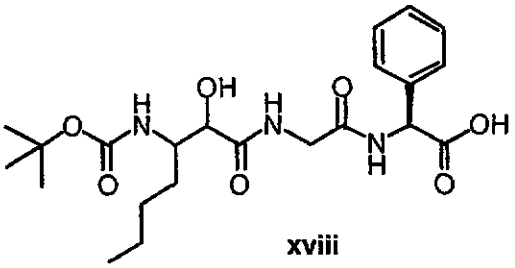
xvii

To a solution of **xvi** (5g) in dichloromethane (20 mL) was added TFA (20 mL) and stirred at ambient temperature for 4 hrs. Another portion of TFA (10 mL) was added and left standing for additional 3 hrs. All the volatiles were evaporated and it was dried *in vacuo* to provide quantitative yield of **xvii**. This material was carried further. (Note: The starting material **xvi** was obtained by a similar protocol described for **B**, using nitropentane as precursor).

Step 2



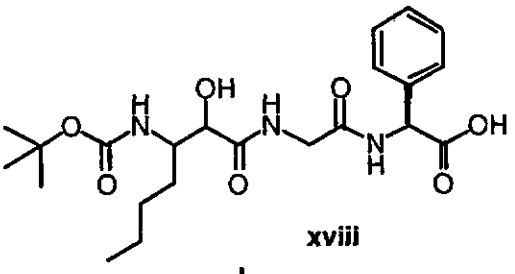
xvii



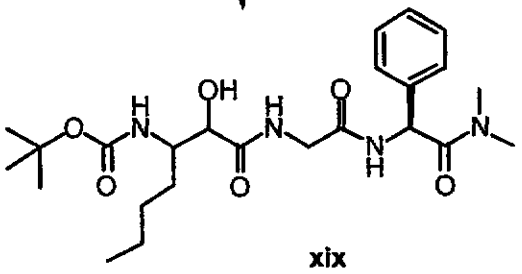
xviii

The desired compound **xviii** was obtained by the method described for Intermediate **A**, Step 3. Sodium carbonate was used as the base instead of NaOH. The crude material **xviii** was carried further without purification.

Step 3



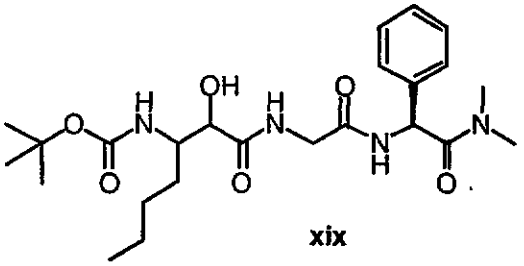
xviii



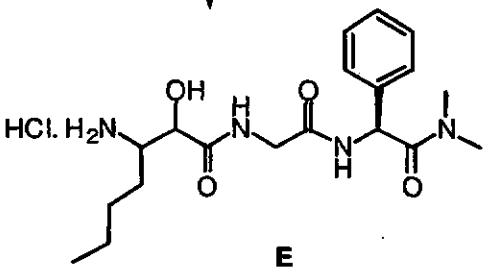
xix

To a cold (-20°C) solution of **xviii** (4.8 g, 10.7 mmol) in dichloromethane/DMF (4/1, 25 mL) was added dimethylamine hydrochloride (959 mg, 11.77 mmol), diisopropylethylamine (4.2 mL, 24.1 mmol) and BOP (6.14 g, 13.89 mmol). It was left standing at -8°C overnight. The reaction mixture was diluted with dichloromethane and washed with 10% citric acid solution, saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography using 97.5/2.5 dichloromethane/MeOH to afford 2.4 g of **xix** (47% yield). HRMS (FAB) Calcd for $C_{24}H_{39}N_4O_6$: 479.2870 $(M+H)^+$. Found: 479.2862.

Step 4



xix

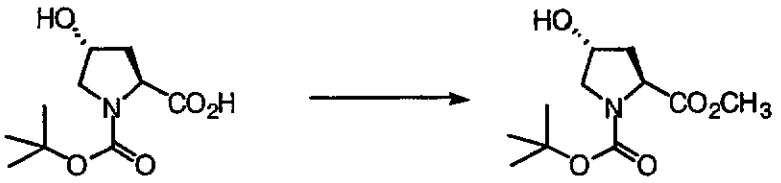


E

The desired product **E** was obtained by the procedure described for Intermediate **A**, Step 7. The crude material was used without further purification.

Intermediate F

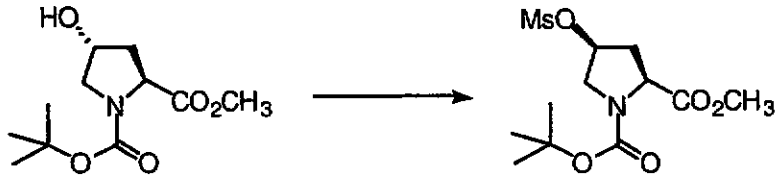
Step 1



xx **xxi**

To a cold (0°C) solution of **xx** (20.0 g, 86.5 mmol) in benzene (300 mL) and MeOH (50 mL) was added trimethylsilyl diazomethane (2M in hexanes, 56 mL, 112 mmol) dropwise till the solution remained yellow. The reaction mixture was concentrated to provide 21 g of **xxi** (99% yield) which was pure enough to be carried further. HRMS (FAB) Calcd for $C_{11}H_{20}NO_5$: 246.1341 $(M+H)^+$. Found: 246.1347.

Step 2

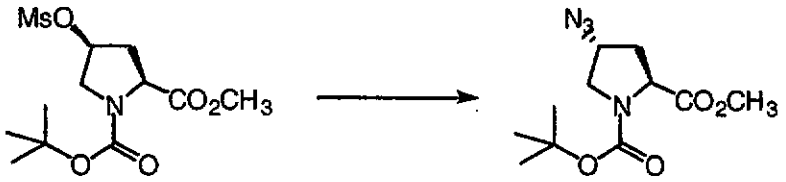


xxi **xxii**

To a cold (~5°C) mechanically stirred mixture of triphenylphosphine (31.97 g, 121.9 mmol) and methanesulfonic acid (7.66 mL, 118.1 mmol) in toluene was added DEAD (26.47 g, 152 mmol) slowly while maintaining the reaction temperature below 35°C. After the addition was complete, the reaction mixture was cooled to 20°C and a solution of **xxi** (23.71 g, 96.8 mmol) in toluene was added followed by triethylamine (5.39 mL, 38.7 mmol). The mixture was heated to 70-75°C for 6 hrs and cooled to 5-10°C for 1 hr. All the solid material were filtered off and the filtrate was washed with 5% KH_2PO_4 solution and brine. The organic layer was dried (Na_2SO_4), and concentrated. Flash column chromatography of the residue using 95/5 dichloromethane/EtOAc provided 26 g

of **xxii** (83% yield). HRMS (FAB) Calcd for $C_{12}H_{22}NO_7S$: 324.1117 $(M+H)^+$. Found: 324.1115.

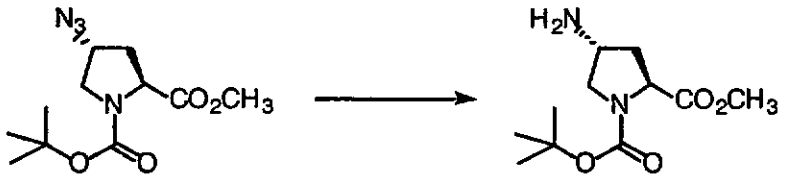
Step 3



xxii **xxiii**

The mesylate **xxii** (26 g, 80.4 mmol) was dissolved in DMF and all the volatiles were evaporated *in vacuo*. (CAUTION: Trace amounts of dichloromethane must be removed by this process). To the remaining solution was added sodium azide (5.75 g, 88.4 mmol) and warmed to 70°C over 5 hrs. The reaction mixture was cooled, diluted with EtOAc and washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to afford 18 g (83% yield) of **xxiii** which was sufficiently pure for further studies.

Step 4

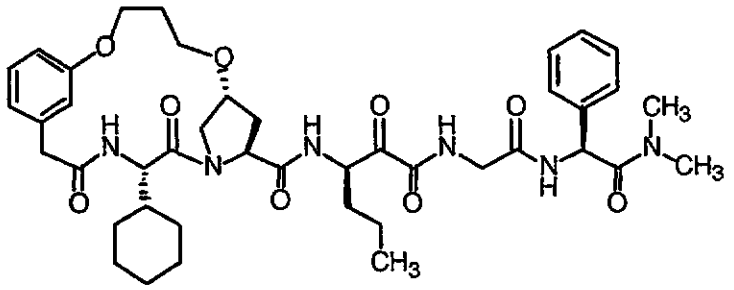


xxiii **F**

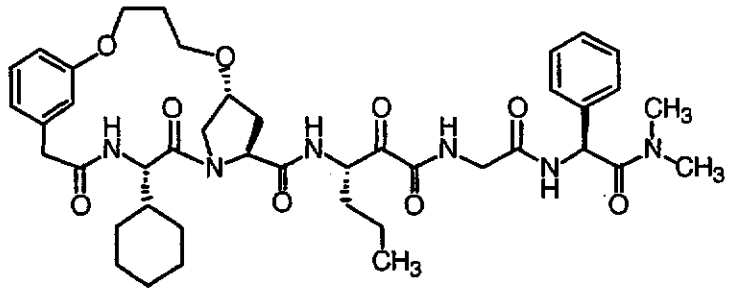
The desired product **F** was obtained by the procedure described for Intermediate **A**, Step 5. The crude material was used without further purification.

Examples

Example 1: Preparation of compounds of Formulas 1A and 1B:

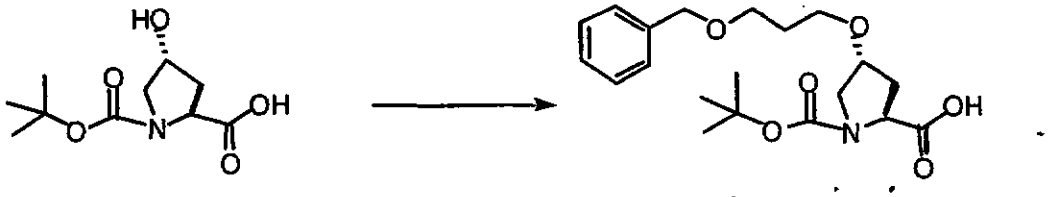


1A



1B

Step A:

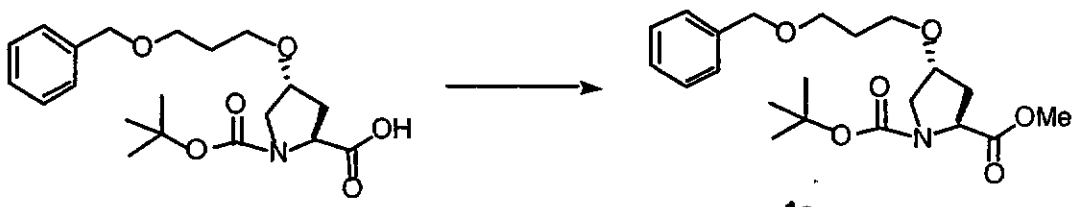


1a 1b

To a solution of Boc-Hyp-OH (7.0 g, 30.3 mmol) and benzyl 3-bromopropyl ether (7.8 g, 34.0 mmol) in anhydrous DMF (400 mL) at room temperature was added sodium hydride (3.5 g, 60% dispersion in mineral oil, 87.5 mmol) and sodium iodide (0.5 g, 3.33 mmols) with stirring. The resulting suspension was vigorously stirred at room temperature overnight (18 h). The reaction was

quenched carefully with a slow addition of water (50 mL) and acidified with 6 N HCl solution (20 mL). After addition of ethyl acetate (800 mL), brine (150 mL) and more water (150 mL), the formed two layers were separated and the organic layer was washed with 5% H_3PO_4 (3X200 mL). It was then dried with $MgSO_4$, filtered and concentrated in vacuo to afford **1b** as an oil which was used in Step B without further purification.

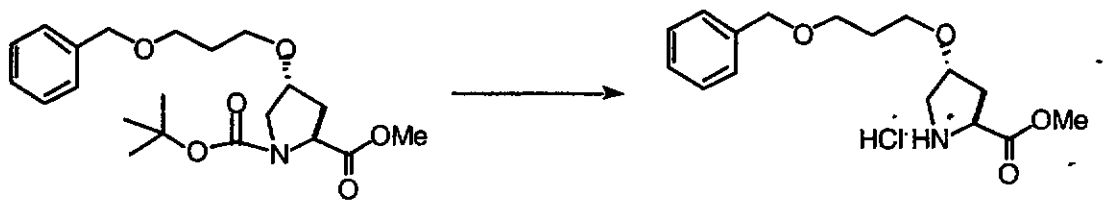
Step B:



1b **1c**

The acid **1b** from Step A was dissolved in benzene (25 mL) and methanol (28 mL). To this solution at room temperature was added a solution of trimethylsilyl diazomethane (27 mL, 2.0 M in cyclohexane) with caution. After being stirred at room temperature for 1 h, it was concentrated in vacuo to yield the methyl ester. Flash chromatography (8 to 20 % EtOAc-CH_2Cl_2) afforded **1c** (5.15 g; 13.1 mmol, 43%, 2 steps) as an oil.

Step C:

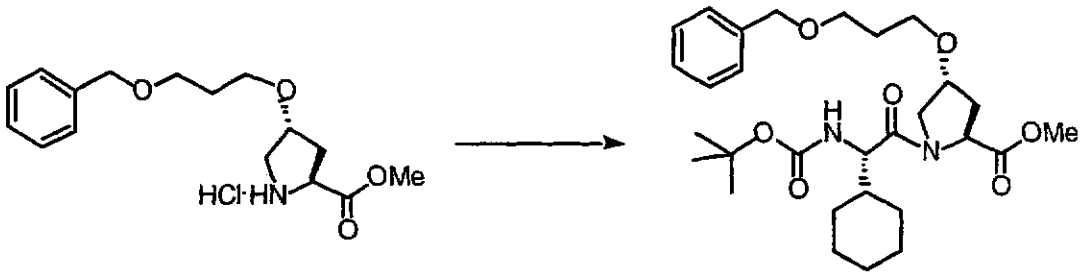


1c **1d**

The Boc-amino methyl ester **1c** (5.83 g, 14.8 mmol) was dissolved in 4 N HCl in dioxane (80 mL, 320 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 5 h, the

solution was concentrated in vacuo and the residue was kept under vacuum overnight to yield a white solid which was used in the next coupling reaction without further purification.

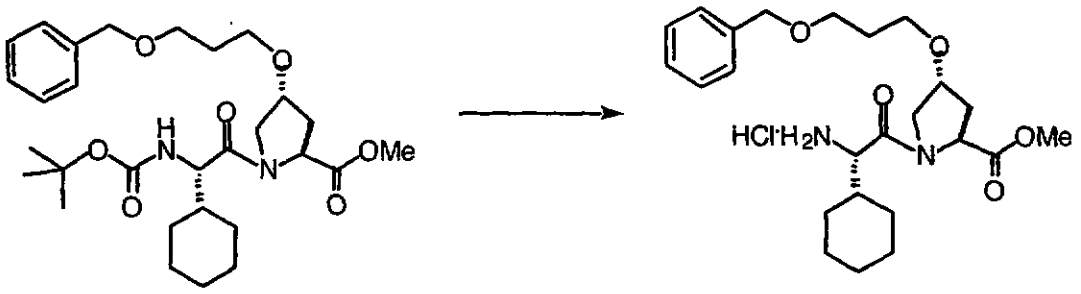
Step D:



1d **1e**

To a solution of the amine ester **1d** (from Step 1B), *N*-Boc-cyclohexylglycine (4.10 g, 14.9 mmol), HOOBt (2.60 g, 15.9 mmol) and EDCI (3.41 g, 17.8 mmol) in anhydrous DMF (150 mL) and CH_2Cl_2 at -20°C, was added NMM (6.50 mL, 59.1 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1h. EtOAc (450 mL), brine (100 mL) and 5% H_3PO_4 (100 mL) were added. The separated organic solution was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (10 to 20 % EtOAc-CH_2Cl_2) afforded **1e** (6.60 g, 84% 2 steps) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.36-7.25 (m, 5 H), 6.87 (d, J = 8.9 Hz, 1 H), 4.46-4.40 (m, 2 H), 4.25 (t, J = 8.3 Hz, 1 H), 4.11 (s, 1 H), 4.05-4.04 (m, 1 H), 4.03-3.94 (m, 1 H), 3.60 (s, 3 H), 3.50-3.41 (m, 4 H), 2.25-2.20 (m, 1 H), 1.95-1.88 (m, 1 H), 1.77-1.55 (m, 9 H), 1.35 (s, 9 H), 1.19-0.90 (m, 4 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.0, 170.7, 155.6, 138.8, 128.2, 127.4, 127.3, 78.0, 77.1, 71.9, 66.6, 65.1, 57.4, 56.3, 51.8, 34.5, 29.6, 28.6, 28.2, 25.9, 25.6, 25.5.

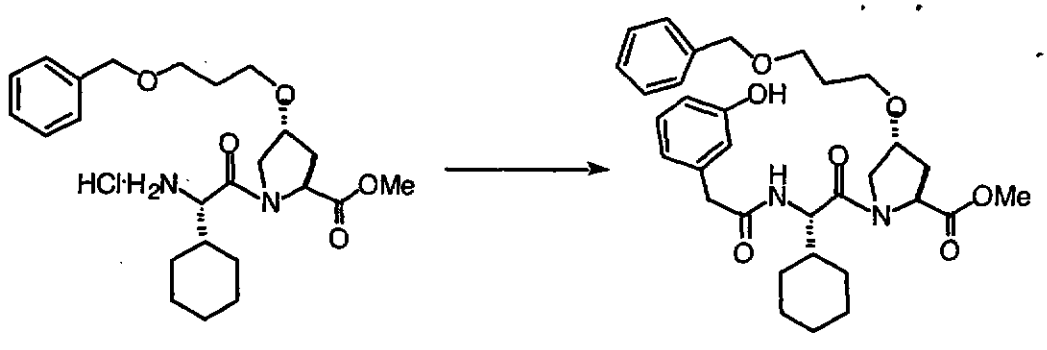
Step E:



1e 1f

The Boc-amino methyl ester **1e** (6.53 g, 12.3 mmol) was dissolved in 4 N HCl (60 mL, 240 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 4 h, the solution was concentrated in vacuo and the residue was kept under vacuum overnight to give a white solid which was used in the next coupling reaction without further purification. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.36-7.27 (m, 5 H), 4.43 (s, 2 H), 4.35-4.31 (m, 1H), 3.88 (d, J = 11.7 Hz, 1 H), 3.62 (s, 3 H), 3.62-3.57 (m, 2 H), 3.53-3.41 (m, 3 H), 2.32-2.27 (m, 1 H), 1.97-1.91 (m, 1 H), 1.79-1.60 (m, 8 H), 1.17-1.07 (m, 5 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 171.5, 167.4, 138.6, 133.3, 129.1, 128.8, 128.2, 127.4, 77.1, 71.9, 66.5, 65.3, 57.8; 54.9, 52.4, 52.0, 34.0, 29.6, 27.7, 27.0, 25.6, 25.5, 25.48; HRMS *m/z* 433.2702 [calcd for $C_{24}H_{36}N_2O_5$, 433.2702].

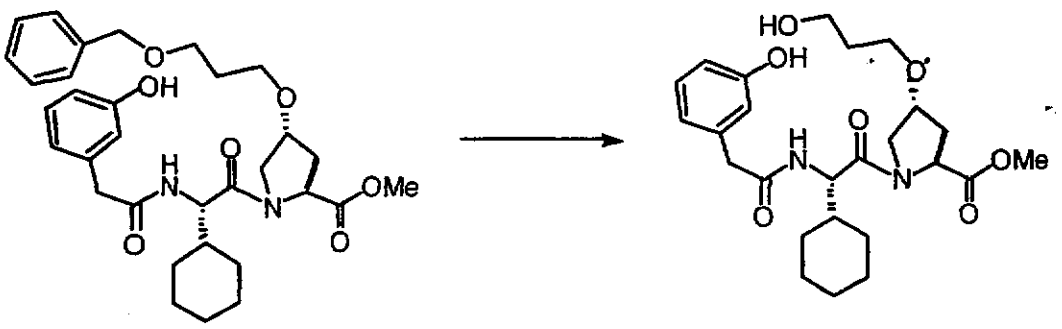
Step F:



1f 1g

To a solution of the amine **1f** (from Step 1D), 3-hydroxy phenylacetic acid (1.90 g, 12.5 mmol), HOOBt (2.10 g, 12.9 mmol) and EDCI (2.85 g, 14.9 mmol) in anhydrous DMF (250 mL) and CH_2Cl_2 (100 mL) at -20°C, was added NMM (4.20 mL, 38.2 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1h. EtOAc (500 mL), brine (100 mL) and 5% H_3PO_4 (100 mL) were added. The separated organic solution was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (10 to 20 % EtOAc-CH_2Cl_2) afforded **1g** (6.30 g, 11.1 mmol, 90 % (2 steps)) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 9.26 (s, 1 H), 8.19 (d, J = 8.5 Hz, 1 H), 7.36-7.25 (m, 5 H), 7.05-7.01 (m, 1 H), 6.66-6.64 (m, 1 H), 6.60-6.57 (m, 1 H), 4.46-4.39 (m, 2 H), 4.34 (t, J = 8.3 Hz, 1 H), 4.29-4.25 (m, 1 H), 4.09-4.08 (m, 1 H), 3.91 (d, J = 11.0 Hz, 1 H), 3.66-3.58 (m, 1 H), 3.61 (s, 3 H), 3.50-3.39 (m, 5 H), 3.30 (d, J = 13.7 Hz, 1 H), 2.24-2.18 (m, 1 H), 1.95-1.89 (m, 1 H), 1.74-1.57 (m, 8 H), 1.18-0.89 (m, 5 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.0, 170.3, 170.0, 157.1, 138.6, 137.6, 128.9, 128.2, 127.4, 127.3, 119.6, 116.1, 113.2, 76.9, 71.8, 66.6, 65.2, 57.4, 54.7, 51.9, 51.8, 41.8, 34.4, 29.6, 28.5, 28.0, 25.5, 25.5; HRMS *m/z* 567.3073 [calcd for $C_{32}H_{42}N_2O_7$, 567.3070].

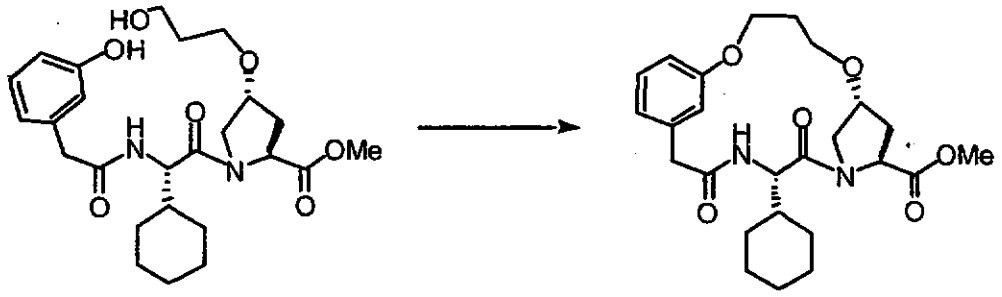
Step G:



1g **1h**

To a solution of the benzyl ether **1g** (6.23 g, 11.0 mmol) in ethanol (200 mL) under nitrogen at room temperature was added 10 % Pd-C (1.5 g) cautiously. The resulting suspension was vigorously stirred at room temperature under hydrogen for 23 h. After careful filtration, the solution was concentrated in vacuo. Flash chromatography (2 to 5 % MeOH-CH_2Cl_2) afforded **1h** (4.54 g, 9.52 mmol, 87 %) as a colorless oil. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.26 (s, 1 H), 8.22 (d, *J* = 8.6 Hz, 1 H), 7.06-7.02 (m, 1 H), 6.66-6.58 (m, 3 H), 4.42-4.40 (m, 1 H), 4.35-4.31 (s, 1 H), 4.27 (t, *J* = 8.3 Hz, 1 H), 4.10-4.09 (m, 1 H), 3.92 (d, *J* = 11.2 Hz, 1 H), 3.64 (dd, *J* = 11.2, 4.3 Hz, 1 H), 3.61 (s, 3 H), 3.59-3.43 (m, 5 H), 3.40-3.38 (m, 1 H), 2.26-2.21 (m, 1 H), 1.97-1.90 (m, 1 H), 1.74-1.55 (m, 8 H), 1.18-0.89 (m, 5 H) ; ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.0, 170.3, 170.1, 157.1, 137.6, 129.0, 119.6, 116.0, 113.3, 76.9, 65.2, 57.6, 57.4, 54.8, 51.9, 51.8, 41.7, 34.4, 32.6, 28.5, 28.0, 25.9, 25.52, 25.49; HRMS *m/z* 477.2606 [calcd for $C_{25}H_{36}N_2O_7$, 477.2601].

Step H:

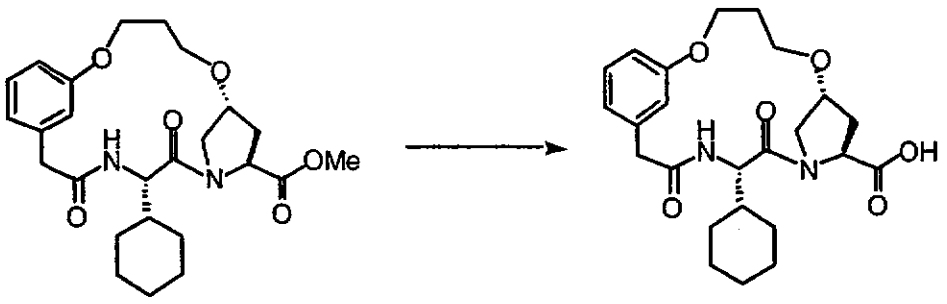


1h **1i**

A solution of the phenol alcohol **1h** (4.50 g, 9.43 mmol) and ADDP (6.60 g, 26.2 mmol) in anhydrous CH_2Cl_2 was bubbled with argon through a frit glass bubbler for 20 min. To this solution at 0°C was added triphenylphosphine (4.10 g, 16.3 mmol). After stirring at 0°C for 20 min, a second portion of triphenylphosphine (3.40 g, 13.5 mmol) was added. The solution was then warmed to room temperature and stirred overnight (24 h) under nitrogen until TLC indicated the complete consumption of the starting material. After removal of solvent in vacuo, the residue was partially purified by flash chromatography (1 to

2 % MeOH in CH_2Cl_2) to afford a mixture of the macrocycle **1i** and triphenylphosphine oxide. ^1H NMR (400 MHz, d_6-DMSO) δ 8.47 (d, J = 9.7 Hz, 1 H), 7.17-7.13 (m, 1 H), 6.79 (s, 1 H), 6.73 (d, J =1.8 Hz, 1 H), 6.71 (d, J =1.8 Hz, 1 H), 4.50-4.45 (m, 1 H), 4.24 (dd, J = 10.3, 7.6 Hz, 1 H), 4.17-4.06 (m, 4 H), 3.68 (d, J = 15.1 Hz, 1 H), 3.63 (s, 3 H), 3.60-3.51 (m, 2 H), 3.37 (d, J = 15.1 Hz, 1 H), 3.35-3.27 (m, 1 H), 2.51-2.43 (m, 1 H), 1.85-1.47 (m, 9 H), 1.22-1.12 (m, 3 H), 0.97-0.88 (m, 2 H) ; ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.0, 170.0, 169.8, 158.4, 138.1, 129.1, 121.8, 115.4, 112.2, 77.0, 64.9, 63.6, 57.0, 54.3, 53.4, 51.8, 41.3, 33.2, 28.9, 28.5, 28.2, 26.0, 25.2; HRMS *m/z* 459.2495 [calcd for $C_{25}H_{34}N_2O_6$, 459.2495].

Step I:

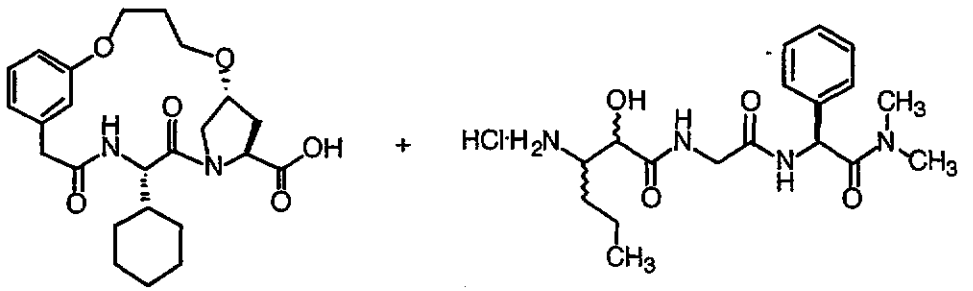


1i **1j**

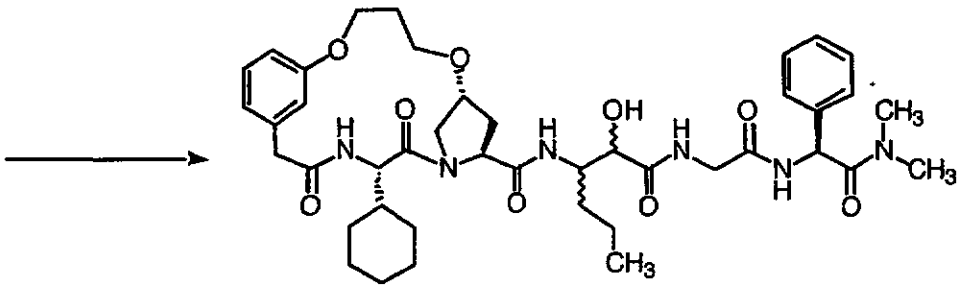
An aqueous lithium hydroxide solution (0.45 g in 30 mL H_2O) was added to a 0°C solution of the methyl ester **1i** in THF (30 mL) and methanol (30 mL). The mixture was stirred in an ice bath and warmed to room temperature along with it in 4 h. The progress of the reaction was monitored by TLC. After the volatiles were removed in vacuo, EtOAc (150 mL) and water (30 mL) were added and the two layers separated. The aqueous solution was extracted again with CH_2Cl_2 (150 mL), after which it was acidified to pH = 1. EtOAc (200 mL) was then added and the aqueous solution was saturated with solid sodium chloride. After separation of the layers, the aqueous layer was extracted with EtOAc (2 X 150 mL). Organic solutions were combined, dried with magnesium sulfate, filtered and concentrated in vacuo to afford **1j** (1.45 g, 3.26 mmol, 35 %, 2 steps) as a pale

yellow foam. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.32 (bs, 1 H), 8.45 (d, J = 9.5 Hz, 1 H), 7.17-7.13 (m, 1 H), 6.73-6.70 (m, 1 H), 6.79 (s, 1 H), 6.73-6.70 (m, 2 H), 4.47 (t, J =9.7 Hz, 1 H), 4.17-4.00 (m, 5 H), 3.68 (d, J = 15.1 Hz, 1 H), 3.58-3.45 (m, 2 H), 3.39-3.21 (m, 2 H), 2.47-2.41 (dd, J = 13.4, 7.6 Hz, 1 H), 1.85-1.56 (m, 9 H), 1.19-1.11 (m, 3 H), 0.93-0.87 (m, 2 H) ; ^{13}C NMR (100 MHz, d_6-DMSO) δ 173.2, 170.2, 170.0, 158.4, 138.1, 129.3, 122.0, 115.5, 112.2, 77.3, 65.1, 63.8, 57.3, 54.2, 53.7, 41.5, 33.6, 29.0, 28.6, 28.4, 26..1, 25.4; HRMS *m/z* 445.2335 [calcd for $C_{24}H_{32}N_2O_6$, 445.2339].

Step J:



1j A

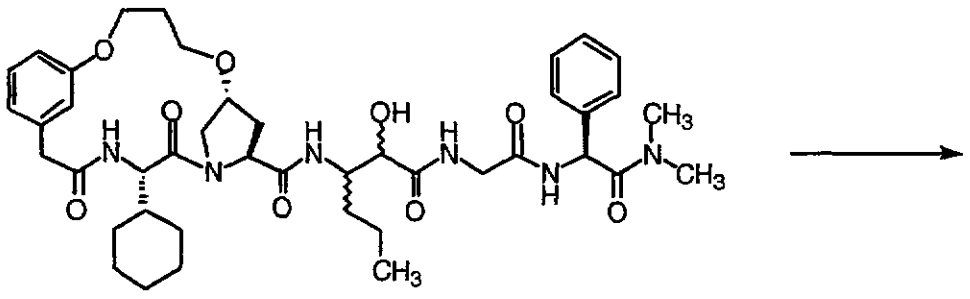


1k

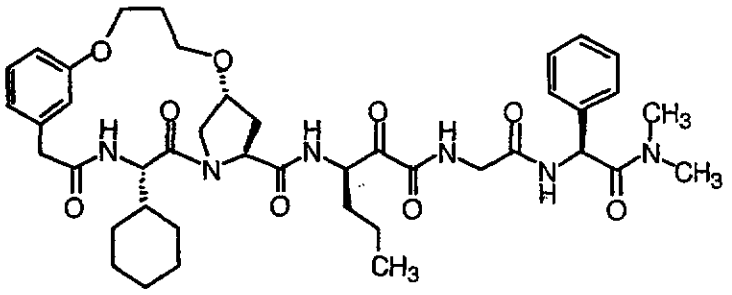
To a solution of the acid **1j** (0.59 g, 1.33 mmol), amine **A** (H_2N-NVa-CH(OH)-CO-Gly-Phg-NMe_2, 0.55 g, 1.37 mmol), HOOBt (250 mg, 1.53 mmol) and EDCI (315 mg, 1.64 mmol) in anhydrous DMF (50 mL) and CH_2Cl_2 (50 mL) at -20°C was added NMM (0.50 mL, 4.55 mmol). After stirred at this temperature for 30 min, the reaction mixture was kept in a freezer for 40 h. Then EtOAc (200

mL), brine (50 mL) and 5% H_3PO_4 (50 mL) were added. The separated organic solution was washed, successively, with 5% H_3PO_4 (80 mL), saturated aqueous sodium bicarbonate solution (2 X 80 mL), water (80 mL), and brine (80 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (4 to 7.5 % MeOH-CH_2Cl_2) afforded **1k** as a mixture of four diastereomers (0.59 g, 0.75 mmol, 56%) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 8.54-8.35 (m, 2 H), 7.95-6.98 (m, 8 H), 6.79-6.77 (m, 1 H), 6.72-6.70 (m, 2 H), 5.96-5.73 (m, 2 H), 4.53-4.45 (m, 1 H), 4.35-3.61 (m, 11 H), 3.54-3.41 (m, 1 H), 3.40-3.22 (m, 1 H), 2.93-2.92 (m, 3 H), 2.84 (s, 3 H), 2.42-2.17 (m, 1 H), 1.87-1.55 (m, 10 H), 1.49-1.06 (m, 7 H), 0.98-0.75 (m, 5 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.1, 171.9, 171.8, 170.8, 170.7, 170.4, 170.4, 170.3, 170.0, 169.8, 169.7, 169.6, 169.2, 169.2, 167.9, 167.8. 167.8, 158.4, 158.3, 138.2, 138.15, 138.11, 138.07, 137.6, 137.50, 137.48, 129.1, 128.5, 128.3, 127.8, 127.7, 121.7, 121.6, 115.4, 115.3, 112.09, 112.07, 112.0, 111.9, 76.9, 76.8, 73.3, 72.1, 71.9, 64.9, 64.8, 63.2, 58.7, 58.5, 57.9, 57.8, 54.6, 54.5, 54.48, 53.8, 53.78, 53.7, 53.66, 53.0, 52.9, 51.0, 50.8, 50.7, 41.6, 41.5, 41.4, 41.3, 36.6, 35.3, 33.9, 33.86, 33.5, 32.9, 32.1, 29.9, 29.0, 28.9, 28.5, 28.4, 28.3, 26.0, 25.9, 25.3, 25.25, 25.2, 18.6, 18.56, 18.5, 13.8, 13.7; HRMS *m/z* 791.4339 [calcd for $C_{42}H_{58}N_6O_9$, 791.4344, error = 1 ppm].

Step K:

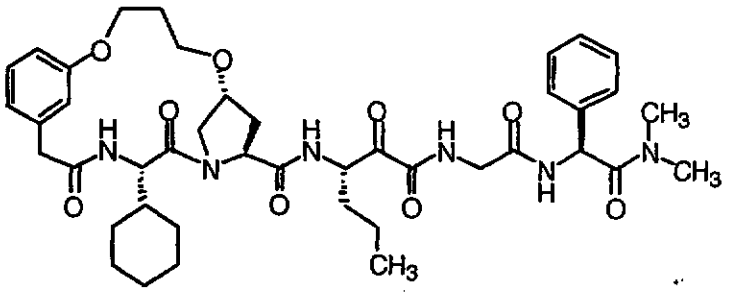


1k



1A

+

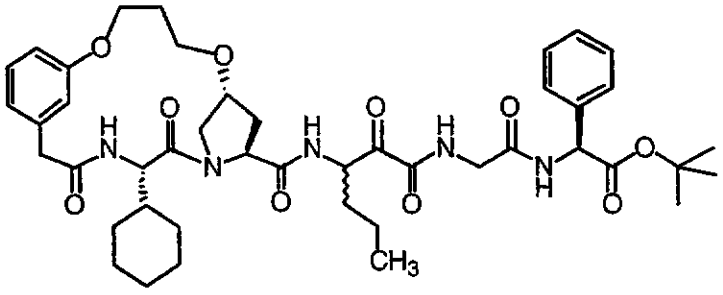


1B

To a mixture of the hydoxy amide **1k** (0.57 g, 0.72 mmol) and Des-Martin reagent (0.76 g, 1.8 mmol) at 0°C was added anhydrous CH_2Cl_2. The resulting white suspension was vigorously stirred at 0°C and warmed to room temperature along with the ice bath in 4 h. Saturated aqueous sodium bicarbonate and sodium bisulfite solutions (50 mL each) were added and the mixture was vigorously stirred for 10 min before layers were separated. The aqueous solution was extracted with (2 X 150 mL). Combined organic solution was dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (2

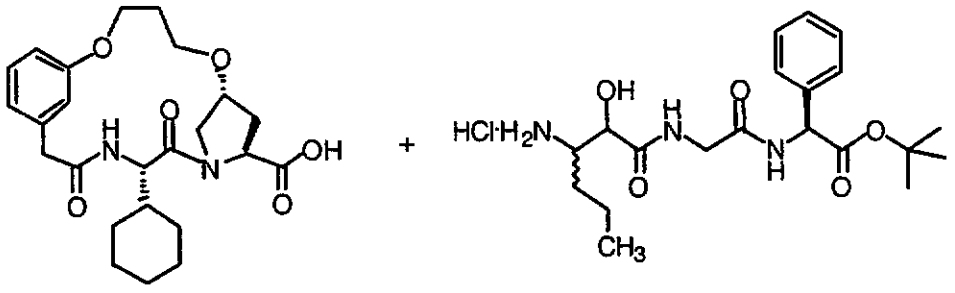
to 4 % MeOH-CH_2Cl_2) afforded two diastereomers **1A** (250 mg, 0.32 mmol) and **1B** (217 mg, 0.28 mmol, 82% combined yield) as white solids.

Example 2: Preparation of Compound 2:

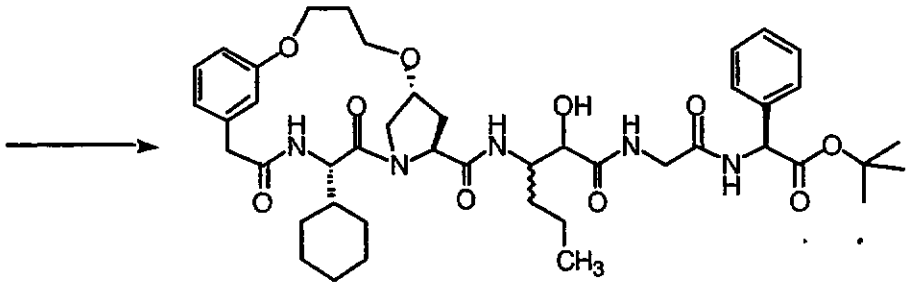


2

Step A:



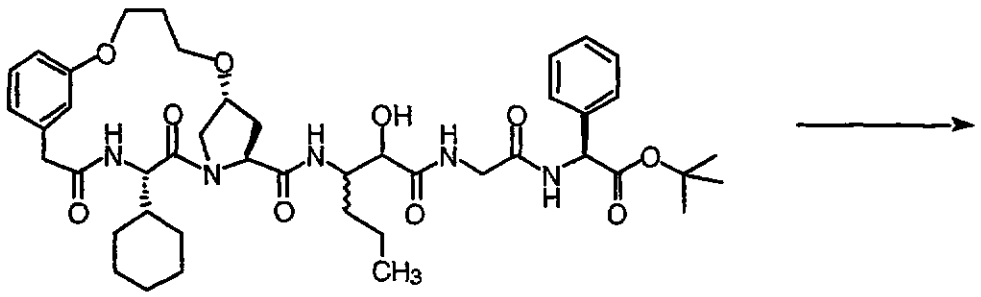
1j **B**



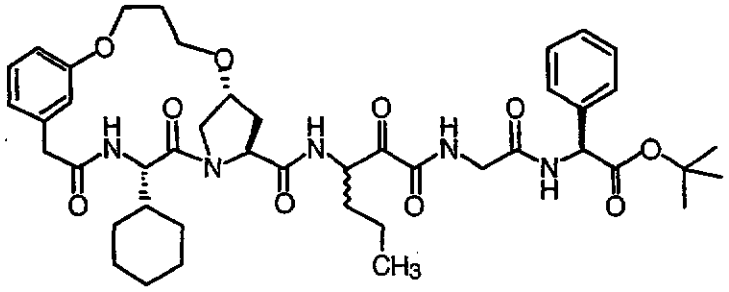
2a

The desired compound **2a** was prepared according to the method of Example 1, Step J, except for substituting the amine **B** for the amine **A**. The hydoxy amide was obtained as a mixture of inseparable diastereomers in the form of a white solid in 60 % yield.

Step B:



2a

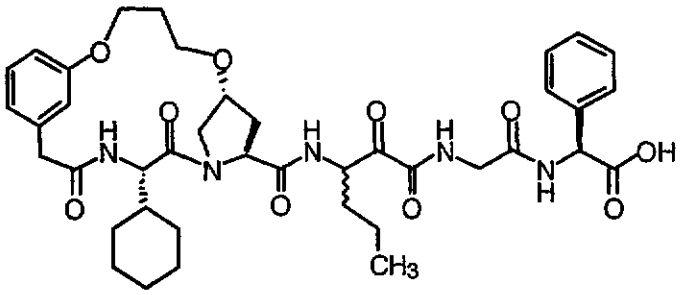


2

The desired ketoamide was prepared from the hydroxy amide **2a** according to the method of Example 1, Step K. The product was obtained as a mixture of inseparable diastereomers in the form of a white solid in 78 % yield. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.69-8.57 (m, 1 H), 8.45- 8.36 (m, 1 H), 7.95-7.72 (m, 1 H), 7.64-7.53 (m, 1 H), 7.41-7.31 (m, 5 H), 7.16-6.97 (m, 1 H), 6.79-6.70 (m, 3 H), 5.97-5.75 (m, 1 H), 5.31-5.27 (m, 1 H), 4.52-4.44 (m, 1 H), 4.35-3.61 (m, 11 H), 3.54-3.41 (m, 1 H), 3.39-3.21 (m, 1 H), 2.42-2.16 (m, 1 H), 1.85-1.54 (m, 9 H), 1.49-1.05 (m, 16 H), 0.95-0.70 (m, 5 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.3, 172.2, 172.0, 171.9, 170.9, 170.7, 170.5, 170.5, 170.4, 170.1, 169.9, 169.7, 169.5, 168.6, 168.5, 158.5, 158.4, 138.2, 138.2, 138.1, 136.7, 132.1, 131.6, 131.5, 129.2, 129.1, 128.8, 128.7, 128.1, 127.7, 127.6, 127.6, 127.5, 127.4, 127.4, 121.7, 116.4, 115.4, 115.4, 113.3, 112.1, 112.1, 112.0, 81.3, 77.0, 76.9, 76.9, 73.4, 72.3, 72.0, 64.9, 64.8, 63.3, 58.8, 56.9, 56.8, 54.7, 54.6, 54.6, 53.9, 53.9, 53.8, 51.1, 50.8, 41.6, 41.4, 41.3, 34.0, 33.9, 29.1, 29.0, 28.6, 28.5, 28.4,

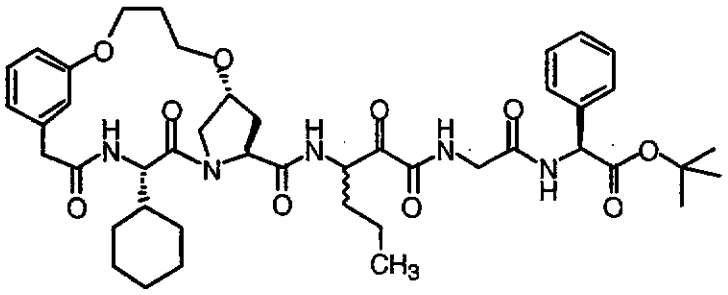
28.4, 28.3, 27.5, 26.0, 26.0, 25.4, 25.3, 25.2, 18.7, 18.6, 18.5, 13.9, 13.8; HRMS *m/z* 820.4493 [calcd for $C_{44}H_{61}N_5O_{10}$, 820.4497].

Example 3: Preparation of the Compound of Formula 3 below:

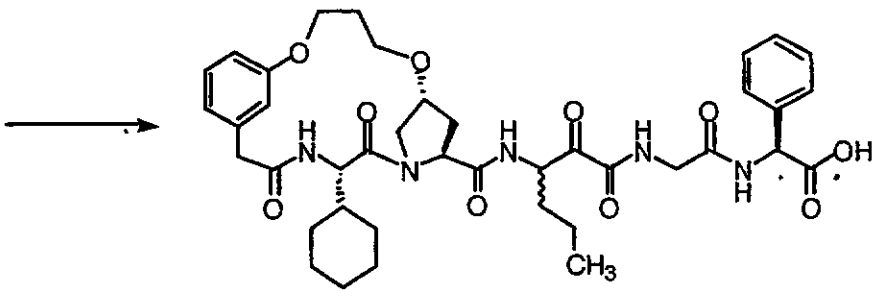


3

Step A:



2

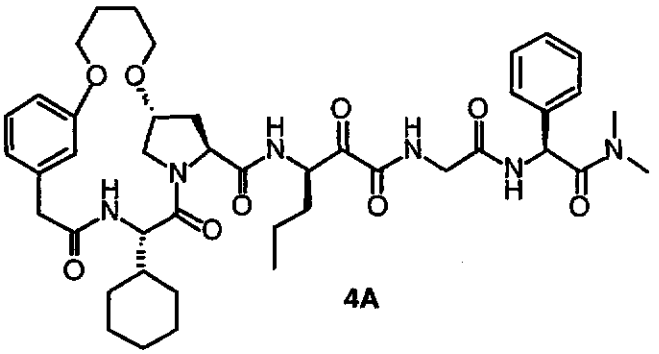


3

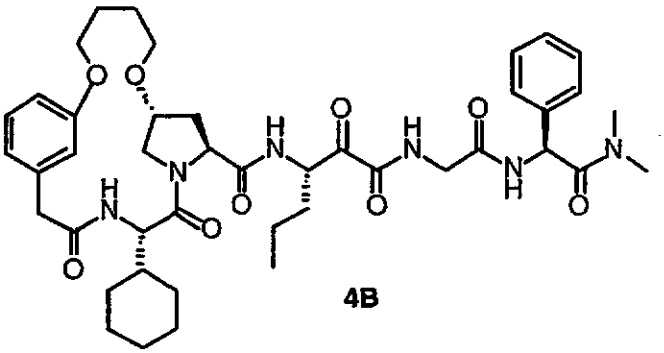
A solution of the *t*-Butyl ester **2** (26 mg, 0.032 mmol) in trifluoroacetic acid (2 mL) and CH_2Cl_2 (2 mL) was stirred at room temperature for 3 h. After the volatiles were removed in vacuo, the residue was dissolved in 50% MeOH-

CH_2Cl_2, and concentrated to dryness in vacuo to afford an off-white solid (24 mg, 0.032 mmol, quant.). ^1H NMR (400 MHz, d_6-DMSO) δ 8.73-8.65 (m, 2 H), 8.40 (dd, J = 9.5, 2.6 Hz, 1 H), 8.24-8.05 (1 H), 7.64-7.55 (m, 1 H), 7.41-7.32 (m, 5 H), 7.15 (t, J = 7.8 Hz, 1 H), 6.80-6.71 (m, 3 H), 5.35 (dd, J = 7.5, 1.9 Hz, 1 H), 5.04-4.96 (m, 1 H), 4.48-4.43 (m, 1 H), 4.37-4.22 (m, 1 H), 4.16-3.27 (m, 11 H), 2.35-2.31 (m, 1 H), 1.84-0.70 (m, 21 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 196.7, 171.7, 171.4, 171.3, 170.0, 169.7, 167.5, 161.0, 160.7, 158.5, 158.5, 158.4, 138.2, 138.2, 137.1, 137.0, 132.1, 132.1, 131.6, 131.5, 131.5, 129.2, 128.8, 128.7, 128.7, 128.6, 128.0, 127.7, 127.5, 127.5, 121.8, 115.4, 112.2, 76.9, 76.8, 65.0, 64.9, 63.4, 63.3, 58.2, 5 7.4, 56.3, 56.2, 56.2, 54.6, 54.5, 53.8, 53.4, 53.2, 41.5, 41.5, 41.4, 40.2, 33.9, 33.7, 31.9, 31.7, 29.2, 29.0, 28.6, 28.3, 26.1, 25.3, 18.7, 18.6, 13.5; HRMS *m/z* 762.3705 [calcd for $C_{40}H_{51}N_5O_{10}$, 762.3714].

Example 4: Preparation of Compounds of Formulas 4A and 4B:

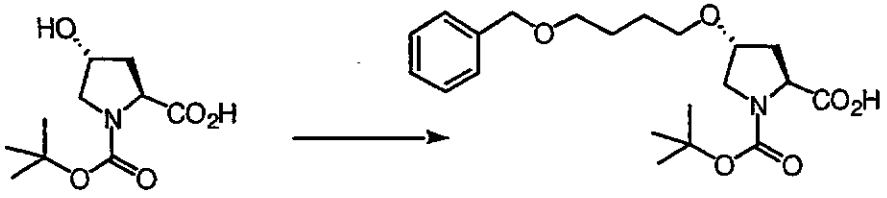


4A



4B

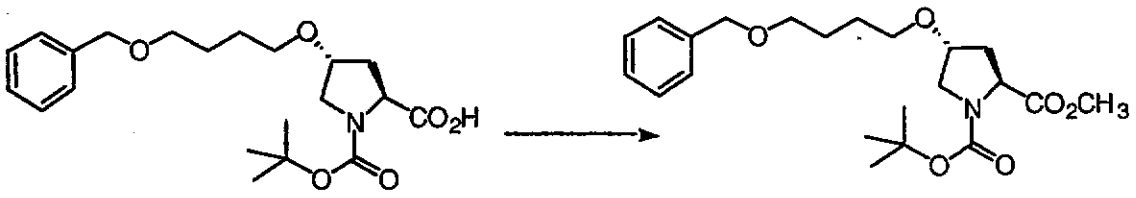
Step A:



1a 4a

The desired product **4a** was obtained by the method described for Example 1, Step A. The crude material was carried to the next step as it was.

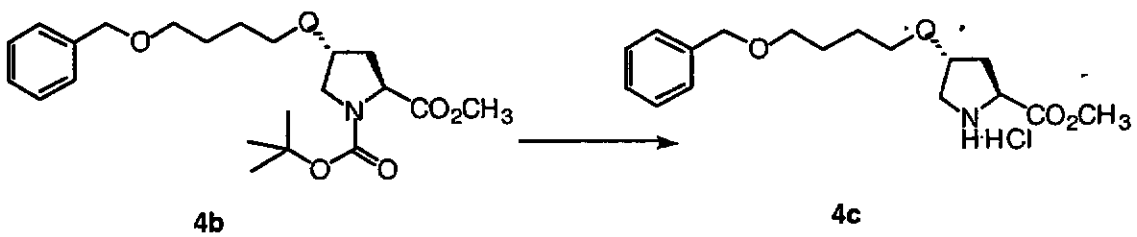
Step B:



4a 4b

The desired product **4b** was obtained by the method described for Example 1, Step B. The material was purified by flash column chromatography using 80/20 to 75/25 hexanes/ethyl acetate to provide **4b** in 50% yield as a colorless oil.

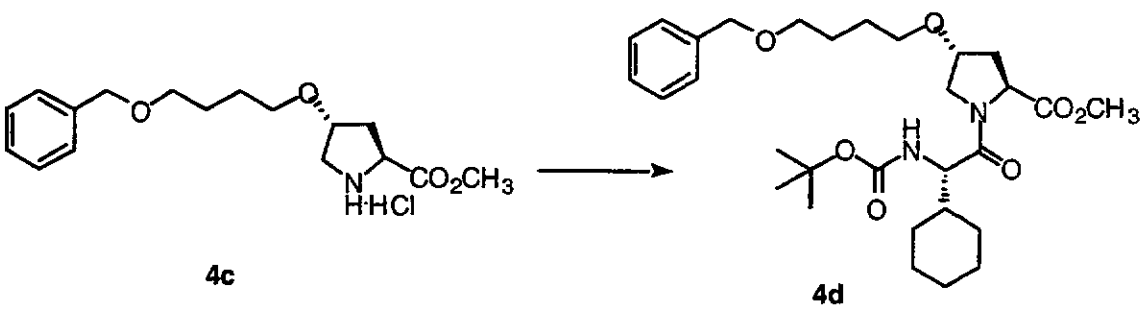
Step C:



4b 4c

The desired compound **4c** was prepared by the protocol described for Example 1, Step C. The material was carried forward as it was.

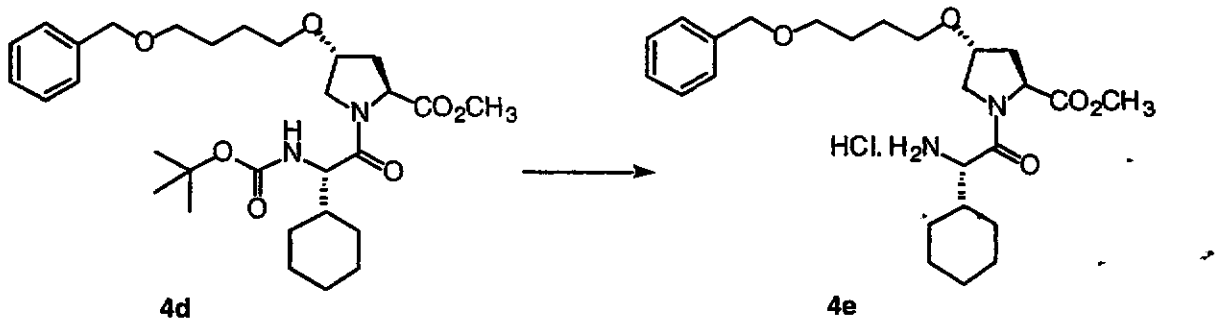
Step D:



4c **4d**

The desired product **4d** was obtained by the method described in Example 1, Step D. The material after work-up was sufficiently pure to be carried to the next step. HRMS (FAB) Calcd for $C_{30}H_{47}N_2O_7$: 547.3383 $(M+H)^+$. Found: 547.3372.

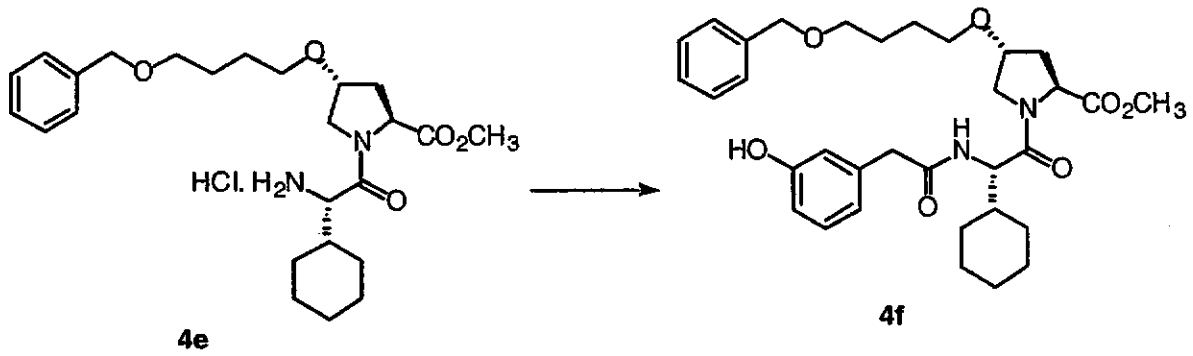
Step E:



4d **4e**

The desired product **4e** was obtained by the method described in Example 1, Step E. The crude material was carried to the next step as was.

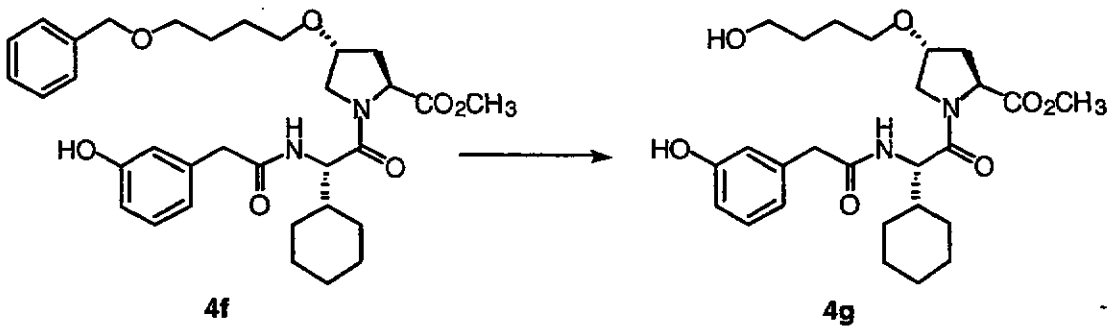
Step F:



4e 4f

The desired product **4f** was obtained by the method described in Example 1, Step F. The material was purified by flash column chromatography using 80/20 to 60/40 dichloromethane/ethyl acetate to provide **4f** in 85% yield. HRMS (FAB) Calcd for $C_{33}H_{45}N_2O_7$: 581.3227 $(M+H)^+$. Found: 581.3222.

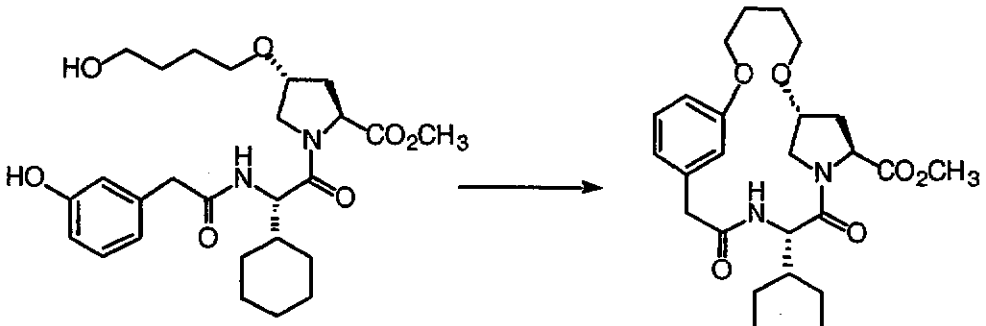
Step G:



4f 4g

The desired product **4g** was obtained by the method described in Example 1, Step G. The crude material was carried to the next step as was. HRMS (FAB) Calcd for $C_{26}H_{39}N_2O_7$: 491.2757 $(M+H)^+$. Found: 491.2761.

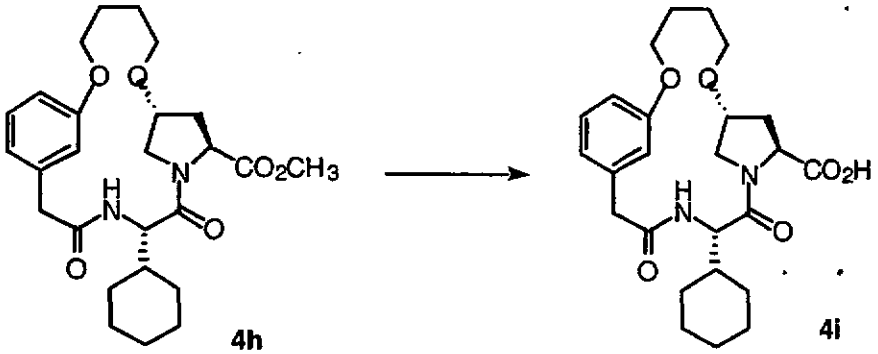
Step H:



4g 4h

The desired product **4h** was obtained by the method described in Example 1, Step H. Purification by column chromatography using 99/1 dichloromethane/methanol afforded **4h** along with triphenylphosphine oxide. This mixture was taken to the next step.

Step I:

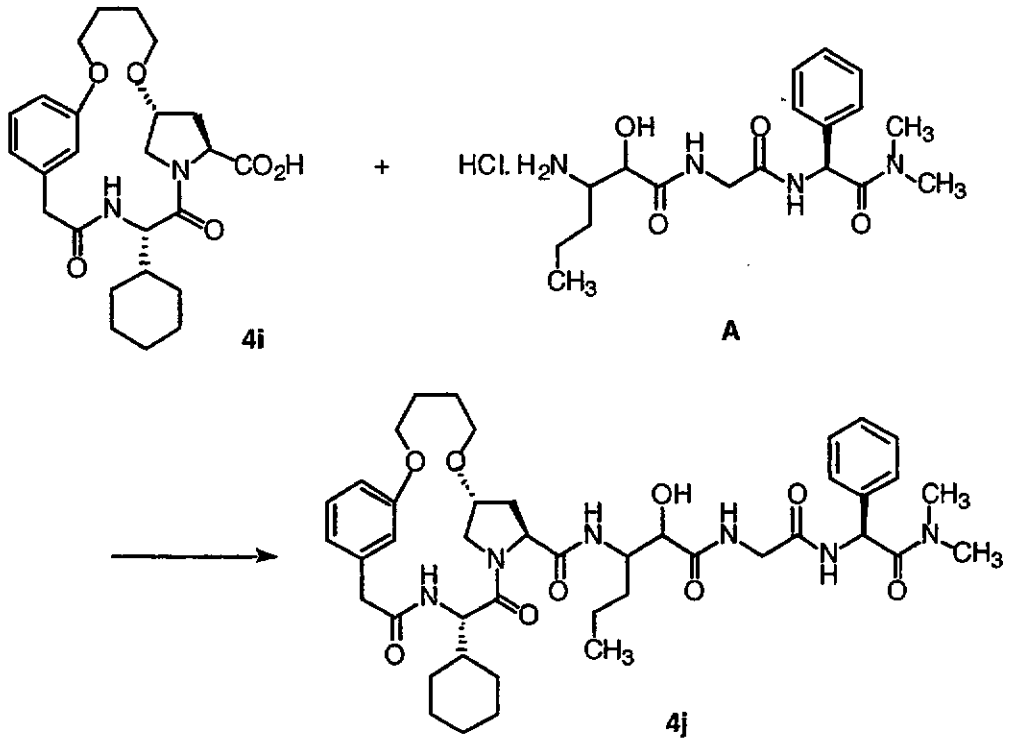


4h 4i

The desired product was obtained by the method described in Example 1 Step I. Yield of **4i** (for 2 steps) = 24%. ^{1}H NMR (DMSO-d_6) δ 0.90-0.95 (m, 2H), 1.10-1.16 (m, 3H), 1.51-1.79 (m, 11H), 2.43 (dd, 1H), 3.29-3.32 m, 2H), 3.50-3.54

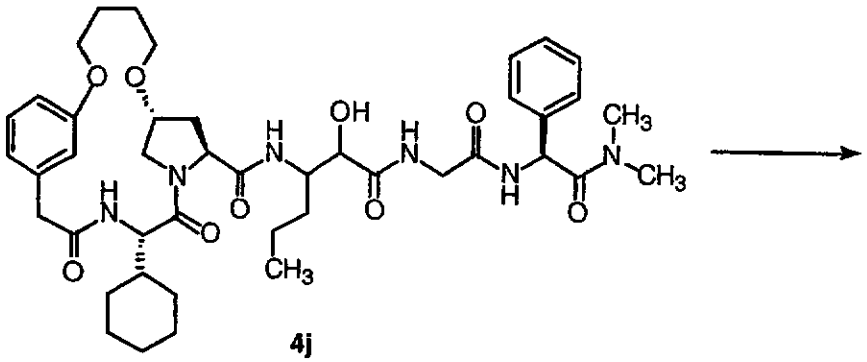
(m, 1H), 3.62-3.68 (m, 2H), 3.91-3.99 (m, 3H), 4.04-4.08 (m, 2H), 4.46 (t, 1H), 6.67-6.72 (m, 3H), 7.13 (app. t, 1H), 8.36 (d, 1H), 12.40 (br. s, 1H); ^{13}C NMR (DMSO-d_6) δ 25.26, 25.31, 25.97, 26.62, 28.42, 33.28, 39.75, 41.49, 53.50, 54.28, 57.45, 67.57, 67.98, 77.25, 111.07, 115.23, 121.48, 129.11, 137.99, 158.33, 170.07, 172.92; HRMS (FAB) Calcd for $C_{25}H_{35}N_2O_6$: 459.2495 $(M+H)^+$. Found: 459.2494.

Step J:

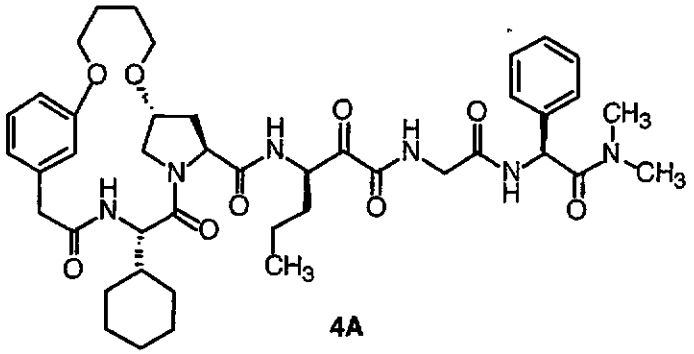


The expected product **4j** was synthesized as described earlier for the Example 1 Step J. The material after work-up was of sufficient purity to be carried forward to the next step. HRMS (FAB) Calcd for $C_{43}H_{61}N_6O_9$: 805.4500 $(M+H)^+$. Found: 805.4492.

Step K:

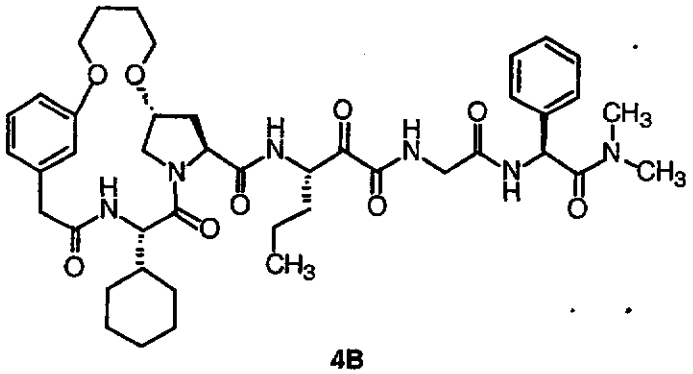


4j



4A

+

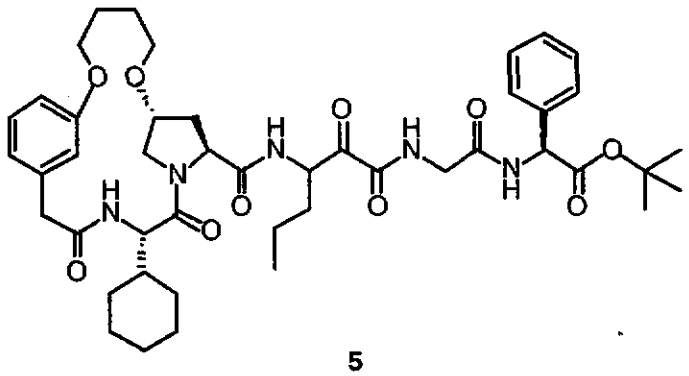


4B

The desired products **4A** and **4B** were obtained by the oxidation protocol described previously for Example 1 Step K. Purification by flash column chromatography using 100/0 to 99/1 dichloromethane/methanol afforded separate isomers **4A** and **4B**, and some mixture. Combined yield = 34% (for 2 steps).

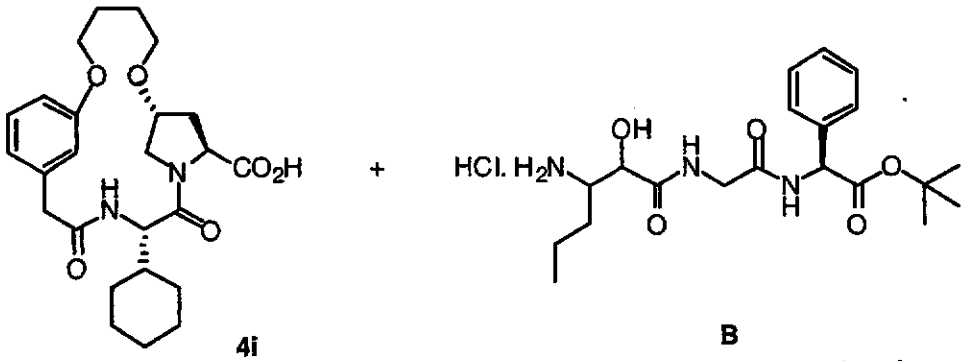
HRMS (FAB) Calcd for $C_{43}H_{59}N_6O_9$: 803.4344 $(M+H)^+$. Found: 803.4339 (**4A**), 803.4347 (**4B**).

Example 5: Preparation of Compound 5:

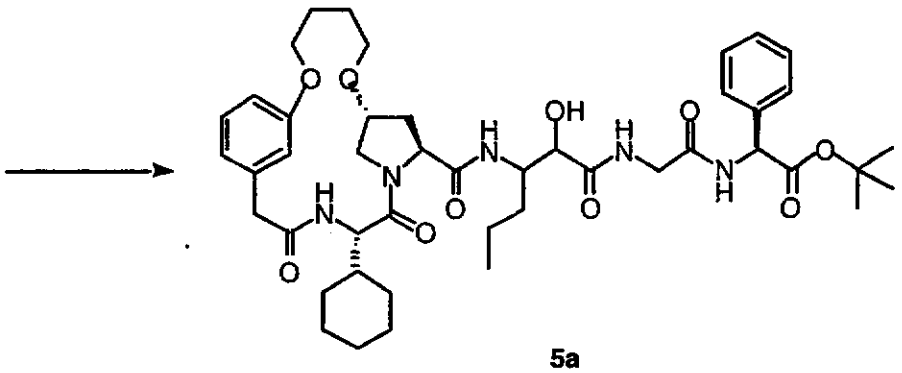


5

Step A:



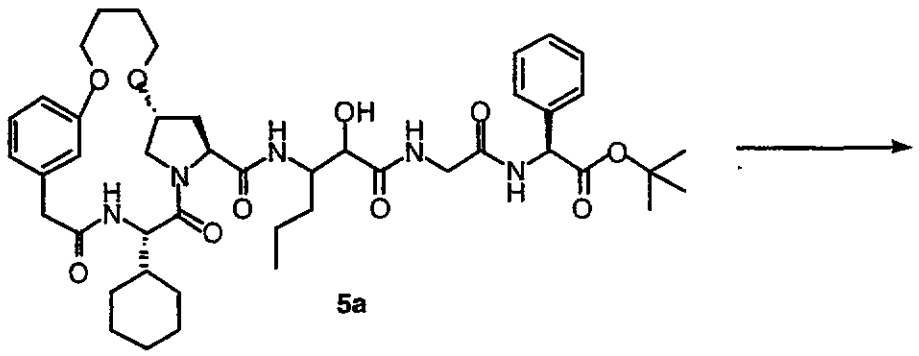
4i **B**



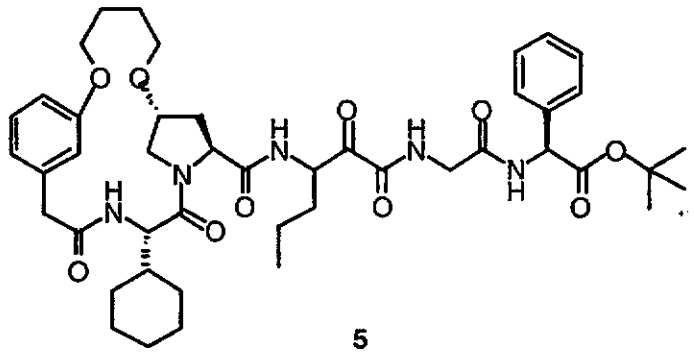
5a

The expected product **5a** was synthesized as described earlier for the Example 2, Step A. The material after work-up was of sufficient purity to be carried forward to the next step. HRMS (FAB) Calcd for $C_{45}H_{64}N_5O_{10}$: 834.4653 $(M+H)^+$. Found: 834.4648.

Step B:



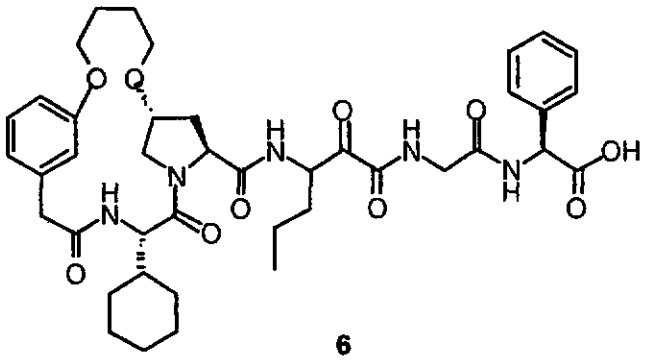
5a



5

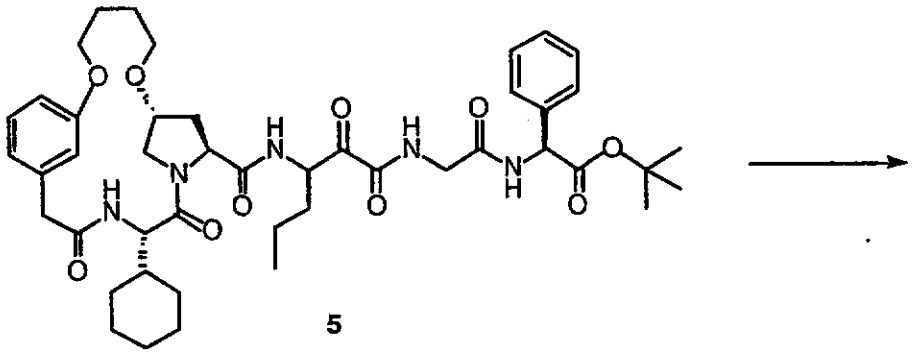
The desired product **5** was obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 99/1 dichloromethane/methanol afforded **5** as a mixture of diastereomers in 31% yield (for 2 steps). HRMS (FAB) Calcd for $C_{45}H_{62}N_5O_{10}$: 832.4497 $(M+H)^+$. Found: 832.4497.

Example 6: Preparation of Compound 6:

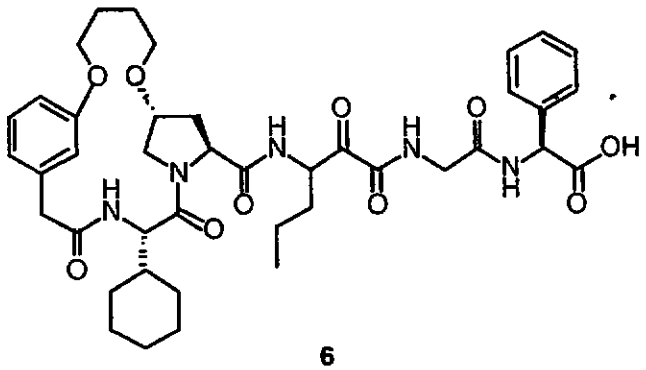


6

Step A:



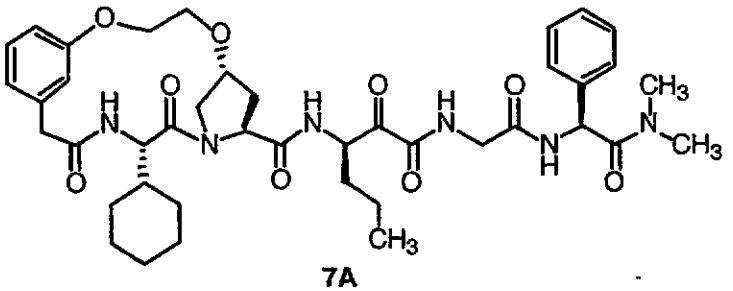
5



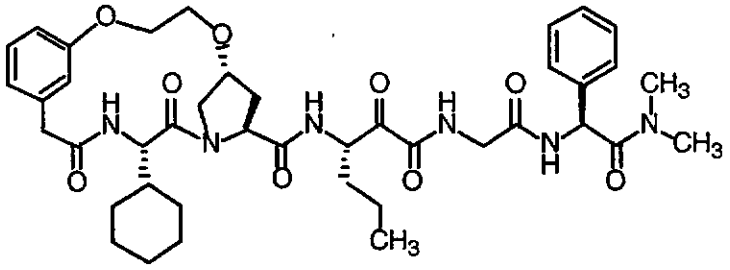
6

The expected product **6** was synthesized as described earlier for the Example 3, Step A in quantitative yield. HRMS (FAB) Calcd for $C_{41}H_{54}N_5O_{10}$: 776.3871 $(M+H)^+$. Found: 776.3865.

Example 7: Preparation of compounds 7A and 7B:

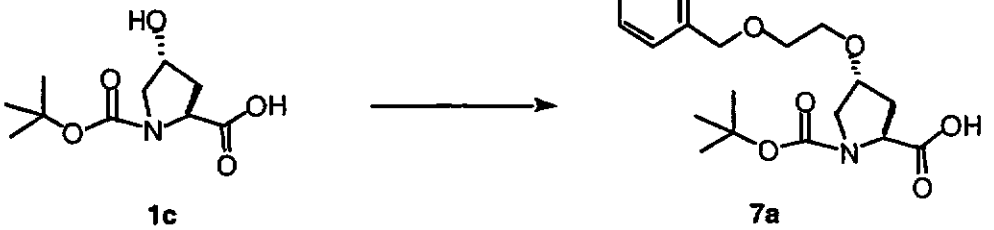


7A



7B

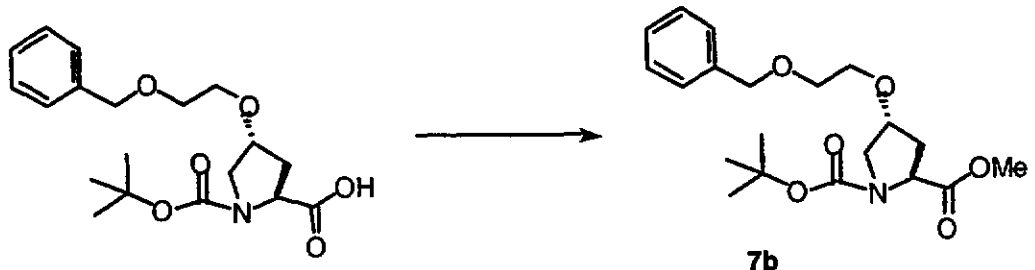
Step A:



1c **7a**

The desired compound **7a** was prepared from **1c** according to the procedure of Example 1, Step A. The crude product was used in Step B without further purification.

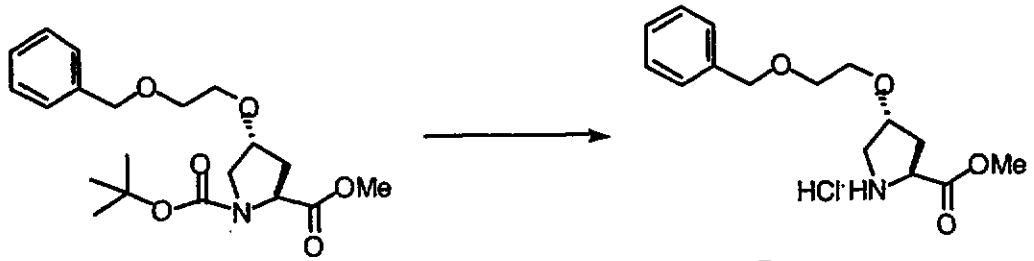
Step B:



7a 7b

The desired compound **7b** was prepared from **7a** according to the procedure of Example 1, Step B.

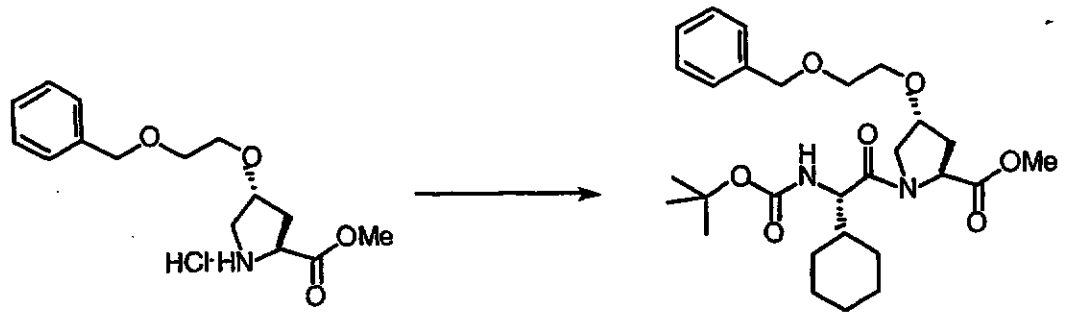
Step C:



7b 7c

The desired compound **7c** was prepared from **7b** according to the procedure of Example 1, Step C. The product was used in Step D without further purification.

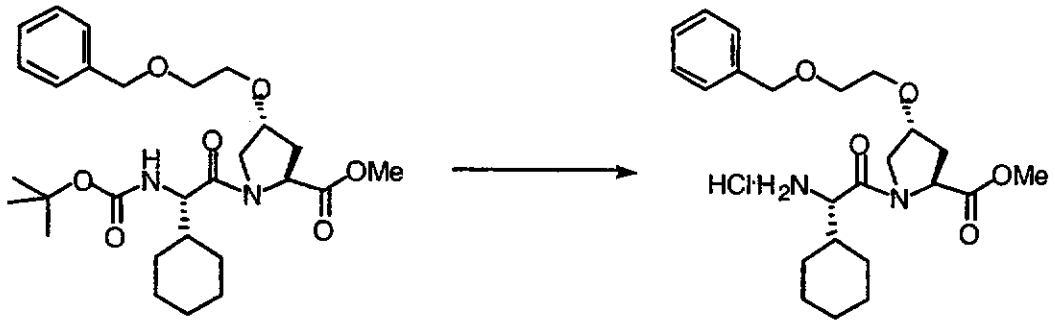
Step D:



7c 7d

The desired compound **7d** was prepared from **7c** according to the procedure of Example 1, Step D.

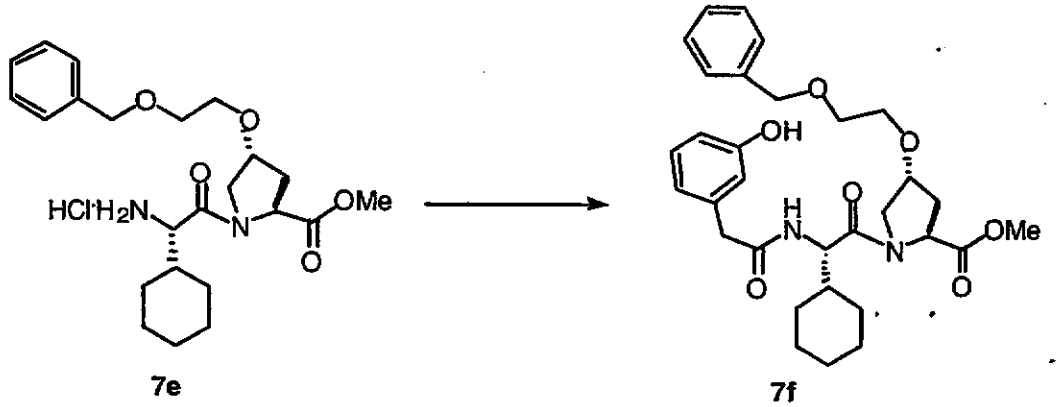
Step E:



7d **7e**

The desired compound **7e** was prepared from **7d** according to the procedure of Example 1, Step E. The product was used in Step F without further purification.

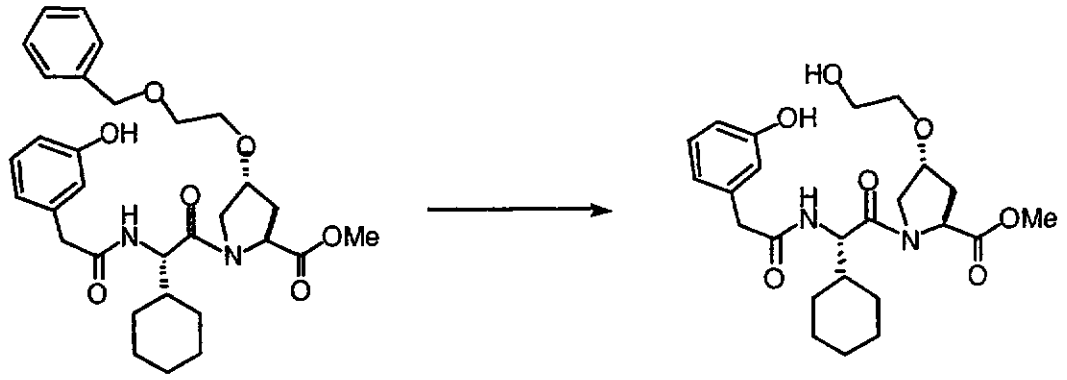
Step F:



7e **7f**

The desired compound **7f** was prepared from **7e** according to the procedure of Example 1, Step F.

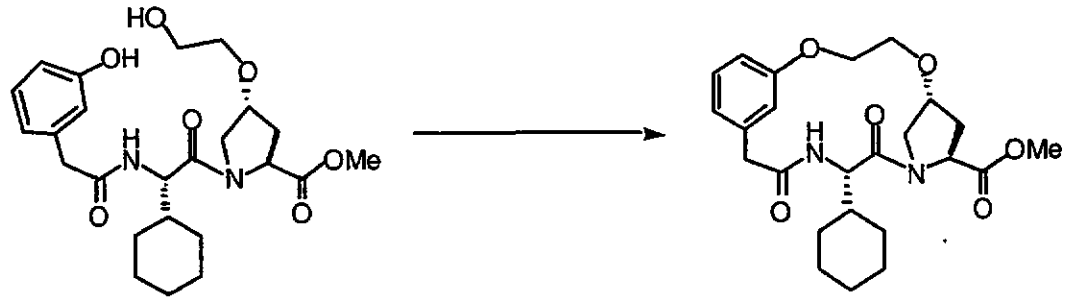
Step G:



7f 7g

The desired compound **7g** was prepared from **7f** according to the procedure of Example 1, Step F.

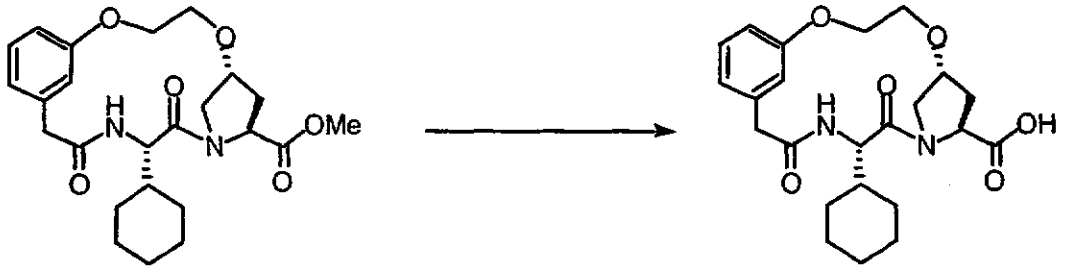
Step H:



7g 7h

A solution of the phenol alcohol **7g** (830 mg, 1.79 mmol) and ADDP (1.36 g, 5.39 mmol) in anhydrous CH_2Cl_2 (200 mL) was bubbled with Argon through a frit glass bubbler for 20 min. To this solution at 0°C was added triphenylphosphine (1.41 g, 5.38 mmol). After stirring at 0°C for 20 min, the solution was warmed to room temperature and stirred overnight (20 h) under nitrogen. After removal of solvent in vacuo, the residue was purified by flash chromatography (1 to 3 % MeOH in CH_2Cl_2) to afford a mixture of the desired product **7h** and triphenylphosphine oxide, which was used in Step I without further purification.

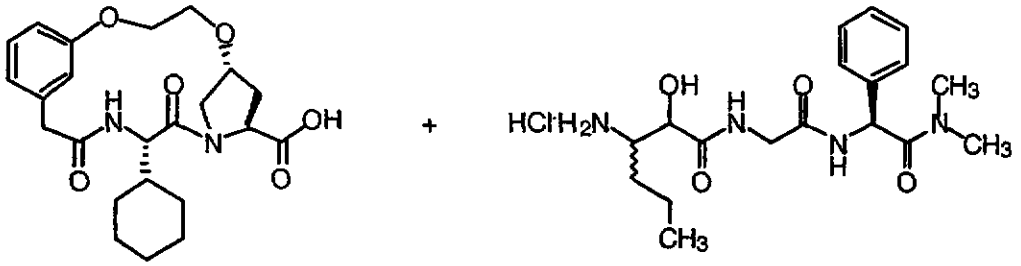
Step I:



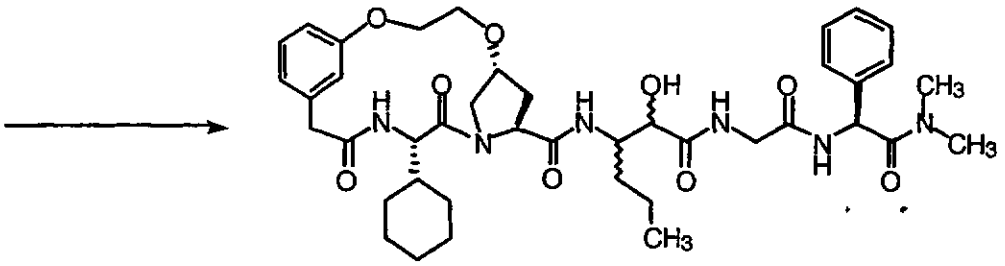
7h 7i

The desired compound **7i** was prepared from **7h** in 36 % yield (2 steps) according to the procedure of Example 1, Step I.

Step J:



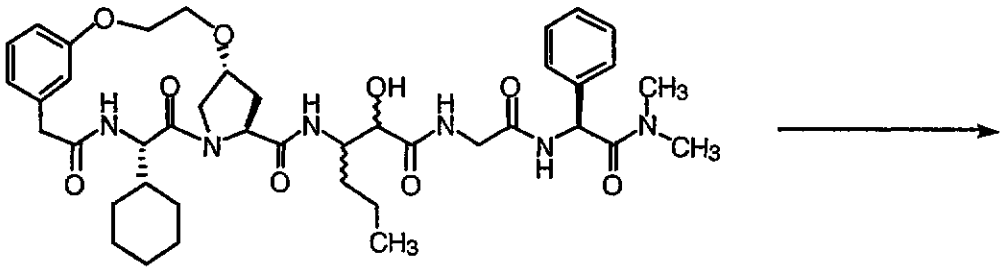
7i A



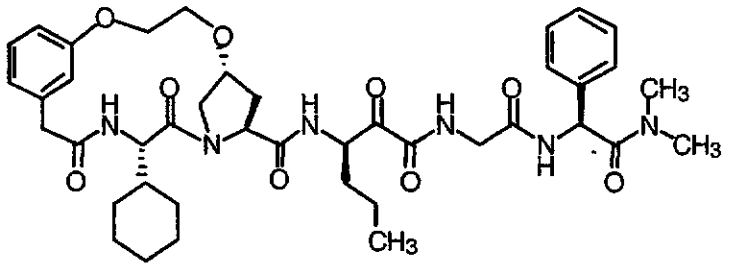
7j

The desired compound **7j** was prepared from **7i** and **A** in 56 % yield according to the procedure of Example 1, Step J.

Step K:

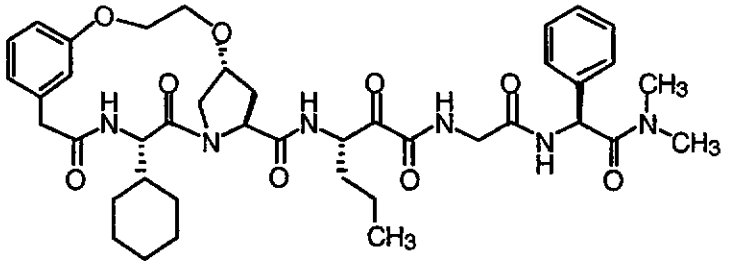


7j



7A

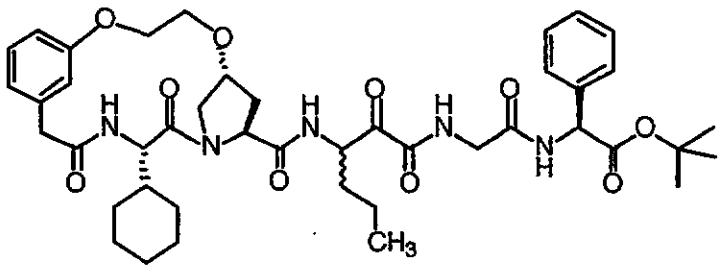
+



7B

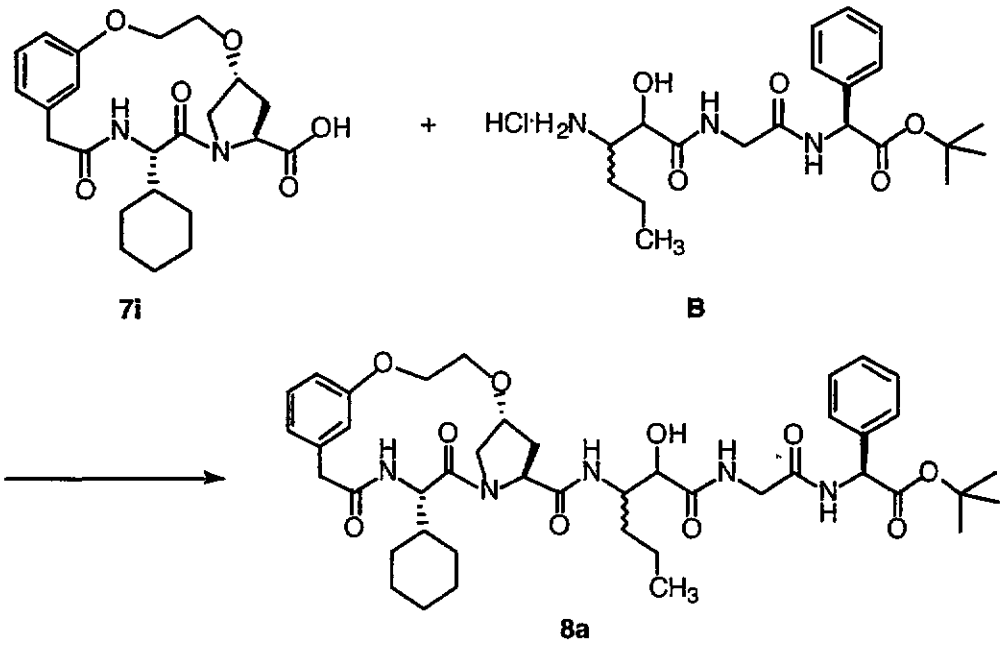
The desired compound **7A** and **7B** were prepared from **7j** according to the procedure of Example 1, Step K.

Example 8: Preparation of Compound of Formula 8:



8

Step A:

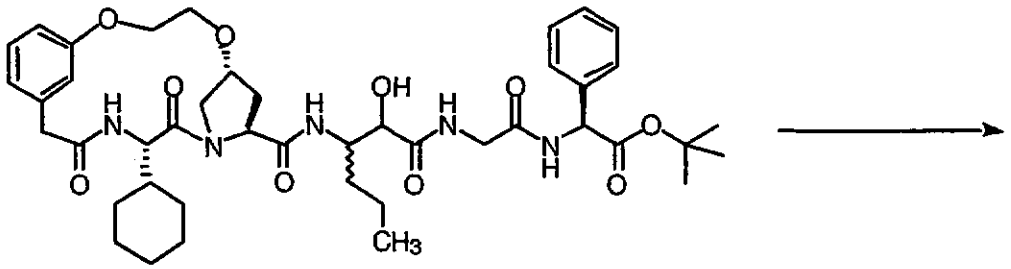


7i B

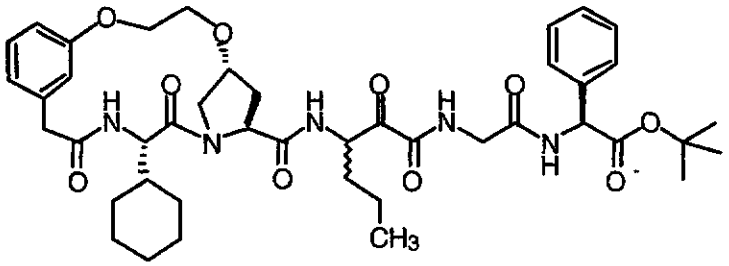
8a

The desired compound **8a** was prepared according to the method of Example 1, Step J, except substituting amine **B** for amine **A**. The product was obtained as a mixture of inseparable diastereomers in the form of a white solid in 57 % yield.

Step B:



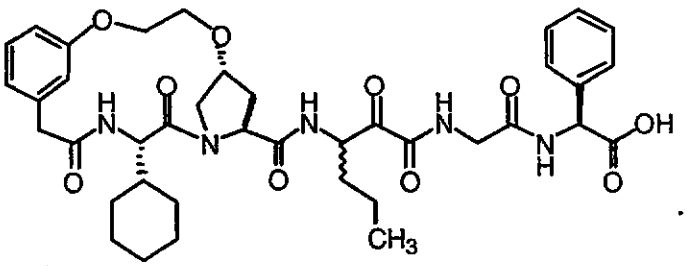
8a



8

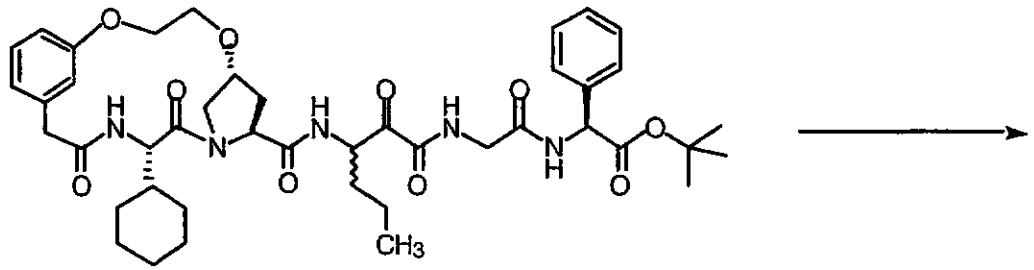
The desired compound **8** was prepared in 72 % yield from **8a** according to the method of Example 1, Step K.

Example 9: Preparation of Compound of Formula 9:

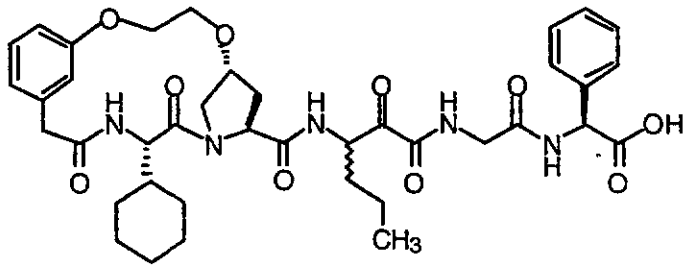


9

Step A:



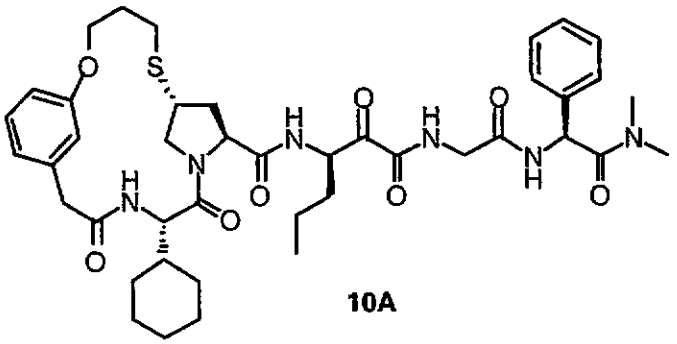
8



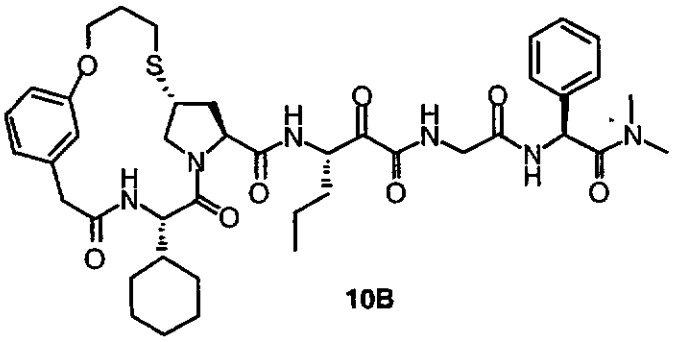
9

The desired compound **9** was prepared quantitatively from **8** according to the method of Example 3, Step A.

Example 10: preparation of Compounds of Formula 10A and 10B:

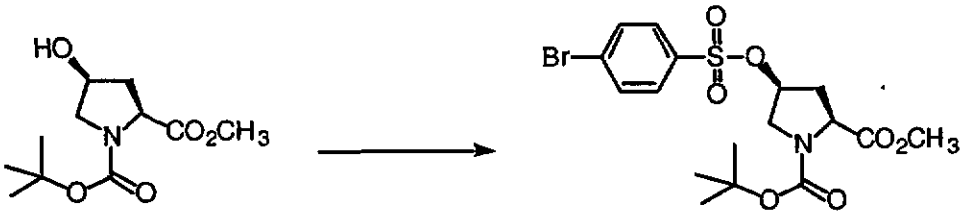


10A



10B

Step A:



10a 10b

To a 0°C solution of **10a** (10 g, 41 mmol) in dichloromethane (60 mL) was added triethylamine (28.68 mL, 204 mmol) slowly. 4-bromobenzenesulfonyl chloride (20.91 g, 82 mmol) and DMAP (few crystals) were then added and the temperature was maintained at 0°C for 30 min. The reaction mixture was left standing in the refrigerator (~5°C) overnight followed by slow warming to ambient temperature over two hours. At this time TLC analysis revealed complete consumption of the starting material. The reaction mixture was diluted with

dichloromethane, washed with saturated sodium bicarbonate solution, and 10% aqueous citric acid solution. The organic layer was dried (Na_2SO_4) and concentrated. The crude mixture was purified by flash column chromatography using 100/0 to 95/5 dichloromethane/ethyl acetate to provide 18.4g (97% yield) of the brosylate **10b** as a white solid; ^1H NMR (mixture of rotamers, $CDCl_3$) δ 1.41 and 1.45 (2s, 9H), 2.40-2.50 (m, 2H), 3.59-3.69 (m, 5H), 4.33-4.37 and 4.46 (2dd, 1H), 5.11 (m, 1H), 7.72-7.74 (m, 4H); ^{13}C NMR (mixture of rotamers, $CDCl_3$) δ 28.18, 28.27, 36.01, 36.98, 51.59, 52.03, 52.20, 52.35, 56.95, 57.22, 57.28, 78.35, 79.53, 80.66, 129.10, 129.26, 132.66, 135.66, 135.81, 153.25, 153.64, 171.45, 171.78; HRMS (FAB) Calcd for $C_{17}H_{23}NO_7SBr$: 464.0379 $(M+H)^+$. Found: 464.0375.

Step B:

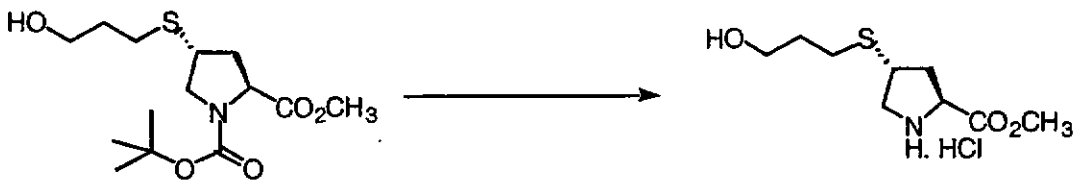


10b **10c**

To a suspension of sodium hydride (60% dispersion in mineral oil, 187 mg, 4.68 mmol) in DMF at 0°C was added 3-mercaptopropanol (0.42 mL, 4.85 mmol) under argon atmosphere. The mixture was stirred for 30 min while maintaining the temperature. A solution of brosylate **10b** (1.5 g, 3.23 mmol) in DMF (total volume = 10 mL) was added slowly and the mixture was warmed to ambient temperature over 2 hrs. The reaction was quenched by pouring into cold 10% citric acid solution. The aqueous layer was extracted with ethyl acetate, the organic layer was dried (Na_2SO_4) and concentrated. The crude material was purified by flash column chromatography using 85/15 dichloromethane/ethyl acetate to provide 800 mg (78% yield) of the sulfide **10c** as an oil; ^1H NMR (mixture of rotamers, $CDCl_3$) δ 1.41 and 1.47 (2s, 9H), 1.83-1.89 (m, 2H), 2.13-

2.34 (m, 2H), 2.69 (t, 2H), 3.23-3.49 (m, 2H), 3.73-3.78 (m, 5H), 3.86-3.95 (m, 1H), 4.33-4.37 and 4.42-4.46 (2dd, 1H); ^{13}C NMR (mixture of rotamers, $CDCl_3$) δ 28.21, 28.30, 32.15, 32.23, 36.65, 37.27, 40.45, 40.89, 52.16, 52.35, 52.50, 52.84, 58.32, 58.55, 61.22, 61.41, 80.35, 153.49, 153.99, 173.05, 173.23; HRMS (FAB) Calcd for $C_{14}H_{26}NO_5S$: 320.1532 $(M+H)^+$. Found: 320.1528.

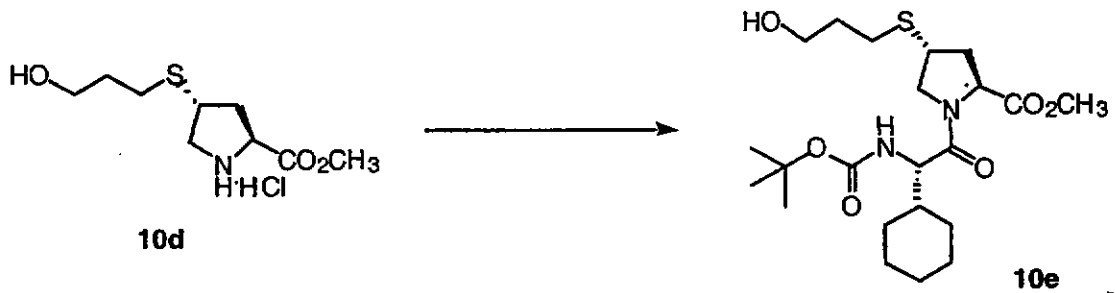
Step C:



10c **10d**

The desired compound **10d** was prepared by the protocol described for Example 1, Step C. Reaction conditions were 0°C, 1hr. The material was carried to the next step as it was.

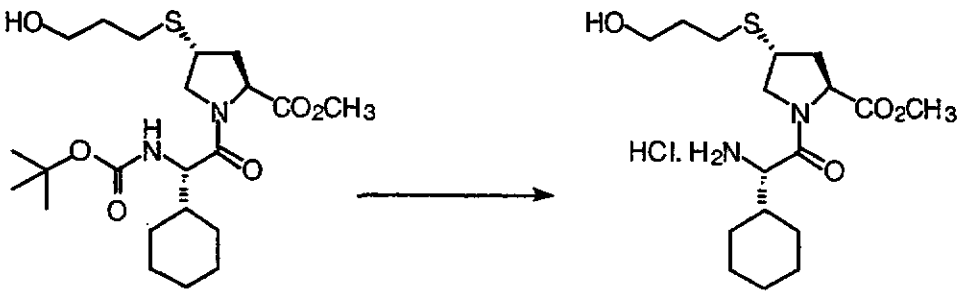
Step D:



10d **10e**

The desired compound **10e** was prepared by the method described for Example 1, Step D. The coupling reaction was carried out at -8°C for 2 days. After workup the product **10e** was sufficiently pure by TLC and was obtained in 80% yield; HRMS (FAB) Calcd for $C_{22}H_{39}N_2O_6S$: 459.2529 $(M+H)^+$. Found: 459.2523.

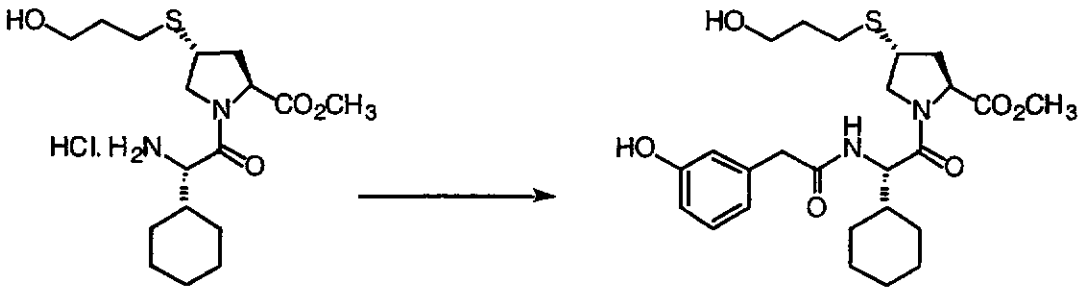
Step E:



10e 10f

The desired compound **10f** was prepared by the protocol described for Example 1, Step E. The material was carried forward as it was.

Step F:

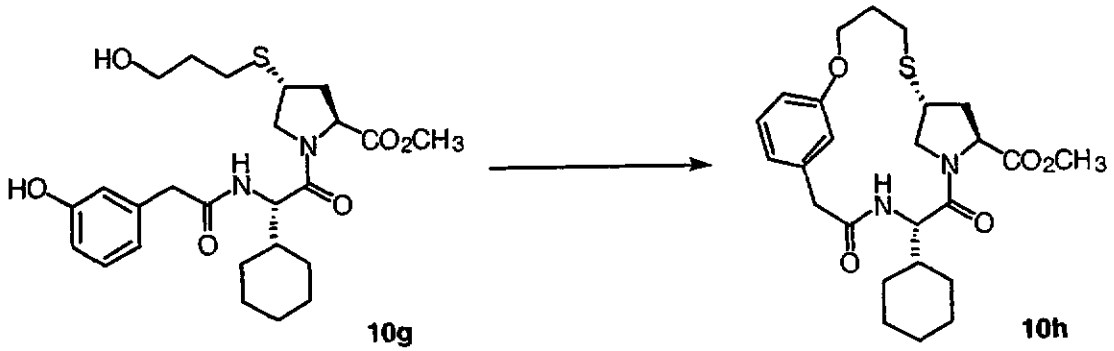


10f 10g

The desired compound **10g** was prepared by the procedure described for Example 1, Step F. The crude product was purified by flash column chromatography using 98/2 of dichloromethane/methanol to provide **10g** in 40% yield as a white solid; ^{1}H NMR (mixture of rotamers, $CDCl_3$) δ 0.90-1.26 (m), 1.66-1.88 (m), 2.22-2.31 (m, 2H), 2.73 (t, 2H), 3.47 (s), 3.5-3.55 (m), 3.65-3.75 (m), 3.88-3.94 (dd, 1H), 4.07-4.12 (dd, 1H), 4.53 (t, 1H), 4.62 (t, 1H), 6.73-6.80 (m, 4H), 7.17 (t, 1H); ^{13}C NMR (mixture of rotamers, $CDCl_3$) δ 25.80, 25.89, 26.14, 27.71, 28.55, 29.22, 31.88, 35.46, 40.58, 42.44, 43.16, 52.32, 52.90, 55.49, 58.46, 60.30, 114.59, 116.27, 121.01, 130.02, 135.90, 156.73, 171.25,

171.87, 171.96; HRMS (FAB) Calcd for $C_{25}H_{37}N_2O_6S$: 493.2372 $(M+H)^+$. Found: 493.2364.

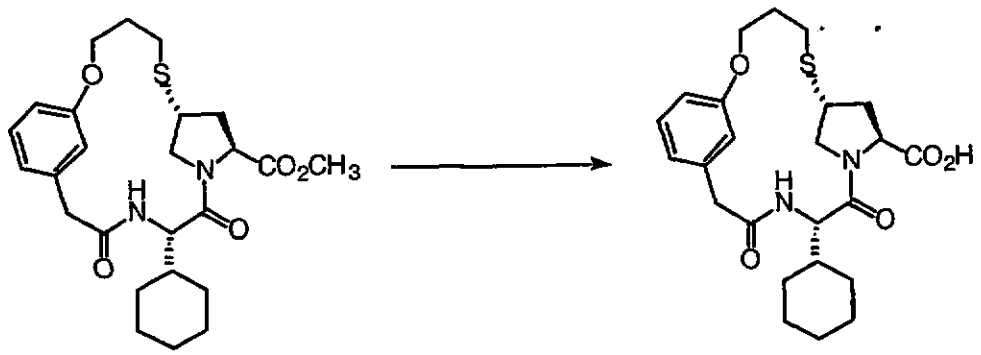
Step G:



10g 10h

The desired compound **10h** was prepared by the protocol described for Example 1, Step G. The crude product was suspended in 80/20 ethyl acetate/hexane, and the solid material was filtered off. The filtrate was concentrated and purified by flash column chromatography using 80/20 hexane/acetone to yield 22% of **10h** as a solid. ^1H NMR ($CDCl_3$) δ 0.98-1.30 (m), 1.64-1.90 (m), 2.06-2.14 (m, 1H), 2.16-2.21 (dd, 2H), 2.62-2.70 (m, 2H), 3.38-3.46 (m, 2H), 3.60-3.66 (m, 3H), 3.71 (s, 3H), 3.88-3.94 (dd, 1H), 4.07-4.15 (m, 1H), 4.22-4.29 (m, 1H), 4.48 (t, 1H), 4.60 (t, 1H), 5.97 (br t, 1H), 6.76-6.81 (m, 2H), 6.99 (br s, 1H), 7.20 (dd, 1H); HRMS (FAB) Calcd for $C_{25}H_{35}N_2O_5S$: 475.2267 $(M+H)^+$. Found: 475.2260.

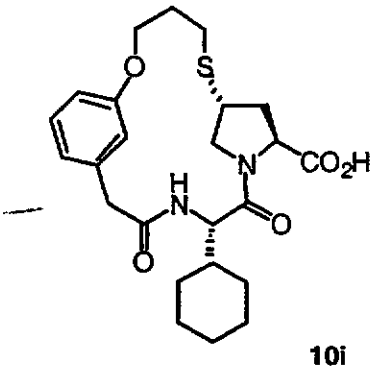
Step H:



10h 10i

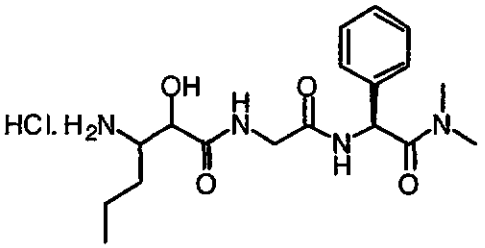
The advanced intermediate **10i** was synthesized as described for Example 1, Step H, in quantitative yield as a white solid; ^{1}H NMR (DMSO-d_6) δ 0.88-0.96 (m, 2H), 1.10-1.14 (m, 3H), 1.59-1.76 (m, 7H), 1.88-1.94 (m, 1H), 2.09 (app. t, 1H), 2.61 (dd, 1H), 3.32 (app. d, 1H), 3.40-3.45 (m, 2H), 3.61 (app. d, 1H), 3.83 (q, 1H), 4.13 (app. t, 1H), 4.19 (t, *J = 7.32 Hz*, 1H), 4.40 (t, *J = 9.52 Hz*, 1H), 6.76-6.79 (m, 2H), 6.89 (s, 1H), 7.16 (app. t, 1H), 8.39 (d, 1H), 12.5 (br. s, 1H); ^{13}C NMR (DMSO-d_6) δ 25.33, 25.41, 26.01, 26.44, 28.09, 28.62, 29.24, 34.90, 39.50, 41.40, 42.30, 53.18, 54.44, 58.06, 66.94, 114.88, 115.25, 122.28, 129.20, 137.84, 157.90, 169.25, 170.29, 172.59; HRMS (FAB) Calcd for $C_{24}H_{33}N_2O_5S$: 461.2110 $(M+H)^+$. Found: 461.2104.

Step I:

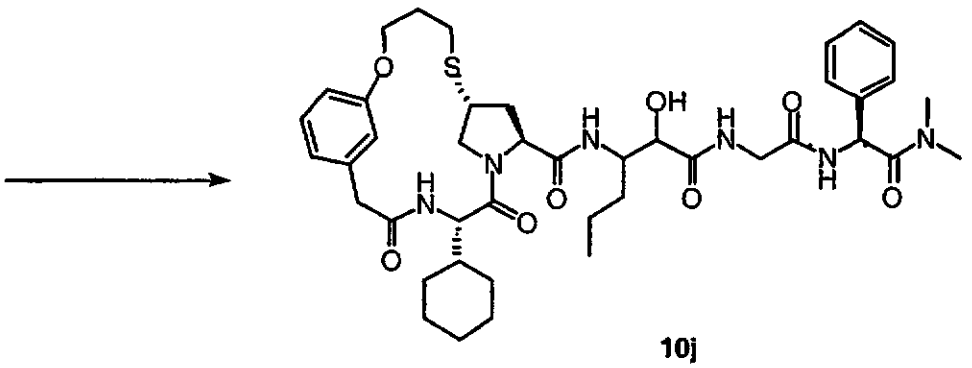


10i

+



A

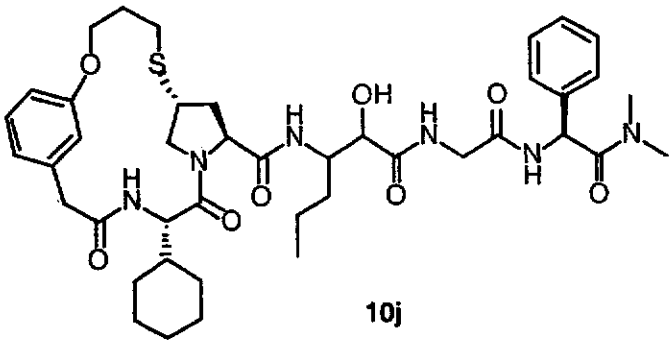


10j

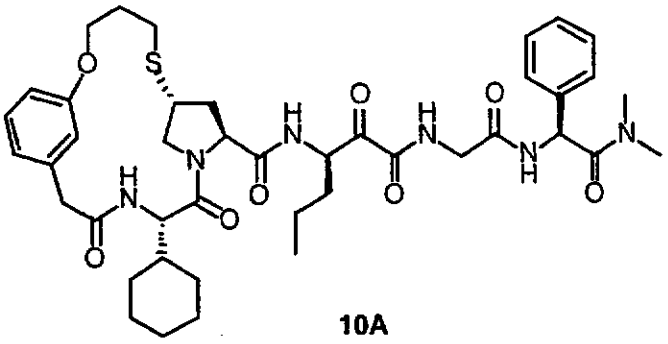
The desired compound **10j** was prepared as described earlier for Example 1, Step I, in quantitative yield as a pale yellow solid. The material obtained after

workup was sufficiently pure by TLC for further manipulations; HRMS (FAB) Calcd for $C_{42}H_{59}N_6O_8S$: 807.4115 $(M+H)^+$. Found: 807.4103.

Step J:

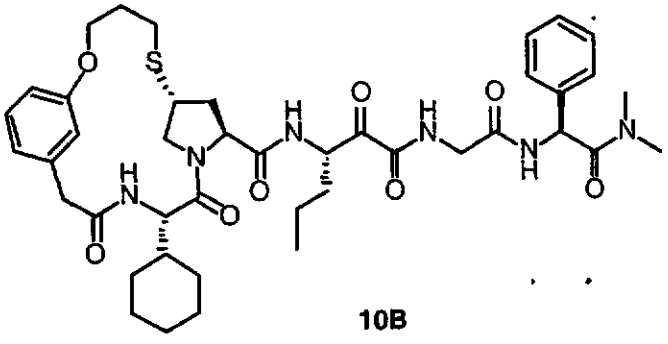


10j



10A

+

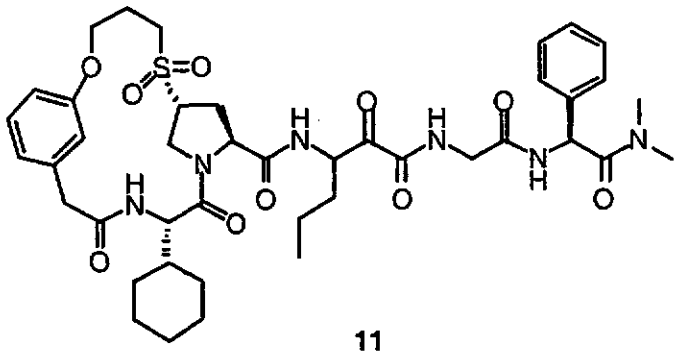


10B

To a solution of **10j** (180 mg, 0.22 mmol) in dichloromethane was added sequentially DMSO (0.313 mL, 4.4 mmol), DCC (908 mg, 4.4 mmol), and dichloroacetic acid (36.4 µL, 0.44 mmol). The reaction mixture was stirred overnight at ambient temperature. It was quenched by addition of aqueous 5% citric acid solution (5mL) and MeOH (1mL) and stirred for 30 min. The solid

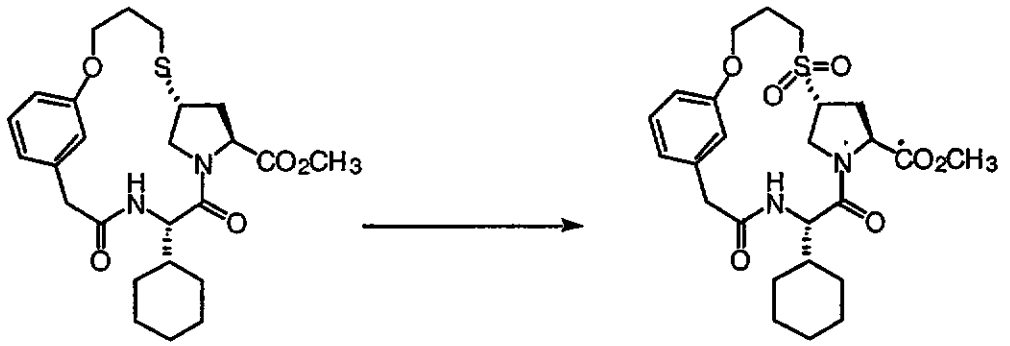
material was filtered off, and the filtrate washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over Na_2SO_4 and solvent removed *in vacuo*. The crude material was purified by flash column chromatography using 100/0 to 98/2 dichloromethane/methanol to yield 105 mg (60%) of **10A** and **10B** as a mixture of diastereomers. A part of the mixture (36 mg) was subjected to column chromatography again to provide pure isomer **10A** (more polar, white solid, 8 mg) and pure isomer **10B** (less polar, white solid, 6 mg), the rest being mixture. HRMS (FAB) Calcd for $C_{42}H_{57}N_6O_8S$: 805.3959 $(M+H)^+$. Found: 805.3958 (**10A**), 805.3950 (**10B**).

Example 11: Preparation of Compound of Formula 11:



11

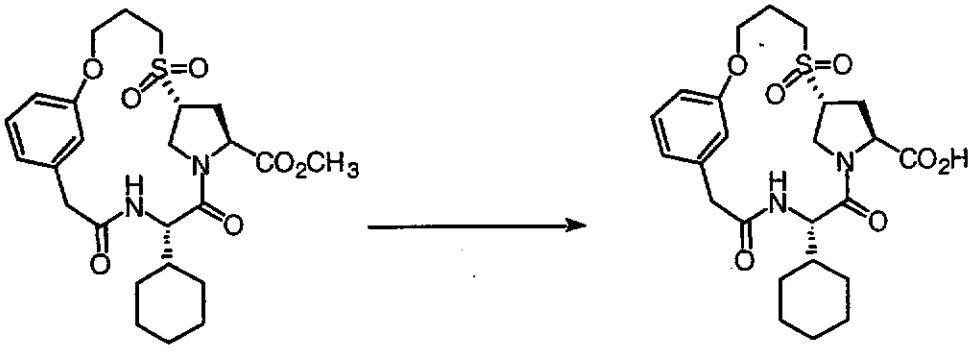
Step A:



10h **11a**

To a cold (0°C) solution of **10h** (200 mg, 0.42 mmol) in dichloromethane (10 mL) was added MCPBA (60%, 364 mg, 1.26 mmol). The reaction mixture was slowly warmed to ambient temperature over 16 hrs. The reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate and sodium bisulfite solution. The organic layer was dried (Na_2SO_4), and concentrated. Purification by flash column chromatography using 98/2 dichloromethane/methanol provided **11a** (138 mg, 65% yield). HRMS (FAB) Calcd for $C_{25}H_{35}N_2O_7S$: 507.2165 $(M+H)^+$. Found: 507.2158.

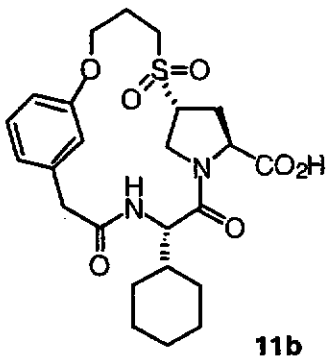
Step B:



11a **11b**

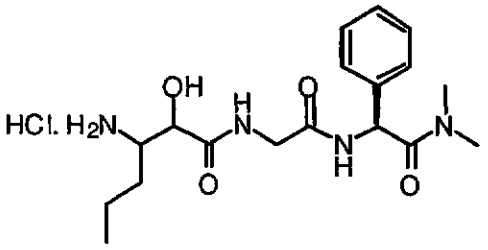
The expected product **11b** was synthesized as described for Example 1, Step I in 90% yield as a white solid; HRMS (FAB) Calcd for $C_{24}H_{33}N_2O_7S$: 493.2008 $(M+H)^+$. Found: 493.2012.

Step C:

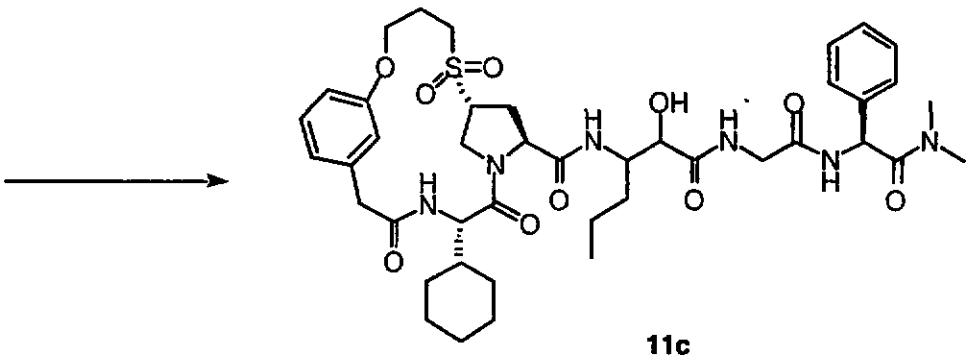


11b

+



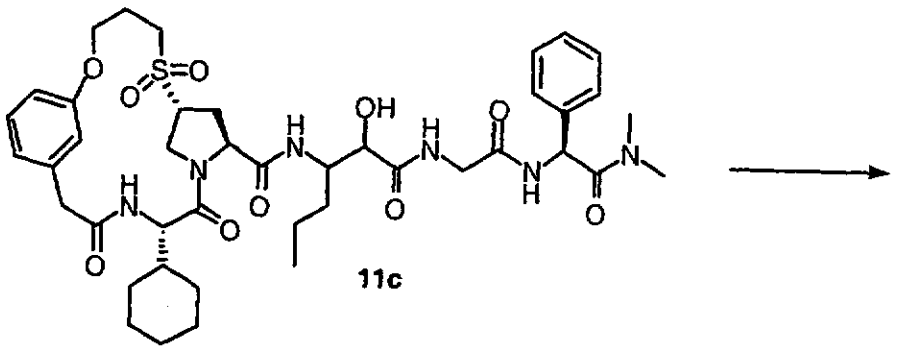
A



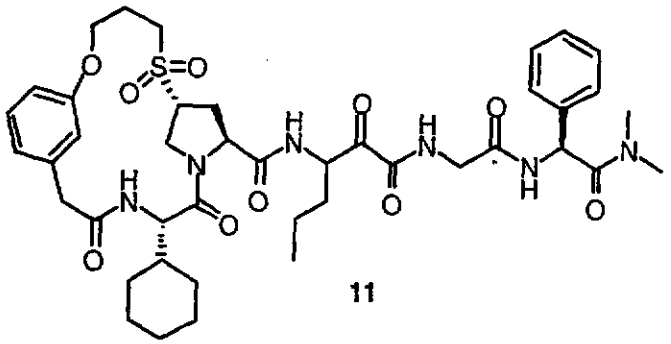
11c

The desired compound **11c** was prepared as described earlier for Example 1, Step J, in quantitative yield. The material obtained after workup was sufficiently pure by TLC for further manipulations. HRMS (FAB) Calcd for $C_{42}H_{59}N_6O_{10}S$: 839.4013 $(M+H)^+$. Found: 839.4019.

Step D:



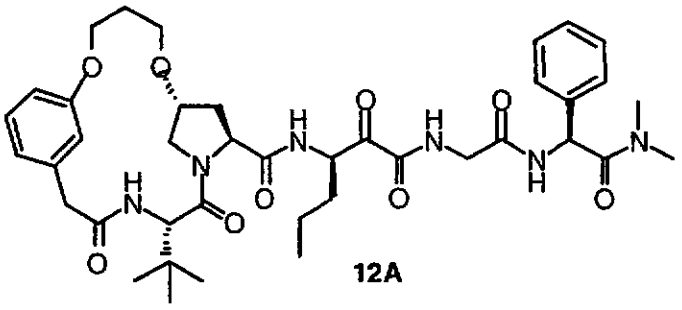
11c



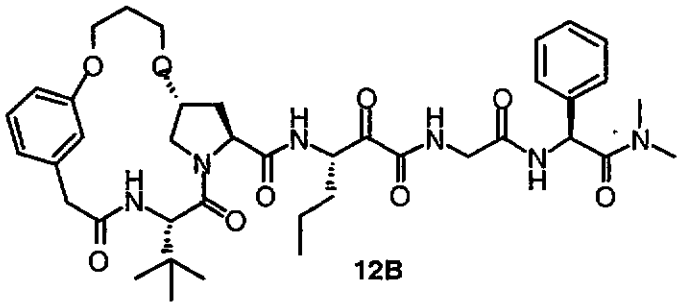
11

The desired product **11** was obtained by the oxidation protocol described earlier for Example 1, Step K. Purification by flash column chromatography using 98/2 dichloromethane/methanol afforded **11** in 4% yield (2 steps). HRMS (FAB) Calcd for $C_{42}H_{57}N_6O_{10}S$: 837.3857 $(M+H)^+$. Found: 837.3865.

Example 12: Preparation of Compounds of Formulas 12A and 12B:

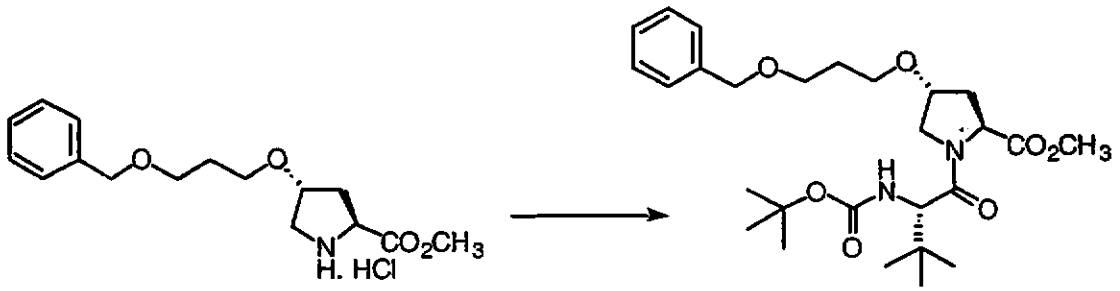


12A



12B

Step A:

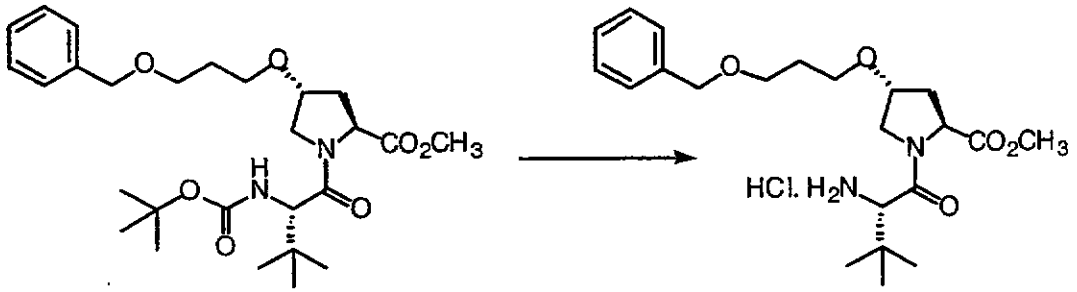


1d 12a

The desired product **12a** was obtained by the method described for Example 1, Step D using N-boc-tert-butylglycine as the coupling partner. The material was purified by flash column chromatography using 90/10 dichloromethane/ethyl acetate to provide **12a** in 73% yield. ^{13}C NMR (mixture of rotamers, $CDCl_3$) δ 26.20, 28.31, 29.07, 30.06, 34.94, 35.86, 37.06, 51.21, 52.16, 52.84, 57.78, 58.33, 65.95, 66.92, 72.97, 75.48, 79.45, 127.55, 127.66, 128.35,

138.45, 155.62, 165.06, 171.13, 172.54; HRMS (FAB) Calcd for $C_{27}H_{43}N_2O_7$: 507.3070 $(M+H)^+$. Found: 507.3077.

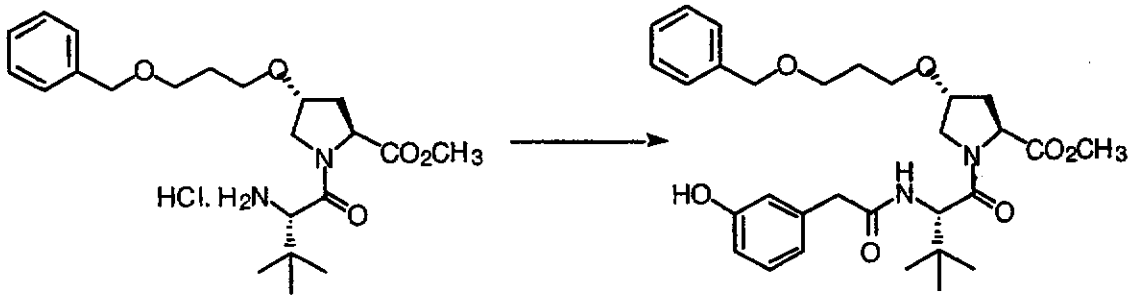
Step B:



12a 12b

The desired compound **12b** was prepared by the protocol described for Example 1, Step E. The material was carried forward to the next step.

Step C:

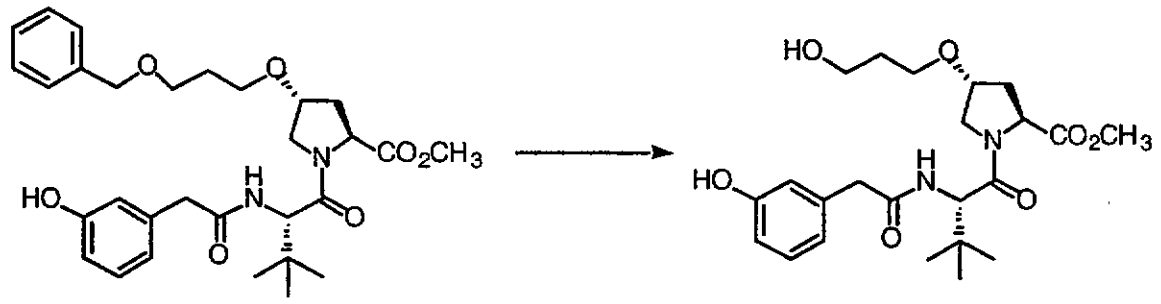


12b 12c

The desired product **12c** was obtained by the procedure described for Example 1, Step F. The material was purified by flash column chromatography using 99/1 dichloromethane/methanol to yield **12c** in 91%. ^{13}C NMR ($CDCl_3$) δ 26.24, 29.93, 34.95, 35.96, 43.48, 52.18, 53.09, 57.06, 58.06, 66.10, 66.92, 72.93, 77.43, 114.59, 116.14, 120.87, 127.58, 127.64, 127.74, 128.37, 130.02,

135.95, 138.39, 156.90, 170.65, 171.06, 172.38; HRMS (FAB) Calcd for $C_{30}H_{41}N_2O_7$: 541.2914 $(M+H)^+$. Found: 541.2921.

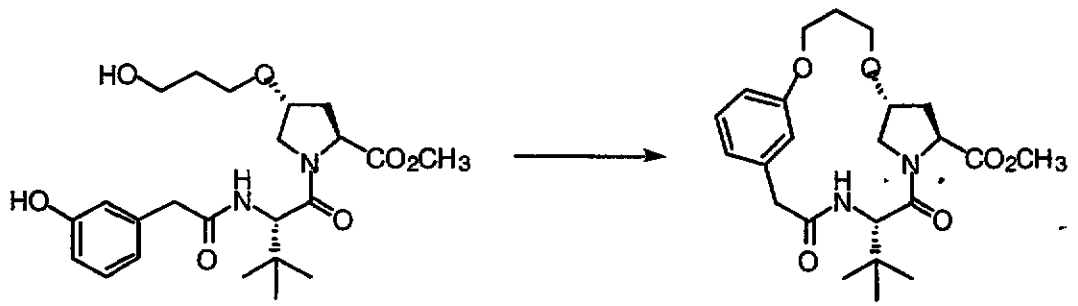
Step D:



12c 12d

The desired product **12d** was obtained by the procedure described for Example 1, Step G. The product obtained after filtering off the catalyst was pure enough for subsequent manipulations. ^{13}C NMR ($CDCl_3$) δ 26.27, 32.09, 35.44, 35.67, 43.19, 52.21, 52.74, 57.60, 58.21, 58.75, 65.78, 77.74, 114.74, 116.02, 120.68, 130.07, 135.66, 157.11, 170.59, 172.05, 172.51; HRMS (FAB) Calcd for $C_{23}H_{35}N_2O_7$: 451.2444 $(M+H)^+$. Found: 451.2436.

Step E:

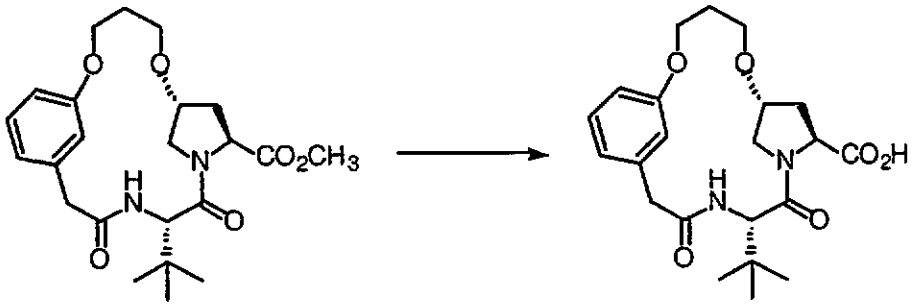


12d 12e

The desired product **12e** was obtained by the procedure described for Example 1, Step H. The crude material was suspended in ethyl acetate/hexane (approx. 1/1) and the undissolved solid material was filtered off. Repeated this

process once again, the filtrate was concentrated and applied on the column as a dichloromethane solution. The column was eluted with 75/25 hexane/acetone to yield 29% of **12e**. HRMS (FAB) Calcd for $C_{23}H_{33}N_2O_6$: 433.2339 $(M+H)^+$. Found: 433.2339.

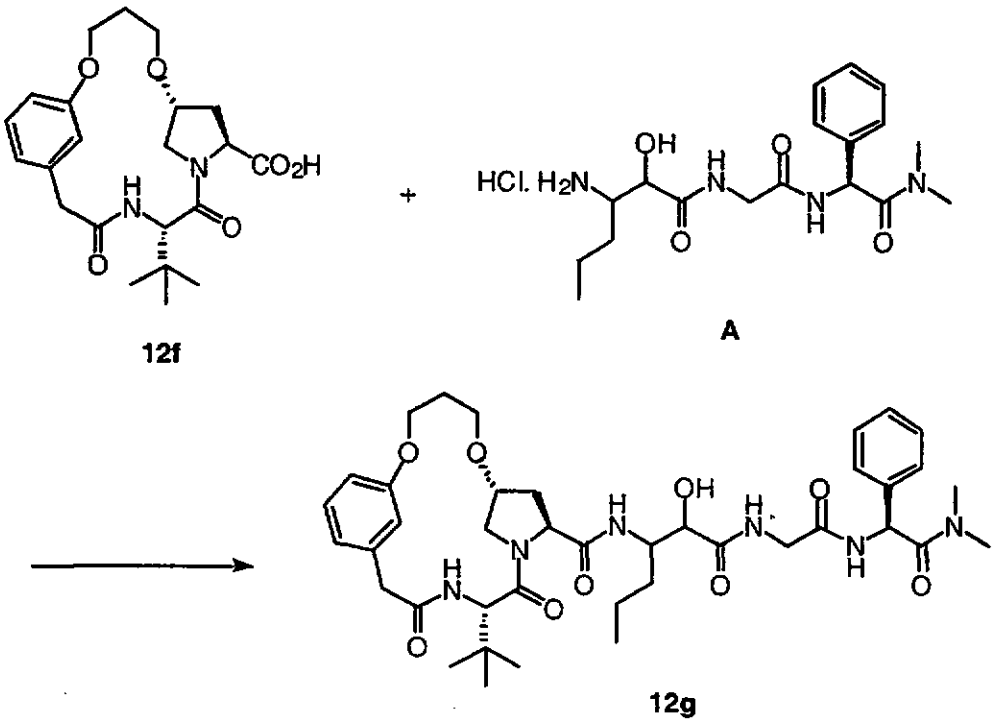
Step F:



12e **12f**

The advanced intermediate **12f** was synthesized as described for Example 1, Step I, in quantitative yield; ^1H NMR (DMSO-d_6) δ 0.96 (s, 9H), 1.66-1.70 (m, 1H), 1.75-1.82 (m, 2H), 2.43 (dd, 1H), 3.32-3.36 (m, 2H), 3.48-3.52 (m, 1H), 3.55 (dd, 1H), 3.84 (app. d, 1H), 3.99 (app. d, 1H), 4.06-4.10 (m, 3H), 4.16 (dd, 1H), 4.69 (d, 1H), 6.70-6.72 (m, 3H), 7.15 (app. t, 1H), 8.42 (d, 1H), 12.43 (br. s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.25, 28.54, 33.31, 34.97, 41.22, 53.96, 56.11, 56.97, 63.36, 64.96, 76.84, 111.94, 115.25, 121.73, 129.13, 138.36, 158.27, 169.85, 170.15, 173.04; HRMS (FAB) Calcd for $C_{22}H_{31}N_2O_6$: 419.2182 $(M+H)^+$. Found: 419.2180.

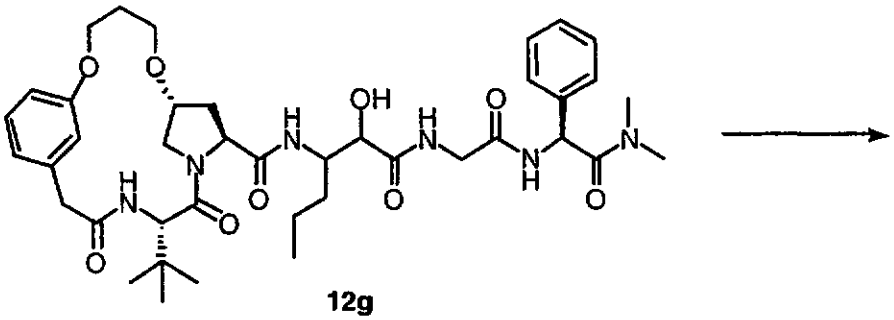
Step G:



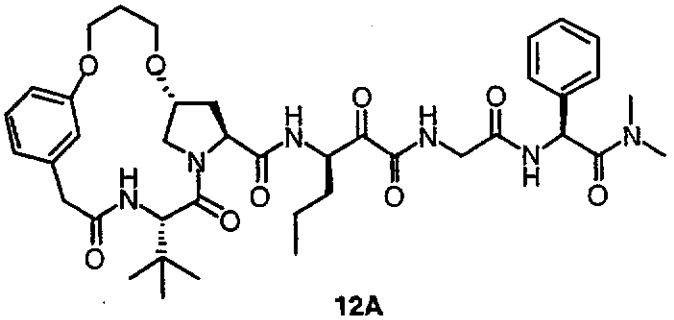
12f + A → 12g

The expected product **12g** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step. HRMS (FAB) Calcd for $C_{40}H_{57}N_6O_9$: 765.4187 $(M+H)^+$. Found: 765.4175.

Step H:

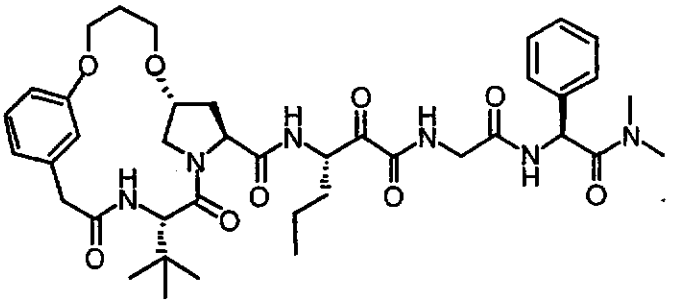


12g



12A

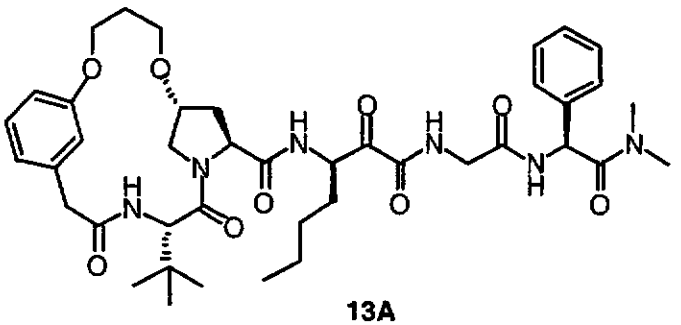
+



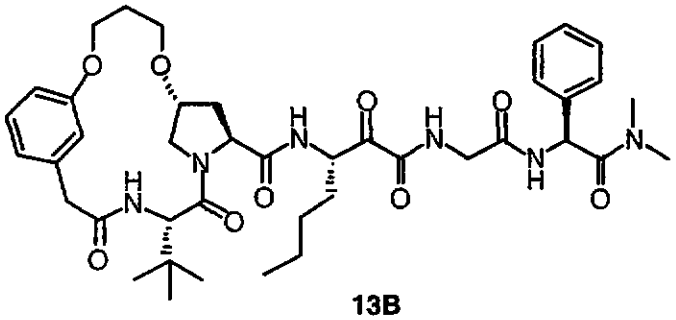
12B

The desired products **12A** and **12B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 98/2 to 96/4 of dichloromethane/methanol afforded separate isomers **12A** and **12B**, and some mixture. Combined yield = 57% (for 2 steps). HRMS (FAB) Calcd for $C_{40}H_{55}N_6O_9$: 763.4031 $(M+H)^+$. Found: 763.4040 (**12A**), 763.4047 (**12B**).

Example 13: Preparation of Compounds of Formulas 13A and 13B:

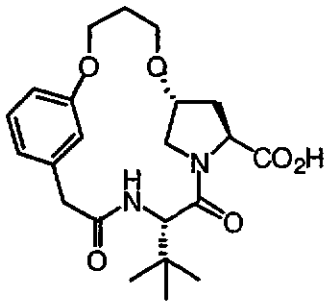


13A



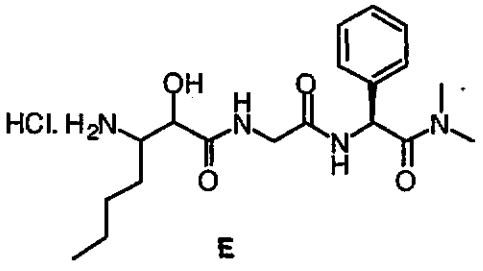
13B

Step A:

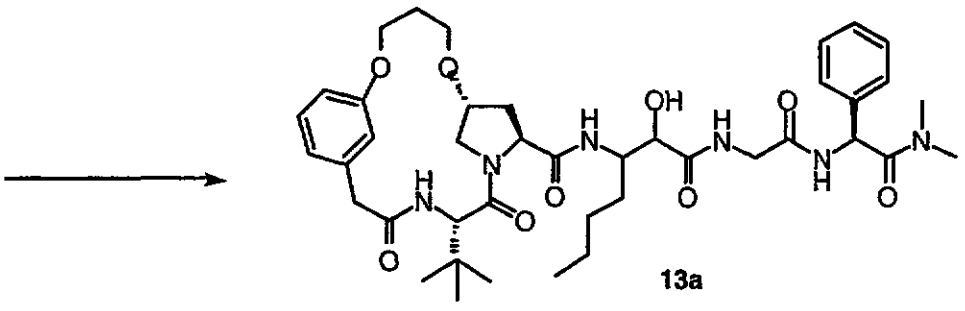


12f

+



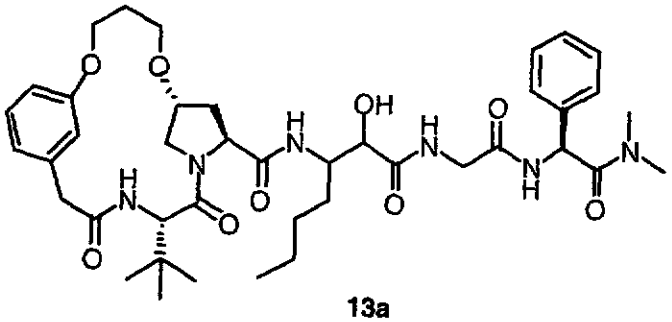
E



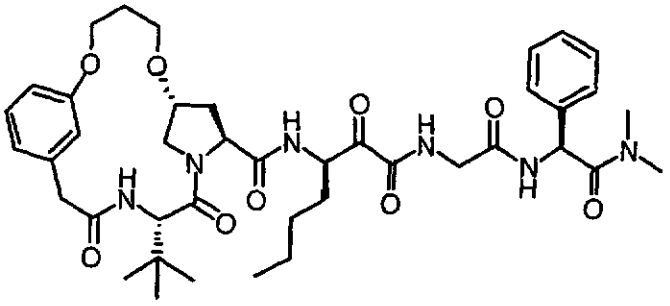
13a

The expected product **13a** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step. HRMS (FAB) Calcd for $C_{41}H_{59}N_6O_9$: 779.4344 $(M+H)^+$. Found: 779.4350.

Step B:

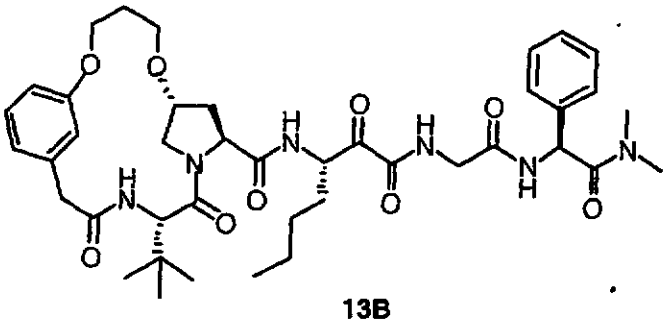


13a



13A

+

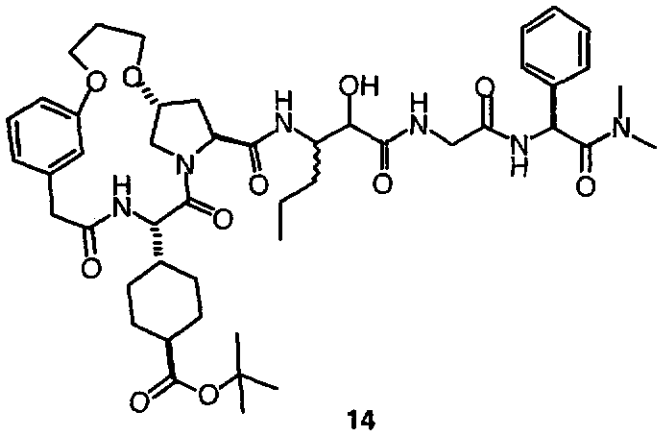


13B

The desired products **13A** and **13B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 100/0 to 96/4 dichloromethane/methanol afforded separate isomers **13A** and **13B**, and some mixture. Combined yield = 50% (for 2 steps).

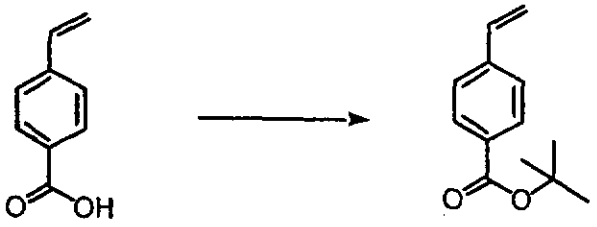
HRMS (FAB) Calcd for $C_{41}H_{57}N_6O_9$: 777.4187 $(M+H)^+$. Found: 777.4177 (**13A**), 777.4185 (**13B**).

Example 14: Preparation of Compound 14:



14

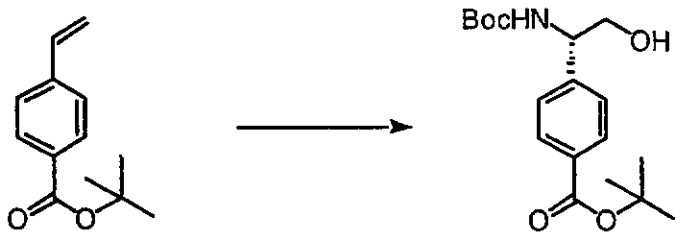
Step A:



14a **14b**

A solution of vinyl benzoic acid **14a** (10g, 68 mmol) in dry benzene (150 mL) was treated with di*tert*-butylacetal of DMF (69 g, 340 mmol, 5.0 equiv.) and heated at reflux for 4h. The reaction mixture was concentrated in *vacuo* and diluted with aq. NaOH (1M, 300 mL). The reaction mixture was extracted in diethyl ether (3x100 mL). The combined organic layer was extracted with aq. NaOH (1M, 100 mL), H_2O (2x100 mL), brine (1x100 mL) dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was distilled under reduced pressure to yield **14b** 9.2 g (66.2 %) of a colorless oil.

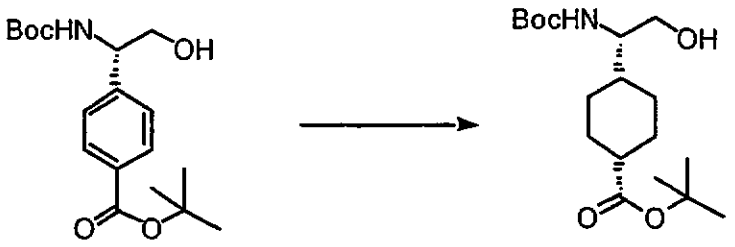
Step B:



14b **14c**

A solution of tert-butyl carbamate (5.96 g, 50.9 mmol) in 1-PrOH (68 mL) was treated with aq. NaOH (128 mL, 0.41 M) and tert-butyl hypochlorite (5.5g, 50.9 mmol). The reaction mixture was cooled to 0° C and $(DHQ)_2Phal$ (780 mg, 1.00 mmol) in 1-PrOH (64 mL) was added. A solution of tert-butyl-4-vinylbenzoate **14b** in 1-PrOH (119 mL) was added followed by $K_2OsO_4 \bullet H_2O$ (248 mg, 0.7 mmol) and the reaction mixture was stirred at 0° C for 4-5 h. The reaction turns green and all the starting material disappears with a new product formed. The reaction mixture was concentrated in vacuo and the residue was diluted with H_2O (300 mL) and extracted with EtOAc (3x100 mL). The combined organic layer was extracted with aq. HCl (200 mL), brine(100 mL) dried (Na_2SO_4) filtered conc. in vacuo and purified by chromatography (SiO_2, EtOAc/Hexanes 1:2) to yield **14c** as a colorless solid (4.6 g, 82%). ^1H NMR (CD_3OD, δ) 7.90 (d, 2 H, J=6.0 Hz), 7.40 (d, 2 H, J=6.3 Hz), 7.22 (bd, 1 H, J=5.7 Hz), 4.69 (bs, 1 H), 3.71-3.62 (m, 2 H) 1.58 (s, 9 H), 1.39 (s, 9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) 169.7, 160.5, 149.8, 134.5, 132.9, 130.4, 84.7, 82.9, 68.7, 60.7, 31.25, 30.9 MS (FAB) 675.2 ($[2M+1]^+$, 15), 338 ($[M+1]^+$, 15), 282 (65), 225 (50), 165 (100); HRMS calcd for $C_{18}H_{28}NO_5$ (M+1): 338.1887; found 338.1967.

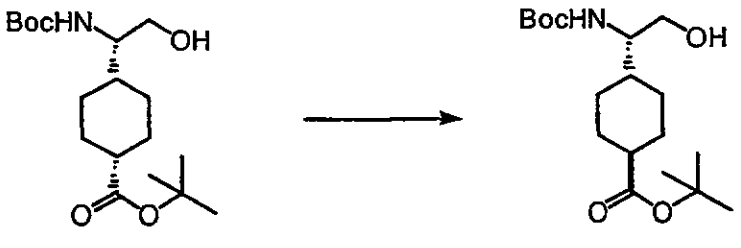
Step C:



14c **14d**

A solution of aromatic compound **14c** (1.0 g, 2.96 mmol) in CH_3OH (20 mL) was treated with Rh/C (10% w/w 100 mg) and hydrogenated (60 psi) for 2d. The reaction mixture was filtered through a plug of celite and the residue was concentrated in vacuo to yield **14d**. The crude product was purified by chromatography (SiO_2, EtOAc/Hex 2:3) to yield the *cis* compound **14d** (830 mg, 83%) which was further purified by crystallizing from hexanes. ^1H NMR (CD_3OD, δ) 6.31 (d, 1 H, *J*=6.9 Hz), 3.58-3.49 (s, 2 H), 3.40 (bd, 1 H, *J*=4.8 Hz), 2.48-2.46 (m, 1 H), 2.1-1.98 (m, 2 H), 1.61-1.2 (m, 7 H), 1.45 (s, 9 H), 1.42 (s, 9 H); ^{13}C NMR (CD_3OD, 75 MHz) 176.2, 158.5, 81.2, 79.8, 63.1, 57.2, 41.8, 38.8, 28.8, 28.3, 27.7, 27.5, 25.9. MS (FAB) 687.2 ($[2M+1]^+$, 5), 344 ($[M+1]^+$, 20), 232 (40), 188(100), 107 (13); HRMS calcd for $C_{18}H_{34}NO_5$ (M+1): 344. 2437; Found: 344.2444. CHN calcd for $C_{18}H_{33}NO_5$ C=64.07%, H= 8.07%,N= 4.15% Found C=64.32%, H=8.21%, N=4.32%.

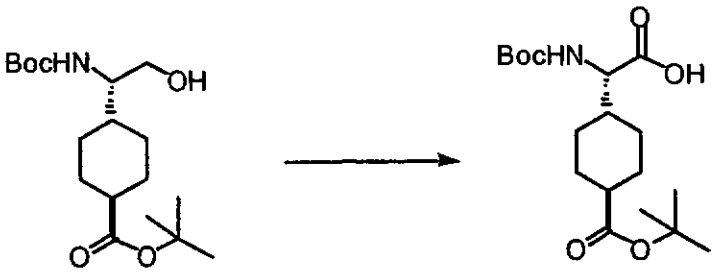
Step E :



14d **14e**

A solution of amino alcohol **14d** (3.3 g, 11.08 mmol) in dry THF (200 mL) was cooled to -78 °C (dry ice/acetone, internal temperature -68°C) was treated with LDA (44 mL, 2M soln in heptanes, 88 mmol, 8.0 equiv.). The reaction mixture was stirred at -78° C for 2 h and quenched with CH_3OH (20 mL). The reaction mixture was treated with aq. HCl (150 mL, 1 M) and extracted with ether (3x100 mL). The combined ether layer was extracted with brine (50 mL) dried ($MgSO_4$), concentrated in vacuo and purified by crystallization from boiling hexanes. The solid separating out from the mother liquor was predominantly *cis* stereo isomer, where concentration of the mother liquor gave the pure *trans* isomer. The above sequence was repeated twice more to obtain 2.7 g of the trans compound and 600 mg of cis/trans mixture. ^{13}C NMR (CDCl3, 75 MHz) 175.3,156.6, 79.8, 63.6, 57.0, 44.1, 38.3, 37.7, 28.9, 28.6, 28.4, 28.1, 26.6, 26.1. MS (electron spray) 344 (M^+, 50), 288 (50) 232 (90), 188 (100).

Step F:

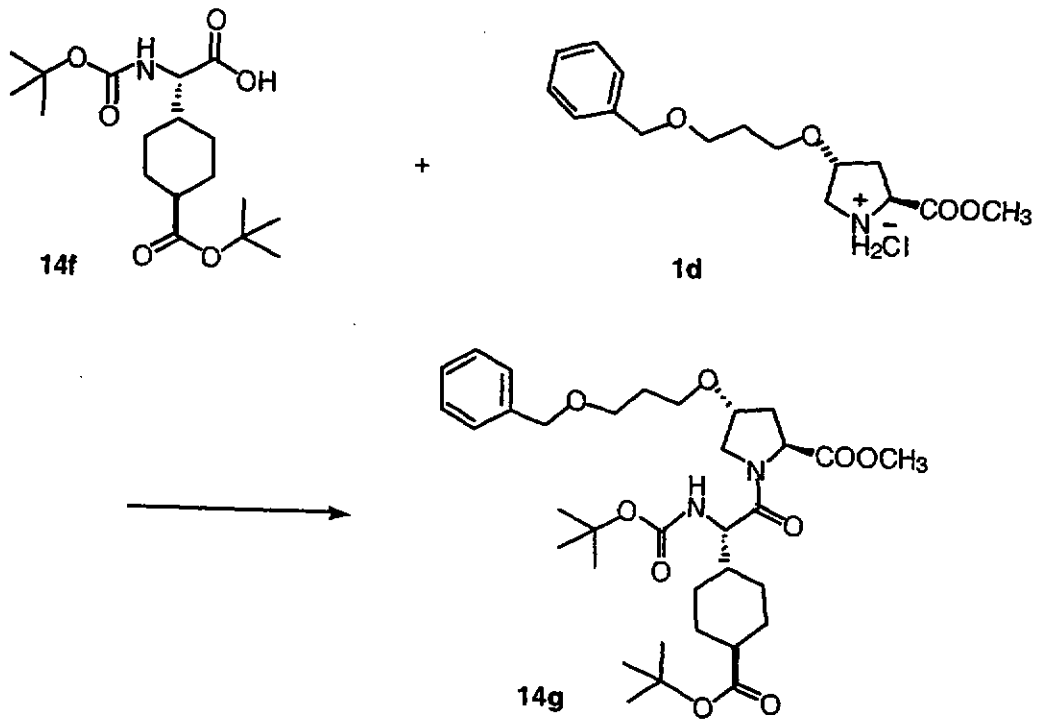


14e **14f**

A solution of alcohol **14e** (2.6 g, 7.6 mmol) in CH_3CN (150 mL) and CCl_4 (150 mL) was treated with H_2O (22 mL), cooled to 0°C, treated with periodic acid (7.05 g, 30.92 mmol, 4.0 equiv.) and $RuCl_3 \cdot 3H_2O$ (60 mg, 0.3 mmol, 4 mol%). The reaction mixture was stirred at rt. for 3h, and concentrated in vacuo. The residue was diluted with water (150 mL) and extracted with EtOAc (3x100 mL). The combined organic layer was extracted with H_2O (100 mL) and with aq. NaOH (1M, 3x100 mL).The combined aq. layers were acidified with HCl (6M, pH ~1) and extracted with EtOAc (3x100 mL). The ethyl acetate layers were pooled, extracted with brine (100 mL) dried (Na_2SO_4) filtered concentrated in *vacuo* to yield acid **14f** (1.8 g, 66%) used for further couplings without further purification. MS (FAB)

380.2 ([M+Na]+, 30) 358 ([M+1]+, 5), 302 (20), 258(20), 246 (100), 202 (70), 200 (20)

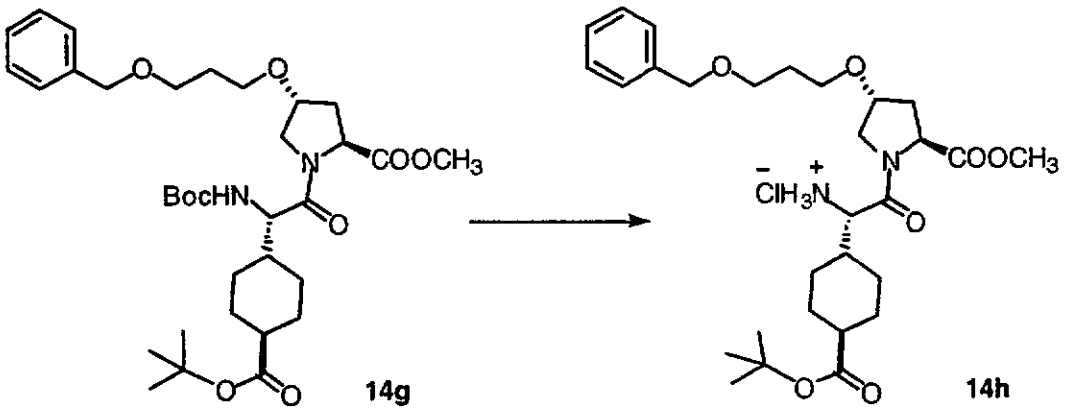
Step G:



A solution of Boc-*trans*-4-tertbutylcarboxyl-cyclohexylgylcine **14f** (1.9 g, 5.3 mmol) in CH_2Cl_2 (30 mL) was treated with proline compound **1d** (1.92g, 5.85 mmol, 1.1 equiv.) and cooled to 0°C. The reaction mixture was treated with Hünigs base (1.51g, 11.7 mmol, 2.2 equiv., 2.15 mL) followed by the addition of BOP reagent (2.6 g, 5.85 mmol, 1.1 equiv.) The reaction mixture was stirred at rt. for 12 h diluted with aq. HCl (1M, 100 mL) and extracted with EtOAc (3x100 mL). The combined ethyl acetate layers were extracted with aq. NaOH (1M, 100 mL) brine (100 mL) dried (Na_2SO4), filtered concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/Hexanes 2:3) to yield **14g** as colorless foam (1.8g, 54%); ^1H NMR (CD_3OD, δ, mixture of rotomers) 7.32-7.23 (m, 5 H), 6.64 (d, 1 H, *J*=9.0Hz), 4.47-4.39 (m, 3 H), 4.19-4.04 (m, 3 H), 3.74 (s, 3 H), 3.66-3.56 (m, 4 H), 2.55-2.10 (m, 2 H), 1.99-1.00 (m, 12H), 1.42 (s, 9 H), 1.40 (s, 9 H). ^{13}C NMR (CD_3OD, δ, mixture of rotamers), 175.6, 174.6, 172.4, 172.0, 156.4, 138.5, 128.1,

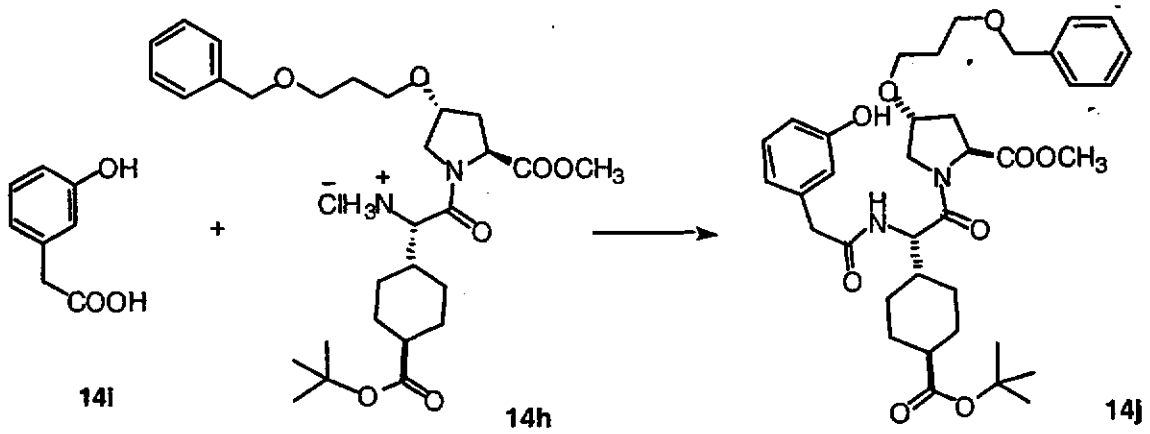
127.5, 127.4, 127.3, 79.8, 79.7, 79.0, 77.5, 72.5, 66.7, 65.4, 58.1, 56.6, 52.1, 51.3, 43.9, 40.4, 39.4, 38.6, 34.6, 29.8, 28.4, 27.9, 27.3, 26.1, 25.4, 24.5; MS (FAB) 633 ([M+1]+, 11), 533 (55), 477 (24), 428 (5), 294 (100), 234 (12) 156 (40), 128 (39); CHN Calcd. for $C_{34}H_{52}NO_9$ C 64.53% H 8.28% N 4.43%; Found C 64.41% H 8.00% N 4.19%.

Step H:



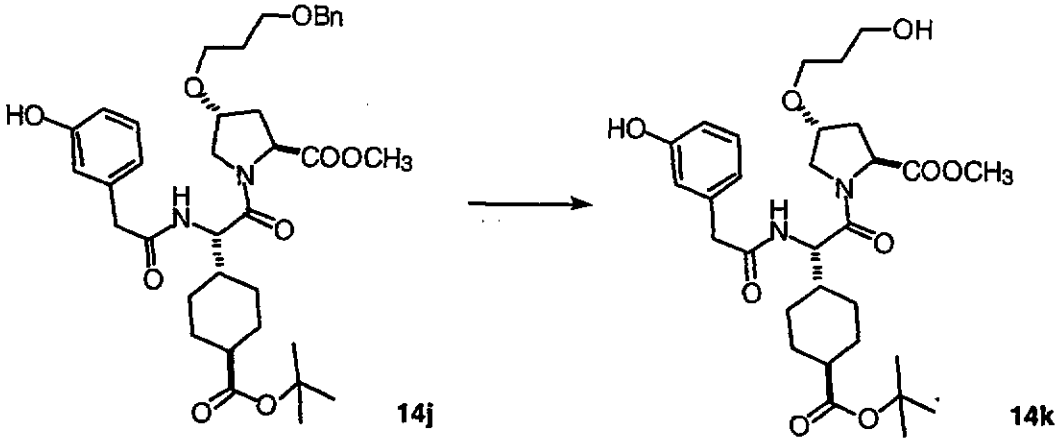
A solution of Boc-trans-4-tertbutylcarboxycyclohexyl glycine **14g** (1.8 g) in HCl (4M soln in dioxane, 60 mL) was stirred at rt. for 4-5 h. The reaction was followed by TLC (EtOAc/Hex 3:7) for the disappearance of starting material and the appearance of base line product. The reaction mixture was concentrated in vacuo and the residue was dried in the pump overnight. The solid **14h** was used for couplings without further purification.

Step I:



A solution of 3-hydroxyphenylacetic acid **14i** (501 mg, 3.29 mmol, 1.8 equiv.) and amine hydrochloride **14h** (1.79g, 2.99 mmol) in dry CH_2Cl_2 (30 mL) was treated with Hünigs base (850 mg, 6.59 mmol, 2.20 equiv., 1.2 mL) and BOP reagent (1.5g, 3.29 mmol, 1.1equiv.) at 0° C and stirred at rt. for 24 h. The reaction mixture was concentrated in vacuo and diluted with aq. HCl (1M, 250 mL). The aq. layer was extracted with EtOAc (3x100 mL). The combined organic layers were extracted with aq. NaOH (1x100 mL), brine (1x100 mL) dried (Na_2SO_4) filtered, concentrated in vacuo and purified by chromatography (EtOAc/Hexanes 1:1) to yield **14j** as a colorless solid (710 mg, 36%).

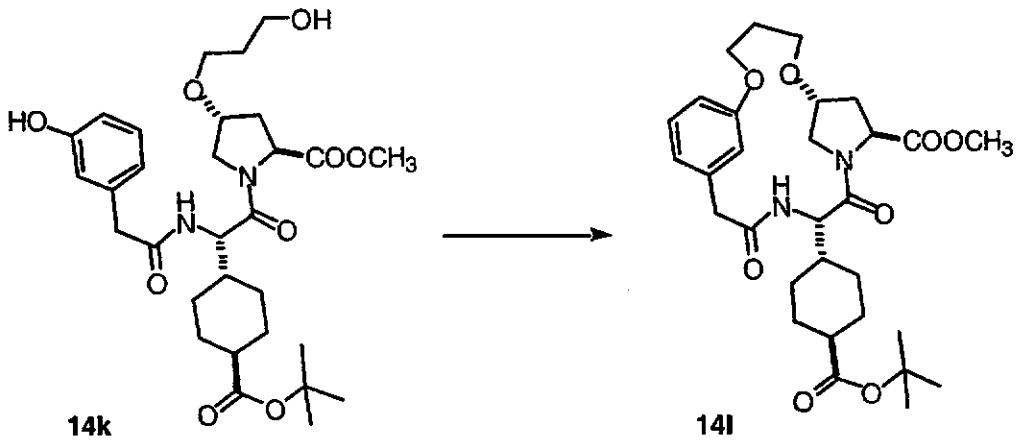
Step J:



A solution of the coupled compound **14j** (710 mg, 1.1 mmol) in CH_3OH (50 mL) was treated with Pearlmans catalyst (10% $Pd(OH)_2/C$) and hydrogenated (H_2, 40 psi) for 12h. The Pd/C was filtered off through a plug of celite and filtrate was concentrate and used for the next cyclization without further purification R_f 0.12 (acetone/Hexanes 3:7); ^1H NMR (CD_3OD, δ, mixture of rotomers) 8.25 (bs, 1H), 7.01 (bt, 1 H, *J*=7.2 Hz), 6.72 (bs, 1 H), 6.65 (d, 2 H, *J*=7.8 Hz), 4.79-4.70 (bs, 3 H), 4.55-4.41 (bs, 2 H), 4.20-4.12 (bs, 2 H), 3.77 (s, 3 H), 3.66-3.44 (bm, 6 H) 2.43-1.04 (bm, 14 H) 1.40 (s, 9 H); ^{13}C NMR (CD_3OD, δ, mixture of rotomers): 175.5, 174.6, 172.6, 172.4, 171.3, 161.1, 157.3, 136.8, 136.7, 129.3, 120.0,

115.7, 113.6, 100.0, 94.8, 79.9, 79.8, 77.5, 65.1, 58.5, 58.2, 55.6, 55.5, 54.3, 52.2, 51.5, 43.9, 42.1, 39.4, 35.0, 32.4, 28.6, 28.4, 27.5, 27.2, 27.1, 26.1, 25.2, 25.0; MS (FAB): 577 ([M+1]$^+$, 70), 521 (10), 443 (10), 387 (10), 374 (10), 318 (15), 290 (100), 248 (30); HRMS calcd. for $C_{30}H_{45}N_2O_9$ $(M+H)^+$: 577.3125; Found 577.3133.

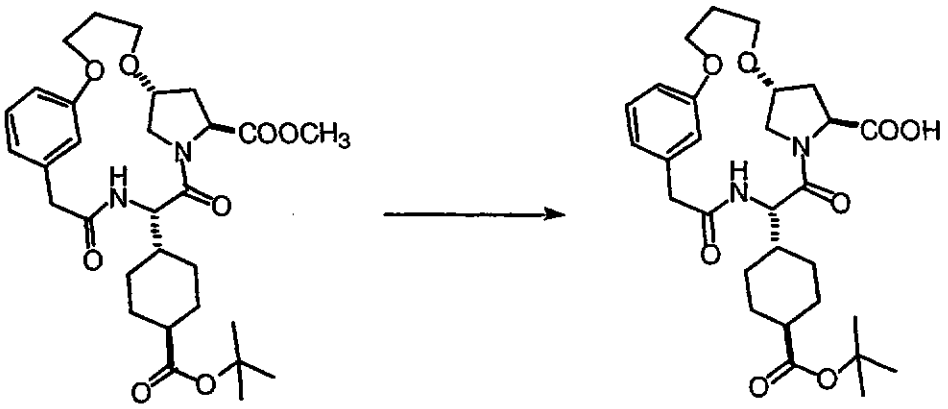
Step K:



A solution of alcohol **14k** (600 mg, 1.05 mmol) and ADDP (787 mg, 3.12 mmol, 3.0 equiv.) in CH_2Cl_2 (30 mL) was treated with Ph_3P (818 mg, 3.12 mmol, 3.0 equiv.) under a positive pressure of dry N_2 at 0 °C. The reaction mixture was stirred at rt. for 24 h, concentrated in vacuo and the residue was purified by chromatography (SiO_2, acetone/Hexanes 2:3) to yield a colorless solid **14l** (120 mg, 22%) of cyclic product; R_f 0.73 (acetone/Hexanes 1:1); ^1H NMR (CD_3OD, δ) 7.13 (t, 1 H *J*=7.8 Hz), 6.76 (s, 1 H), 6.71 (t, 2 H, *J*=8.1Hz), 4.58 (d, 1 H, *J*=9.9 Hz), 4.37 (dd, 1 H, *J*=7.8, 2.7 Hz), 4.23-4.11 (m, 4 H), 3.74-3.61 (m, 2 H), 3.66 (s, 3 H), 3.59-3.40 (m, 2 H), 2.54-2.41 (m, 1 H), 2.19-2.10 (m, 1H), 1.98-1.42 (m, 10 H), 1.43 (s, 9 H); ^{13}C NMR (CD_3OD, δ) 175.6, 172.4, 172.1, 170.8, 159.0, 137.0, 129.1, 121.7, 115.7, 112.2, 94.8, 79.8, 77.4, 65.2, 64.0, 57.6, 55.2, 53.8, 51.3, 44.0, 41.5, 39.1, 33.3, 28.7, 28.1, 26.9; MS (electron spray) 559 ([M+1]$^+$, 100) 327 (10), 189 (20); HRMS calcd. for $C_{30}H_{43}N_2O_8$ $(M+1)^+$: 559.3019; Found:

559.3025; CHN calcd for $C_{30}H_{42}N_2O_8 \bullet 0.5H_2O$ C= 63.47%, H=7.63%, N=4.93%; Found C=63.57%, H=7.46%, N=4.93%.

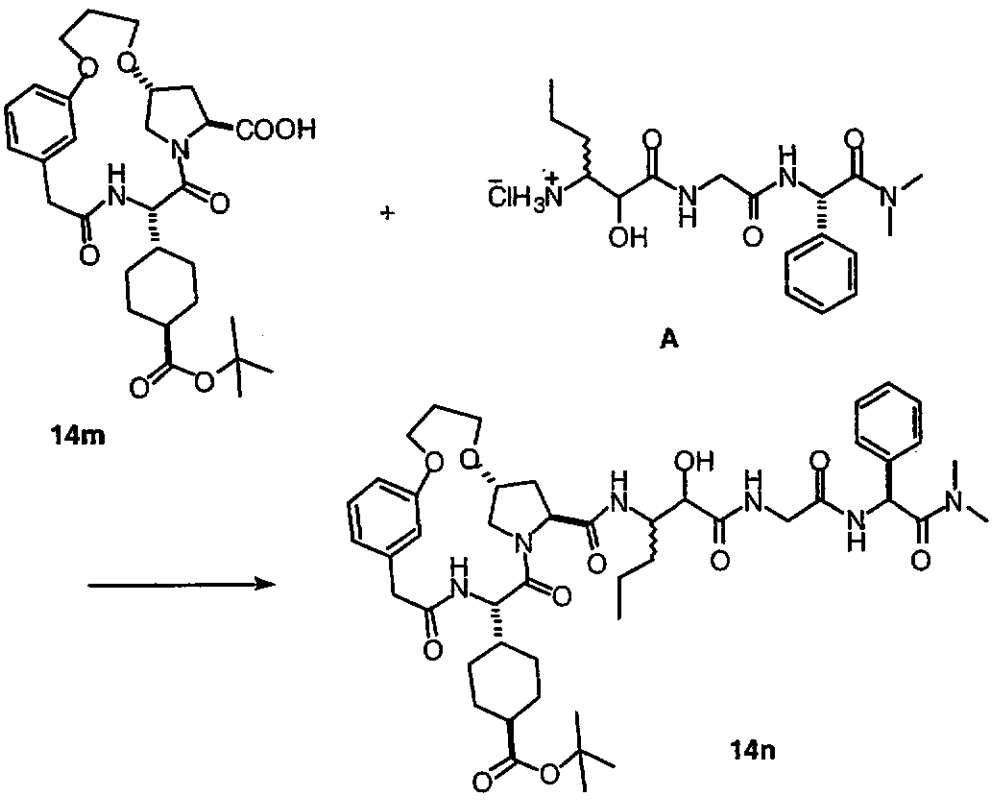
Step L:



14l 14m

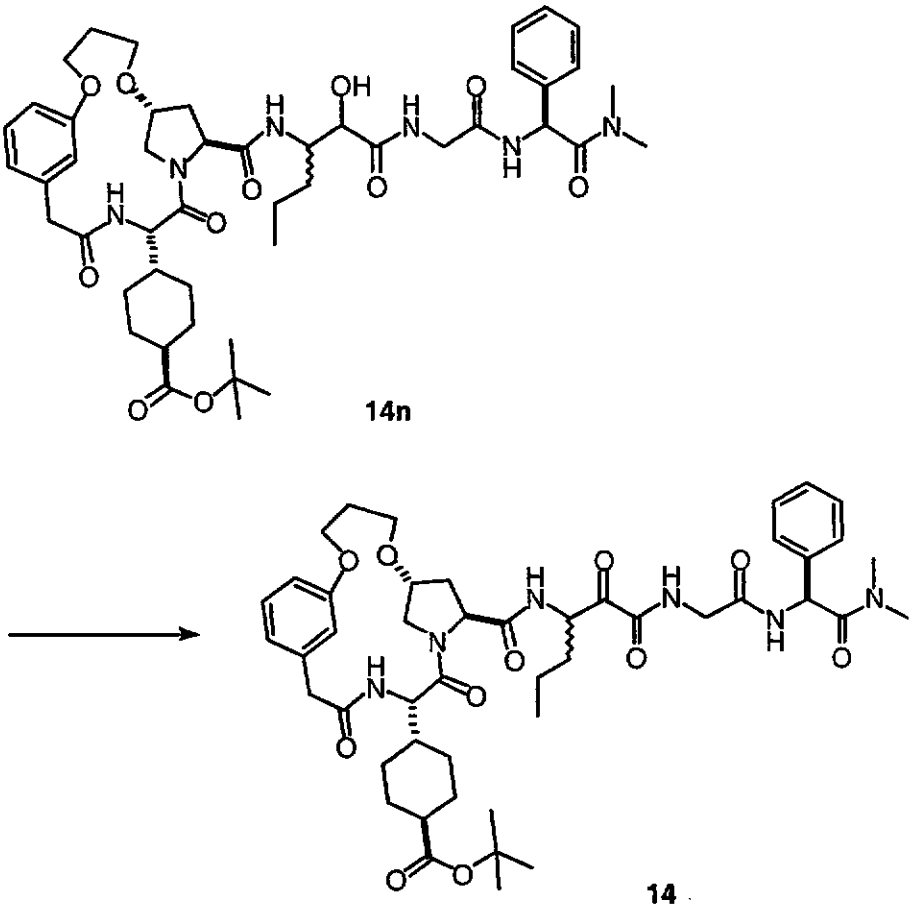
A solution of methyl ester **14l** (120 mg, 0.22 mmol) in THF (5.0 mL) and H_2O (1.0 mL) was treated with LiOH (20 mg, 0.5 mmol, 2.0 equiv.). The reaction mixture was stirred at rt. for 3 h and CH_3OH (1.0 mL) was added and stirred for an additional 1h. The reaction mixture was stirred with HCl (4.0 M in Dioxane, 1 mL) and concentrated in vacuo and the water was lyophilized to yield a colorless solid **14m** which was used for next coupling.

Step M:



A solution of carboxylic acid **14m** (110 mg, 0.21 mmol) in DMF (3.0 mL) and CH_2Cl_2 (5.0 mL) was treated with Hünigs base (109 mg, 0.84 mmol, 4.0 equiv. 155.0 μL) and HOOBt (52 mg, 0.315 mmol, 1.5 equiv.). The reaction mixture was cooled to 0 °C and treated with EDCI (61 mg, 0.31 mmol, 1.5 equiv.) The reaction mixture was stirred at 0 °C and treated with amine hydrochloride **A** after 30 min. The reaction mixture was stirred at rt. for 24 h and concentrated in vacuo to remove DMF and CH_2Cl_2. The residue was diluted with aq. HCl (100 mL) and extracted with CH_2Cl_2 (3x75 mL) The combined organic layers were extracted with aq. NaOH (1M, 3x50 mL), brine (100 mL) and concentrated in vacuo. The residue **14n** (79 mg) was oxidized without further purification.

Step N:

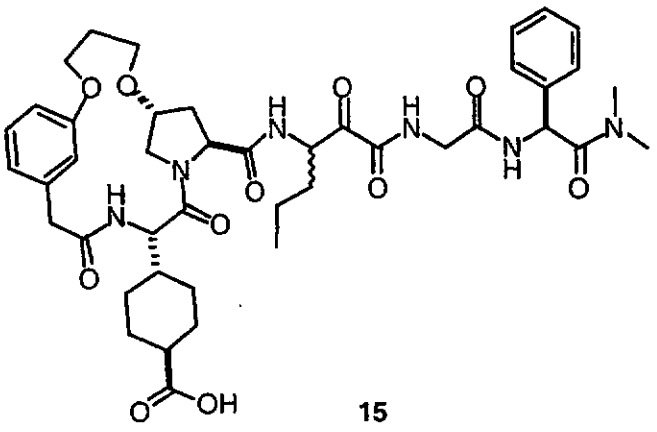


14n

14

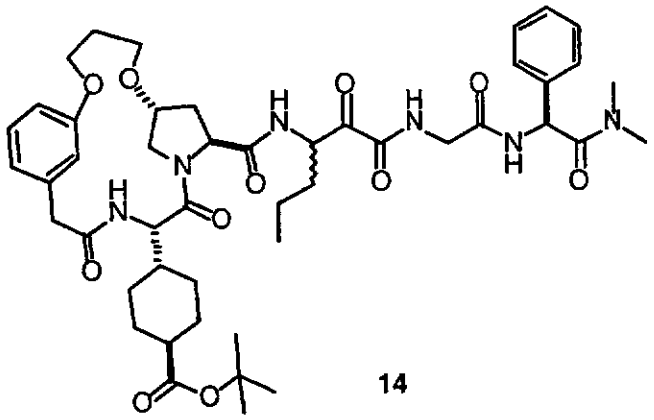
A solution of alcohol **14n** (79 mg, 88 μmol) in CH_2Cl_2 (4.0 mL) was treated with Dess-Martin reagent (110 mg, 0.25 mmol, 2.5 equiv.) The reaction mixture was stirred at rt. for 3 h and the mixture was concentrated in vacuo. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:1) to yield oxidized product **14** (29 mg, 38%) as a colorless solid; MS (FAB) 889 [$(M+1)^+$, 100), 844 (20), 833 (60), 788 (30), 760 (10), 655 (10), 527 (20); HRMS calcd. for $C_{47}H_{65}N_6O_{11}$: 889.4711; Found: 889.4732.

Example 15: Preparation of Compound 15:

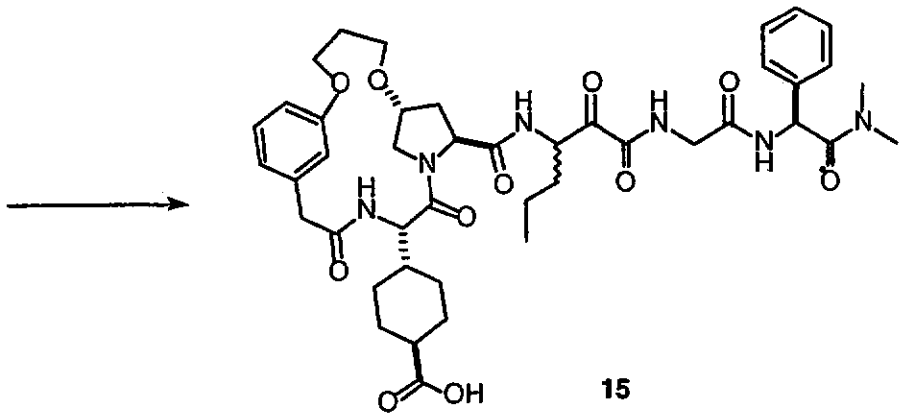


15

Step A:



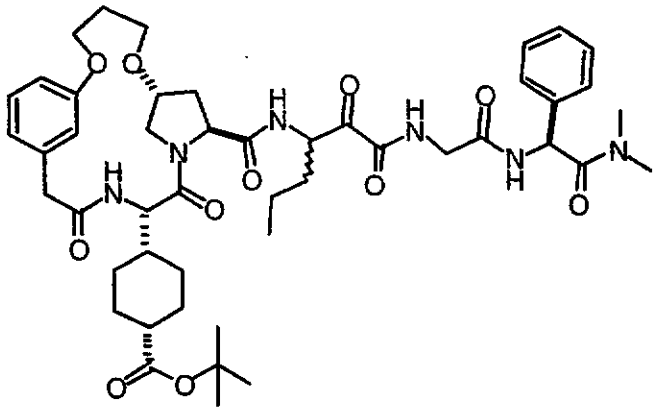
14



15

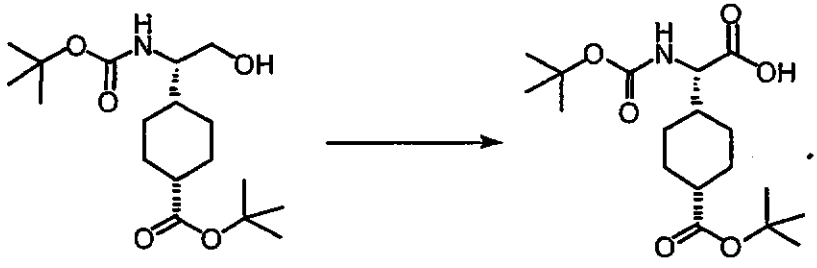
A solution of *tert*-butyl ester **14** (20.0 mg, 22.0 μmol) was treated with TFA/CH_2Cl_2 (1:1, 4 mL) and stirred at rt. for 4 h. The disappearance of the ester to the base line was followed by TLC (CH_3OH/CH_2Cl_2 1:24). After the deprotection was complete the reaction mixture was concentrated in vacuo and the residue was repeatedly treated with CH_2Cl_2/Hexanes and concentrated to yield a white solid **15** (19 mg, 100%); MS (Electron spray) 833 ($[M+1]^+$, 60), 661 (10), 530 (40), 391 (75), 279 (100).

Example 16: Preparation of Compound 16:



16

Step A:

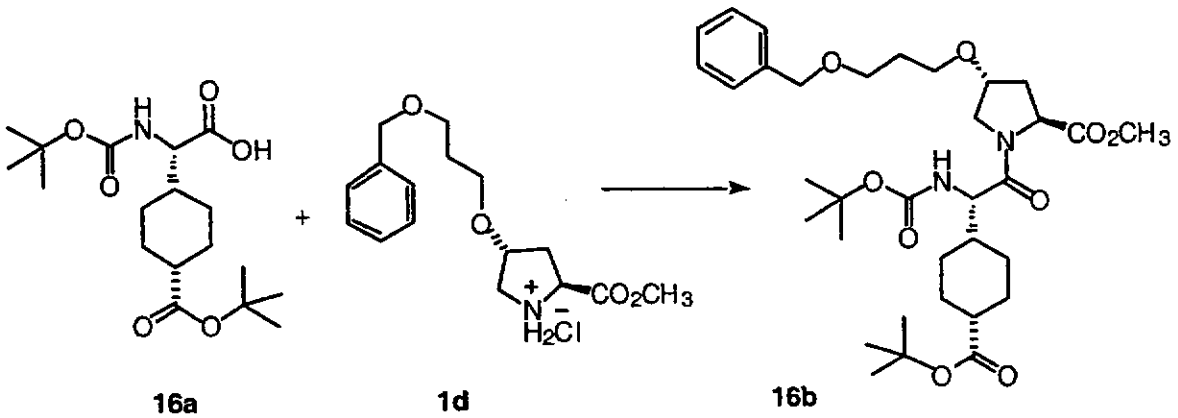


14d **16a**

The desired compound **16a** was prepared from **14d** in 70% yield according to the procedure of Example 14, Step F. It was used for the couplings without further purification's; MS (FAB): 380.2 ($[M+Na]^+$, 30) 358 ($[M+1]^+$, 5), 302 (20),

258(20), 246 (100), 202 (70), 200 (20); HRMS calcd. for $C_{18}H_{32}NO_6$ $(M+1)^+$: 358.2230; Found: 358. 2237.

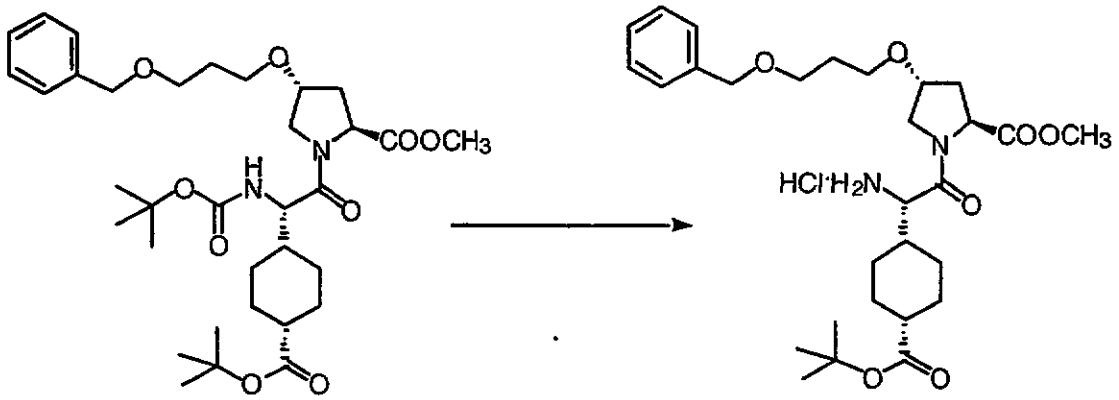
Step B:



16a 1d 16b

The desired compound **16b** was prepared from **16a** in 41% yield according to the procedure of Example 14, Step G; $[\alpha]_D$ -52.7 (*c* 0.3 $CHCl_3$, 25); ^1H NMR ($CDCl_3$, δ) 7.35-7.21 (m, 5 H), 6.63 (d, 1 H, *J* =9.3 Hz), 4.46 (d, 2 H, *J*=4.3 Hz), 4.41 (t, 1 H, *J*=9.3 Hz), 4.38-4.07 (m, 3 H), 3.68 (s, 3 H), 3.66-3.43 (m, 5 H), 2.45 (p, 1 H, *J*=4.2 Hz), 2.32 (dd, 1 H, *J*=7.8, 5.7 Hz), 2.02-1.90 (m, 3 H), 1.90-1.56 (m, 3 H), 1.56-1.24 (m, 24 H); ^{13}C NMR (CD_3OD, δ)174.7, 172.4, 172.0, 156.4, 138.4, 128.0, 127.5, 127.4, 79.8, 79.0, 77.5, 72.5, 66.6, 65.3, 58.0, 55.3, 52.1, 51.3, 40.4, 38.6, 34.7, 29.7, 27.4, 27.03, 26.1, 24.5. MS (FAB) 633.2 [$(M+1)^+$, 100]; HRMS calcd for $C_{34}H_{53}N_2O_9$ $(M+1)^+$: 633.3751; Found 633.3759.

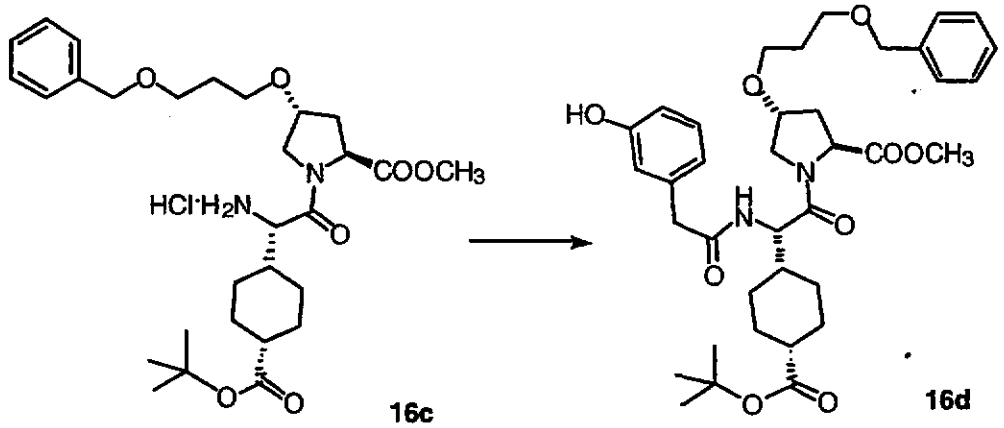
Step C:



16b 16c

The desired compound **16c** was prepared from **16b** according to the procedure of Example 14, Step H. The product was used without further purification.

Step D

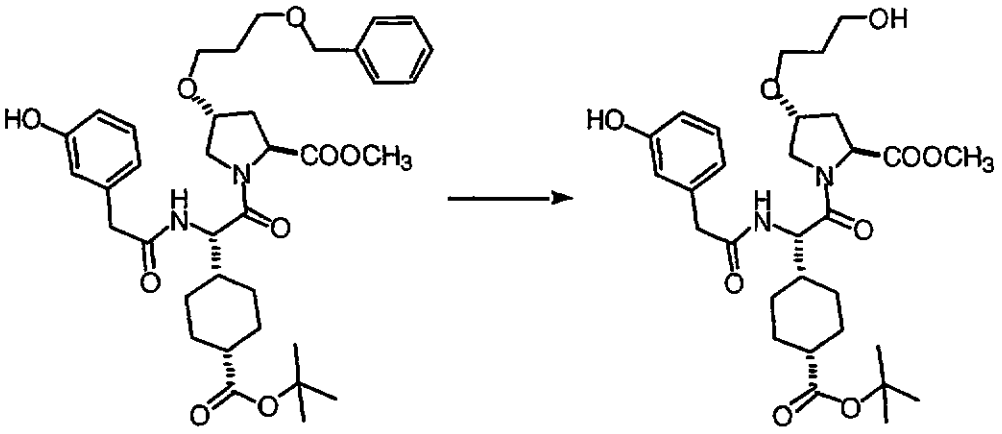


16c 16d

The desired compound **16d** was prepared from **16c** in 41% yield according to the procedure of Example 14, Step I. ^{1}H NMR ($CHCl_3$, δ) 7.34-7.26 (m, 5 H), 7.12 (t, 1 H, *J*=7.5 Hz), 6.72-6.67 (m, 3 H), 4.76-4.64 (m, 1 H), 4.47 (s, 2 H), 4.51-4.42 (m, 1 H), 4.11-4.02 (m, 2 H), 3.68 (s, 3 H), 3.70-3.65 (m, 1 H), 3.55-3.43 (m,

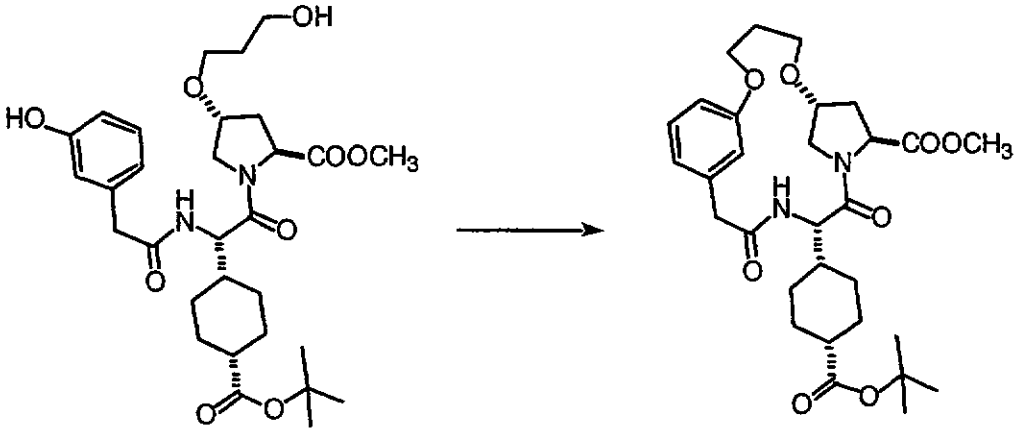
6 H), 2.54-2.42 (m, 1 H), 2.28-2.39 (m, 1 H), 2.1-1.9 (m, 3 H), 1.86-1.64 (4 H), 1.50-1.38 (m, 14 H); ^{13}C NMR ($CDCl_3$, δ) 175.0, 172.4, 171.5, 171.1, 157.1, 138.5, 136.0, 130.1, 128.5, 127.9, 127.7, 121.0, 116.0, 114.8, 80.5, 77.6, 73.0, 66.9, 66.2, 58.2, 54.3, 52.5, 52.3, 43.4, 39.4, 39.9, 34.9, 30.0, 28.2, 26.8, 26.6, 26.0, 24.0; MS (FAB) 689 [$(M+Na)^+$, 35), 667 [$(M+H)^+$, 23), 633 (5), 294 (100), 204 (39), 156 (63).

Step E:



The desired compound **16e** was prepared from **16d** according to the procedure of Example 14, Step J. The product was used without further purification.

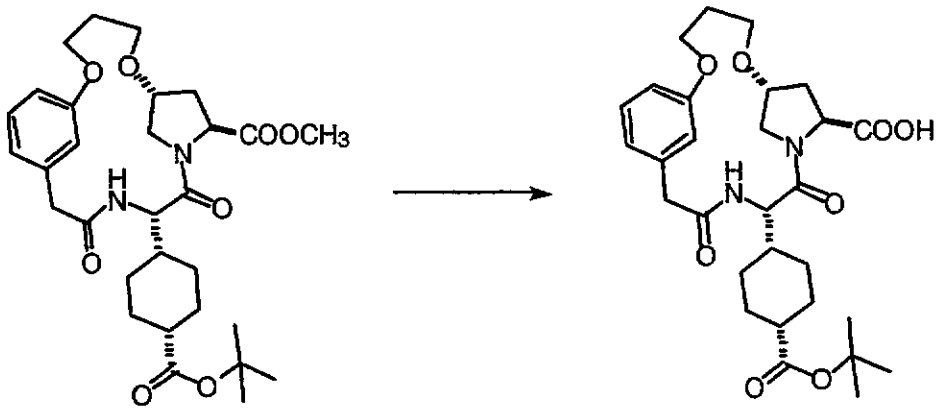
Step F



16e **16f**

The desired compound **16f** was prepared from **16e** in 20% yield according to the procedure of Example 14, Step K. ^{1}H NMR ($CDCl_3$, δ) 8.56 (d, 1 H, *J*= 7.2 Hz), 7.14 (t, 1 H, *J*=6 Hz), 6.86 (s, 1 H), 6.66 (d, 1 H, *J*=6 Hz), 6.73 (dd, 1 H, *J*=6.3, 15 Hz), 4.86-4.77 (m, 1 H), 4.40 (dd, 1 H, *J*=3.0, 2.7 Hz), 4.24-4.13 (m, 4 H), 3.70 (s, 3 H), 3.70-3.66 (m, 2 H), 3.66-3.32 (m, 3 H), 2.53 (dd, 1 H, *J*=5.7, 3.9 Hz), 2.45-2.42 (m, 1 H), 1.99-1.80 (m, 6 H), 1.60-1.57 (m, 4 H), 1.45-1.43 (m, 11 H); ^{13}C NMR ($CDCl_3$, δ) 175.8, 173.3, 173.0, 171.7, 160.0, 138.0, 130.1, 122.7, 116.8, 113.3, 81.0, 78.6, 66.3, 65.2, 58.8, 55.1, 52.5, 42.6, 42.4, 38.9, 34.6, 30.0, 28.2, 28.0, 27.0, 26.9, 26.8, 26.2; MS (FAB) 559 (M^+, 33), 327 (33), 225 (100)

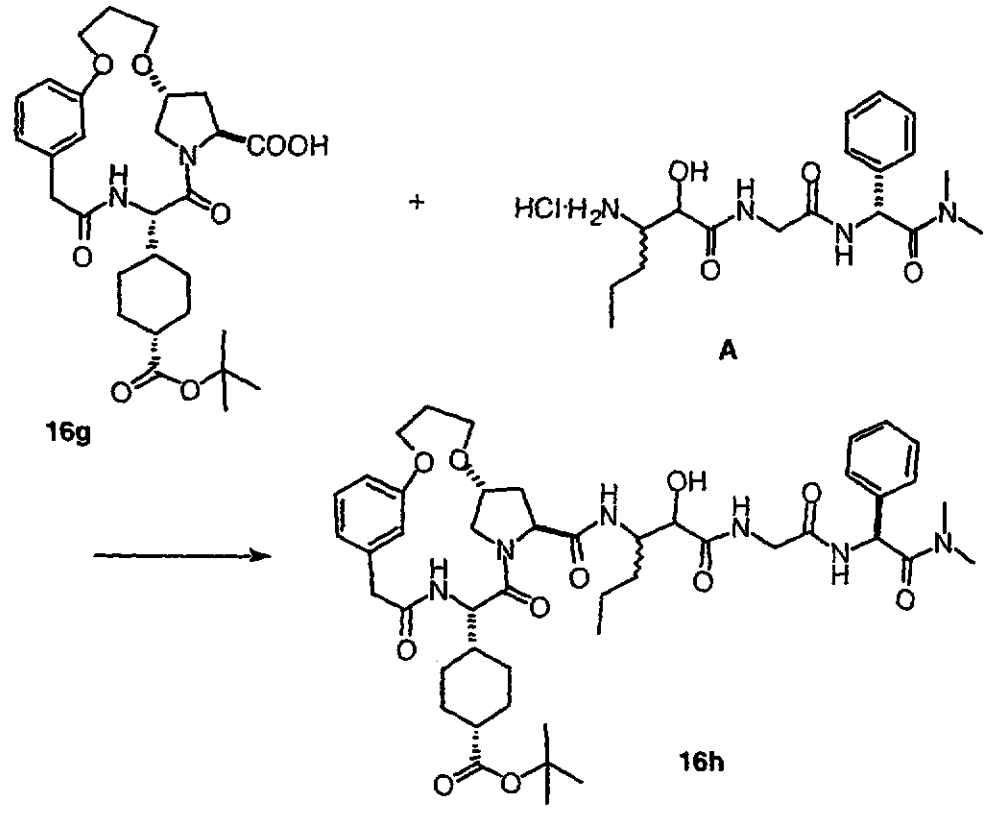
Step G:



16f **16g**

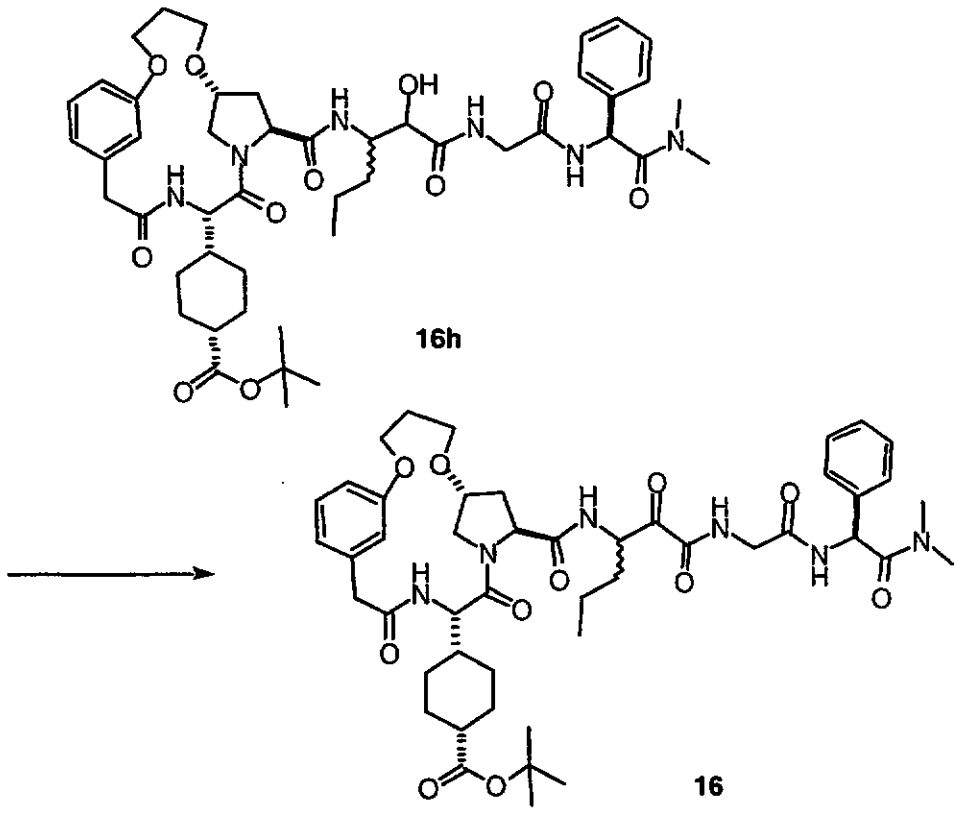
The desired compound **16g** was prepared from **16f** according to the procedure of Example 14, Step H. The product was used without further purification.

Step H:



The desired compound **16h** was prepared from **16g** and **A** according to the procedure of Example 14, Step L. The product was used without further purification.

Step I

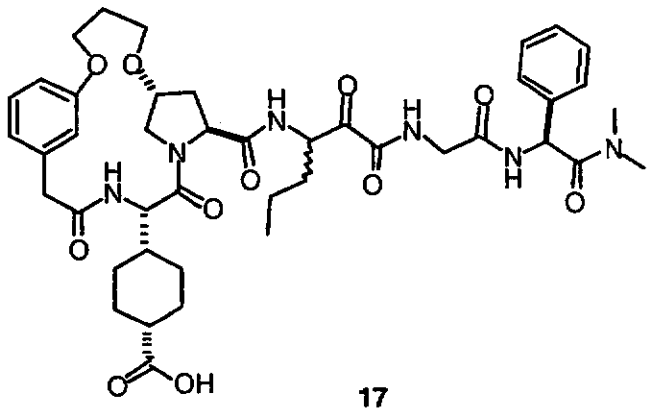


16h

16

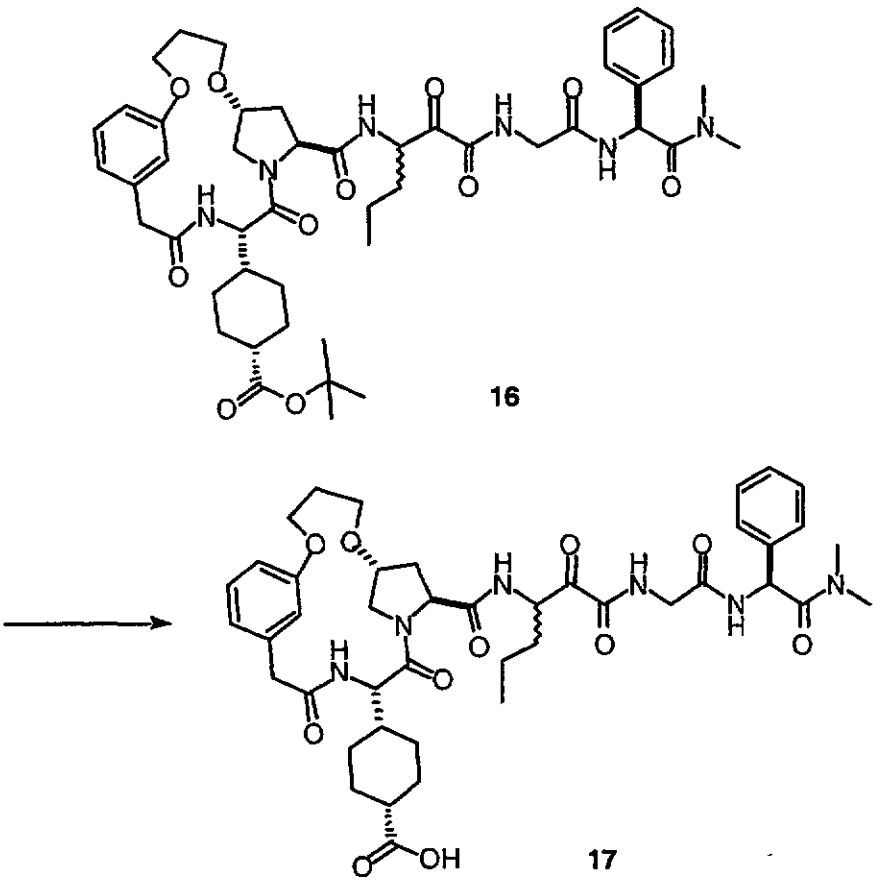
The desired compound **16** was prepared as a colorless solid from **16h** in 40% yield according to the procedure of Example 14, Step N. MS (electron spray) 889 [(M+1)$^+$, 85), 637 (20), 530 (75), 265 (100); HRMS calcd. for $C_{47}H_{65}N_6O_{11}$: 889.4711; Found 889.4699.

Example 17: Preparation of Compound 17:



17

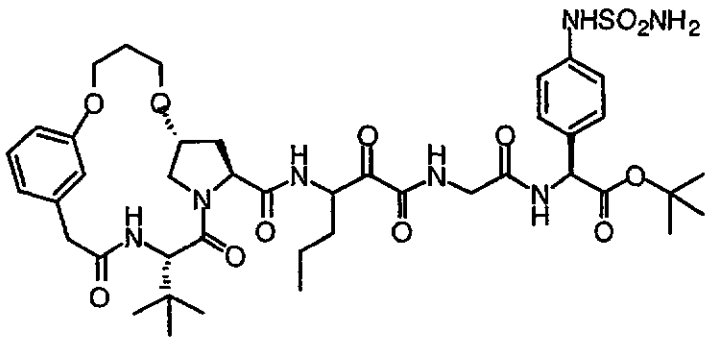
Step A



16 17

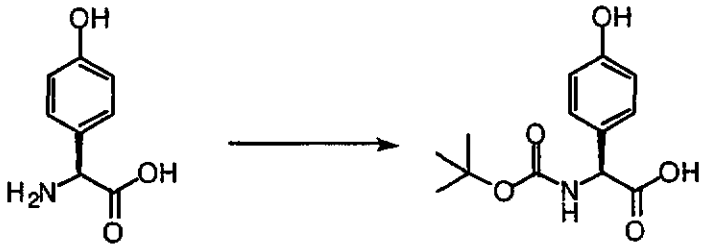
The desired compound **17** was prepared from **16** quantitatively according to the procedure of Example 15, Step A. MS (FAB) 833 [$(M+1)^+$, 100], 788 (10), 723 (5), 308 (100).

Example 18: Preparation of Compound of Formula 18:



18

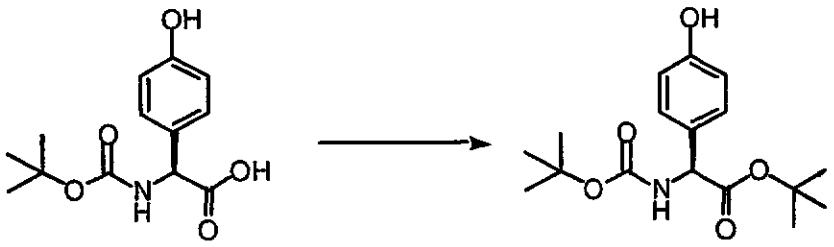
Step A:



18a 18b

To a cold (0°C) slurry of **18a** (15.0 g, 90 mmol) in dioxane (100 mL), water (100 mL), and saturated sodium bicarbonate (100 mL) was added a solution of tert-butoxycarbonyl anhydride (7.2 g, 33 mmol) in dioxane (100 mL). The reaction mixture was slowly warmed to ambient temperature over 6 hr. The reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with diethylether (2 x 150 mL). The ether layer was discarded. The aqueous layer was acidified slowly with solid citric acid (pH ~ 4) and extracted with ethyl acetate (3 x 150 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford **18b** (14.6 g, 61% yield) as a white foam.

Step B:

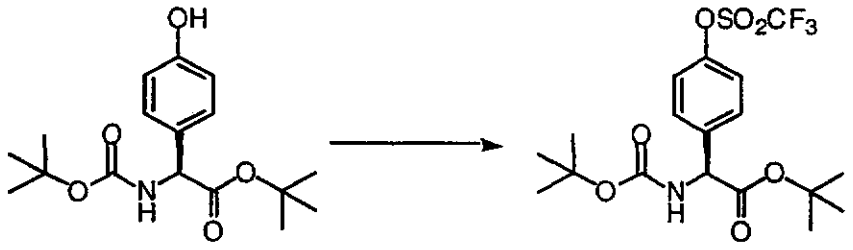


18b 18c

To a 80°C solution of **18b** (14.6 g, 54.68 mmol) in toluene (230 mL) was added DMF-di-tert-butyl acetal (53 mL, 218.72 mmol) dropwise over 2 hrs. The reaction mixture was maintained at the same temperature for 1 hr after the addition was complete. It was then cooled to ambient temperature and

concentrated. The residue was purified by flash column chromatography using 96/4 to 90/10 dichloromethane/ethyl acetate to provide the required compound **18c** (7.53 g, 43% yield). HRMS (FAB) Calcd for $C_{17}H_{26}NO_5$: 324.1811 $(M+H)^+$. Found: 324.1807.

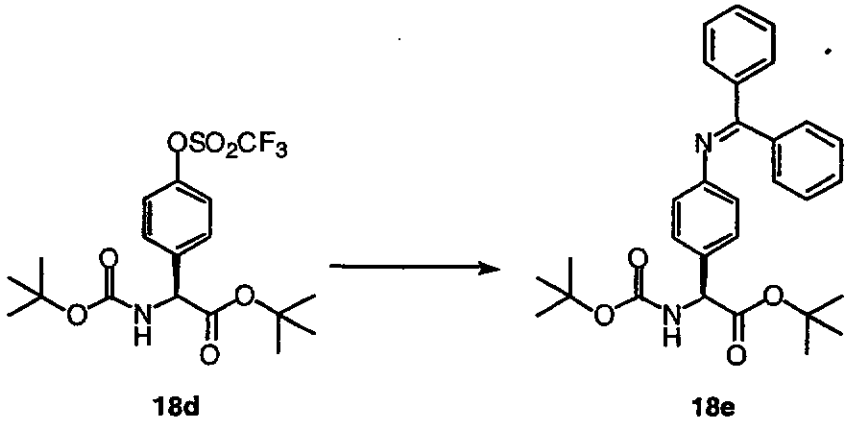
Step C:



18c **18d**

To a cold (0°C) solution of **18c** (7.5 g, 23.22 mmol) in dichloromethane (100 mL) was added triethylamine (7.12 mL, 51.08 mmol) followed by triflic anhydride (4.30 mL, 25.54 mmol) dropwise. The reaction mixture was slowly warmed to ambient temperature over 4 hrs. It was quenched with saturated bicarbonate solution and extracted into dichloromethane. The combined organic layer was washed with saturated bicarbonate and brine, dried (Na_2SO_4) and concentrated. The brown residue was purified by flash column chromatography using dichloromethane to provide 7.74 g of **18d** (73% yield).

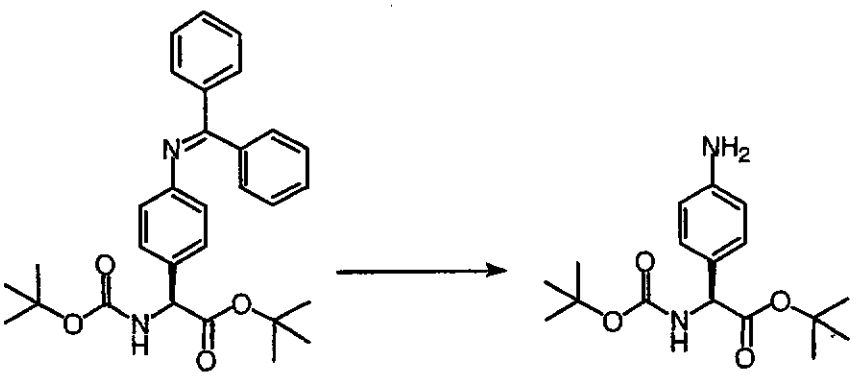
Step D:



18d **18e**

To an oven dried flask was added THF (75 mL, previously deoxygenated by bubbling argon), palladium acetate (74 mg, 0.33 mmol), R-(+)-BINAP (311 mg, 0.495 mmol), and cesium carbonate (5.38 g, 16.5 mmol) under argon atmosphere. To this mixture was added **18d** (5.0 g, 11 mmol) followed by diphenylketimine (2.77 mL, 16.5 mmol). The flask was flushed with argon and heated to reflux for 12 hrs (overnight). Cooled the reaction mixture to ambient temperature and diluted with ether (500 mL). The organic layer is washed with saturated ammonium chloride solution (2 x 300 mL), dried (Na_2SO_4) and concentrated. Purification by flash chromatography using 100/0 to 90/10 dichloromethane/ethyl acetate provided the required product **18e** (3.58 g) in 67% yield.

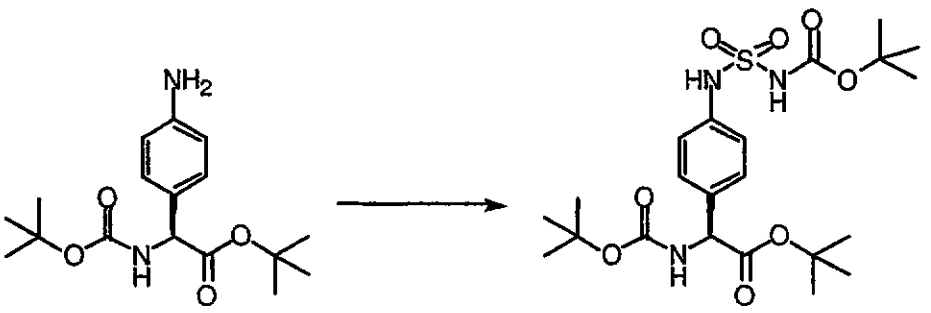
Step E:



18e **18f**

To a solution of **18e** (3.0 g, 6.17 mmol) in methanol (62 mL) was added sodium acetate (1.218 g, 14.8 mmol), and hydroxylamine hydrochloride (0.774 g, 11.11 mmol). The reaction mixture was stirred at ambient temperature for 3 hrs. The reaction mixture was concentrated, diluted with dichloromethane and washed with 0.1 N NaOH solution. The organic layer was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography using 95/5 to 92/8 dichloromethane/ethyl acetate afforded **18f** (1.31 g) in 66% yield.

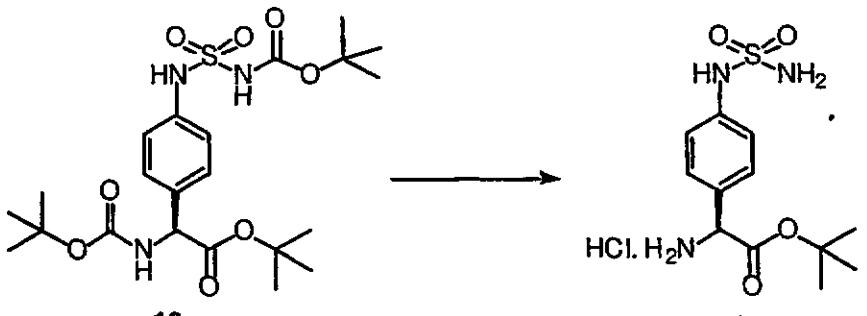
Step F:



18f **18g**

To a cold (-20°C) solution of dichloromethane (2 mL) was added chlorosulfonyl isocyanate (0.16 mL, 1.87 mmol). To this was added tert-butanol (0.18 mL, 1.87 mmol) in dichloromethane (2 mL) and slowly warmed to 0°C over 2.5 hrs. At this time a solution of **18f** (0.6 g, 1.87 mmol) in dichloromethane (6 mL) containing triethylamine (0.52 mL, 3.73 mmol) was added dropwise. The reaction mixture was warmed to ambient temperature over 12 hrs (overnight). Added saturated bicarbonate and dichloromethane and the organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography using 95/5 to 90/10 dichloromethane/ethyl acetate provided **18g** (0.59 g) in 63% yield.

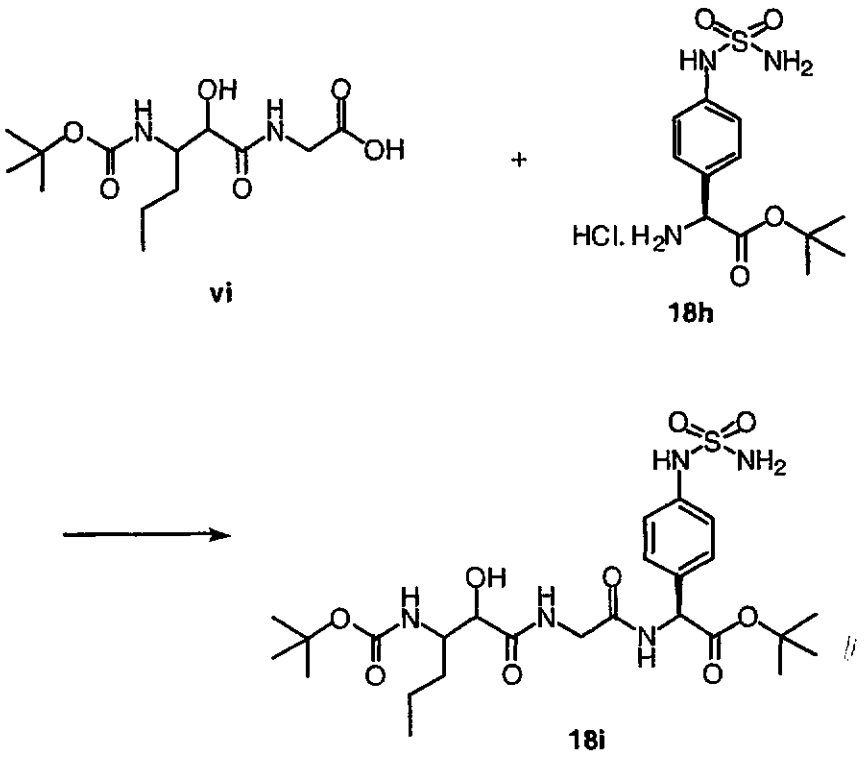
Step G:



18g **18h**

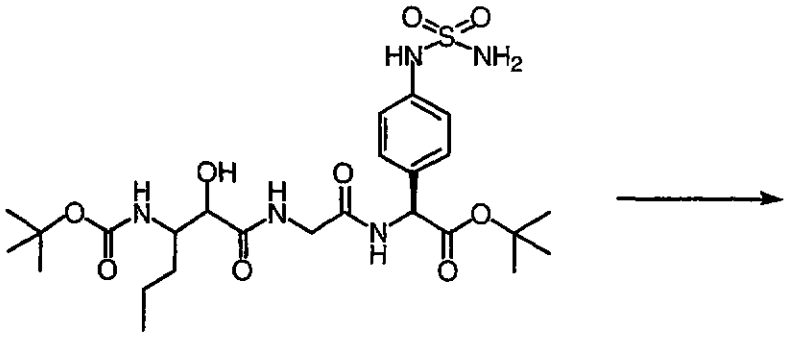
The expected product **18h** was synthesized as described earlier for the Example 1, Step C. The material was carried to the next step as it was.

Step H:

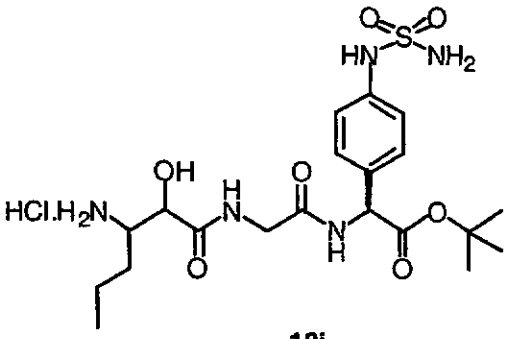


The expected product **18i** was synthesized as described earlier for the Example 1, Step D. The crude material was purified by flash chromatography using 98/2 to 90/10 dichloromethane/methanol to afford **18i** in 34% yield.

Step I:



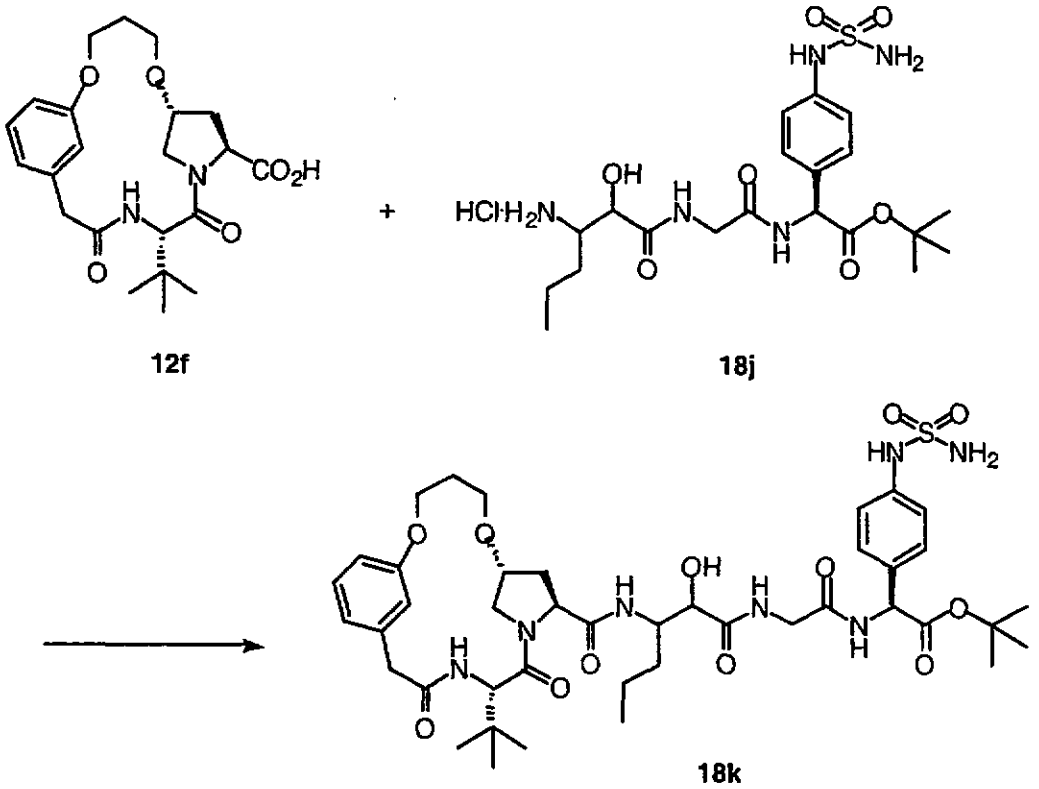
18i



18j

The expected product **18j** was synthesized as described earlier for the Example 1, Step C. The material was carried to the next step as it was.

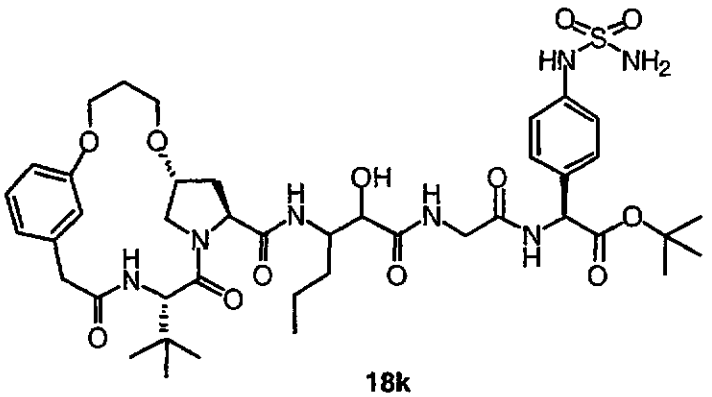
Step J:



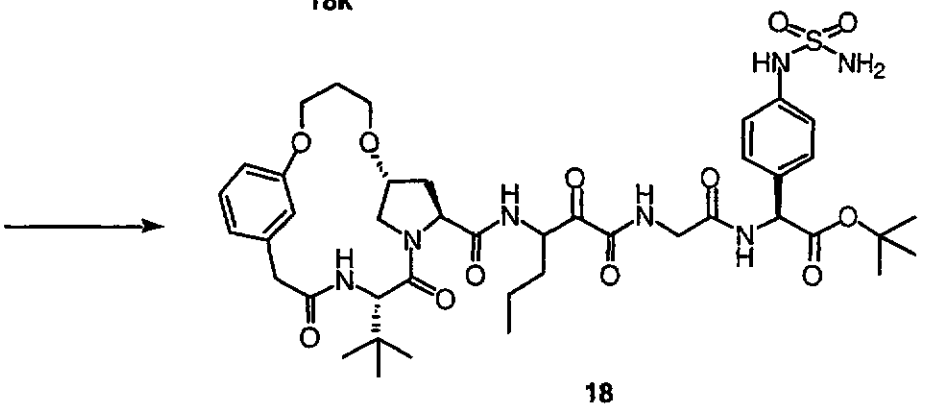
12f + 18j → 18k

The expected product **18k** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step.

Step K:



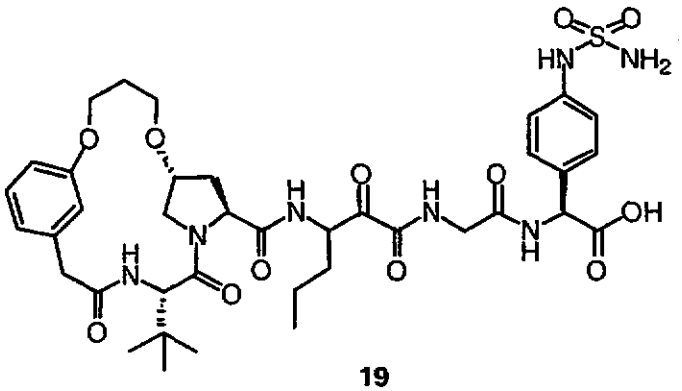
18k



18

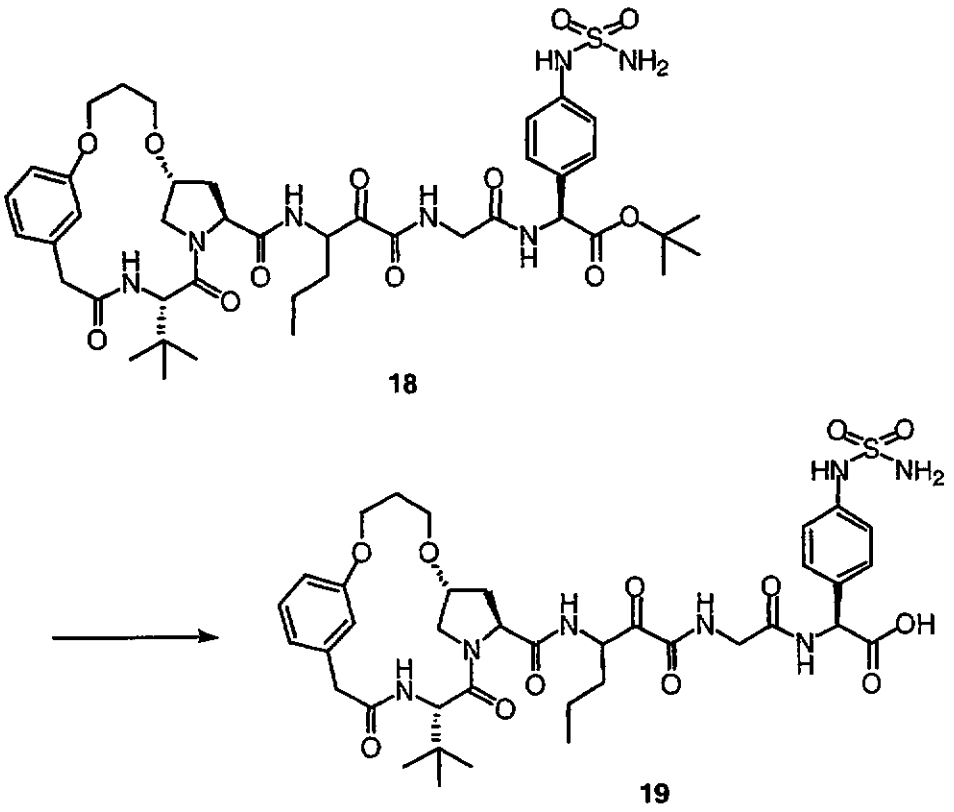
The desired product **18** was obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 98/2 to 92/8 dichloromethane/MeOH afforded **11** as a mixture of diastereomers in 13% yield (for 2 steps).

Example 19: Preparation of Compound of Formula 19:



19

Step A:

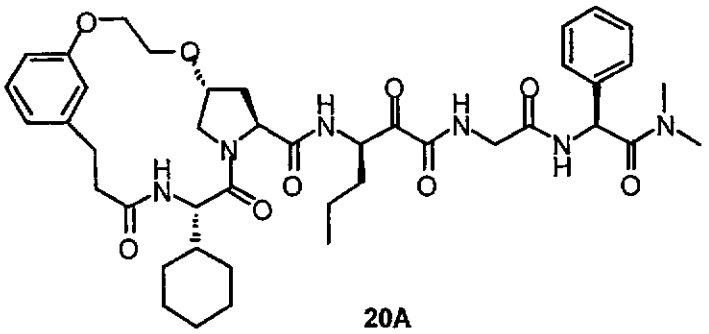


18

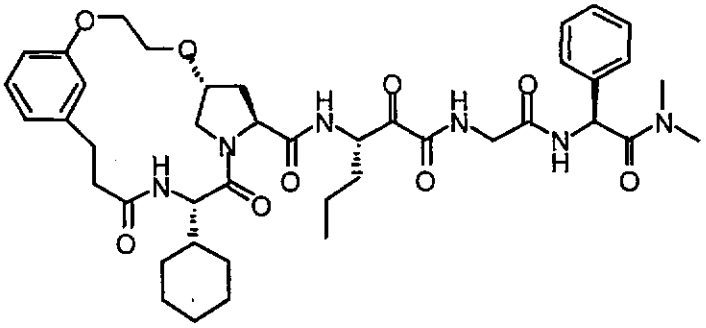
19

The expected product **19** was synthesized as described earlier for the Example 3, Step A, in quantitative yield.

Example 20: Preparation of Compounds of Formulas 20A and 20B:

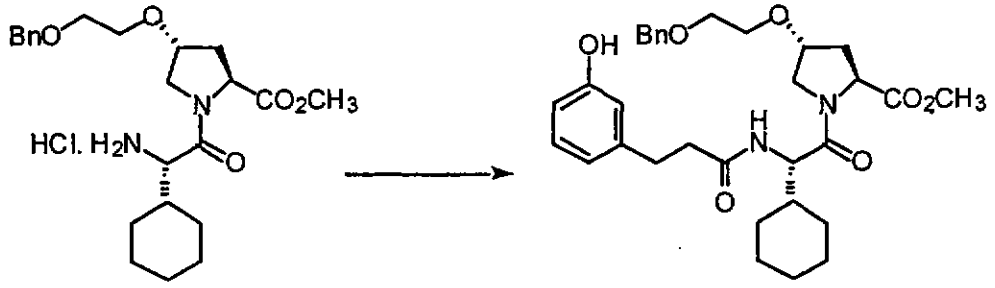


20A



20B

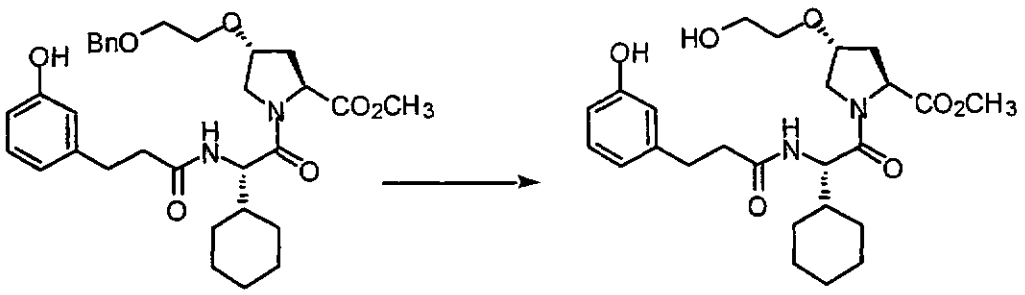
Step A:



7e **20a**

The desired product **20a** was obtained by the method described for Example 1, Step F. The material was purified by flash column chromatography using 98/2 dichloromethane/methanol to provide **20a** in 97% yield. HRMS (FAB) Calcd for $C_{32}H_{43}N_2O_7$: 567.3070 $(M+H)^+$. Found: 567.3073.

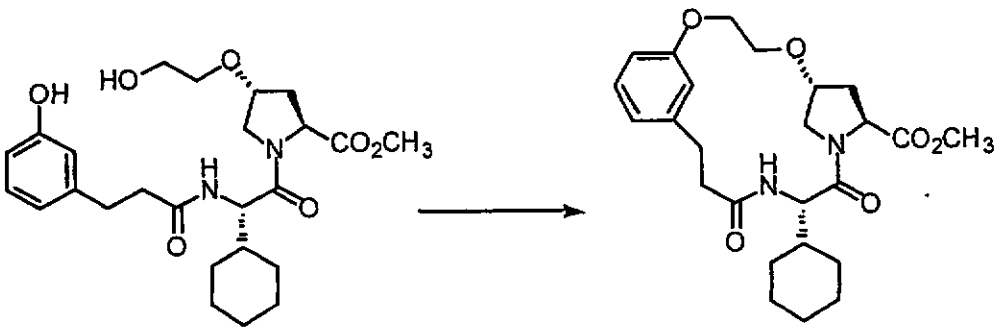
Step B:



20a **20b**

The desired product **20b** was obtained by the method described for Example 1, Step G. The material was purified by flash column chromatography using 98/2 to 96/4 dichloromethane/methanol to provide **20b** in 81% yield. HRMS (FAB) Calcd for $C_{25}H_{37}N_2O_7$: 477.2601 $(M+H)^+$. Found: 477.2606.

Step C:

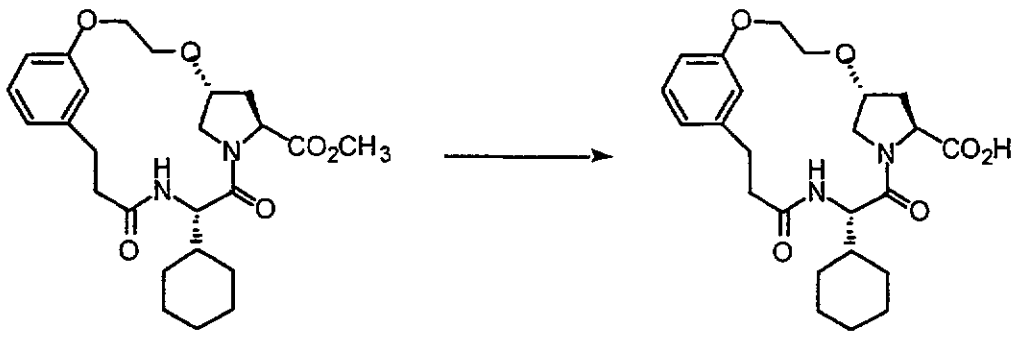


20b **20c**

The desired product **20c** was obtained by the method described for Example 1, Step H. Purification by column chromatography using 99/1 dichloromethane/methanol afforded **20c** along with triphenylphosphine oxide. This mixture was taken to the next step. HRMS (FAB) Calcd for $C_{25}H_{35}N_2O_6$: 459.2495 $(M+H)^+$. Found: 459.2490.

Step D:

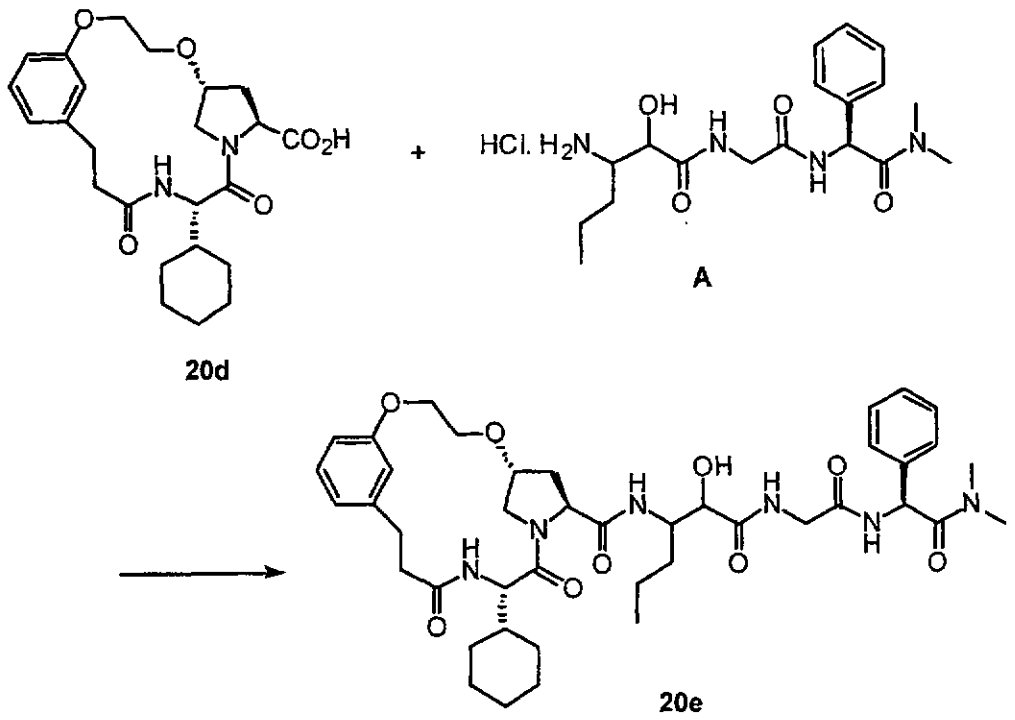
15 SEP 2004



20c 20d

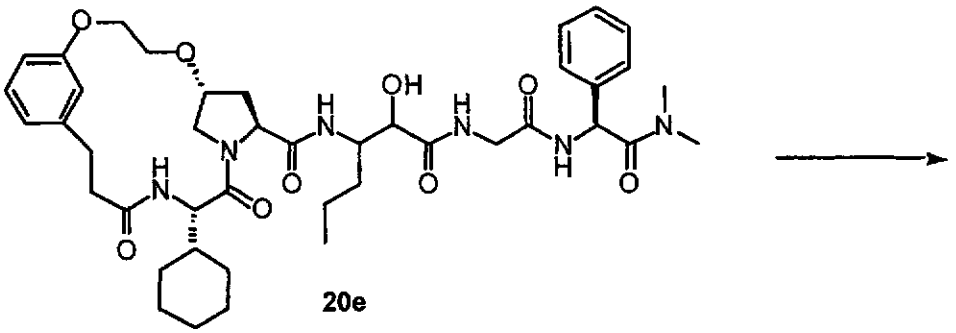
The desired product **20d** was obtained by the method described for Example 1, Step I. Yield of **20d** (for 2 steps) = 23%. ^{1}H NMR (DMSO-d_6) 0.84 (m, 2H), 1.10 (m, 3H), 1.56-1.67 (m, 6H), 1.75-1.81 (m, 1H), 2.32-2.49 (m, 3H), 2.55-2.59 (m, 1H), 2.94 (dt, 1H), 3.50 (dd, 1H), 3.56-3.65 (m, 2H), 3.99 (dd, 1H), 4.06-4.23 (m, 4H), 4.37 (t, 1H), 6.64-6.74 (m, 3H), 7.08 (app. t, 1H), 7.95 (d, 1H), 12.30 (br. s, 1H); ^{13}C NMR δ (DMSO-d_6) 25.25, 25.97, 28.30, 28.55, 30.61, 33.77, 36.04, 39.41, 52.52, 54.02, 57.22, 66.38, 68.03, 77.49, 114.75, 115.37, 121.14, 128.86, 142.66, 158.92, 169.87, 170.83, 172.99; HRMS (FAB) Calcd for $C_{24}H_{33}N_2O_6$: 445.2339 $(M+H)^+$. Found: 445.2343.

Step E:

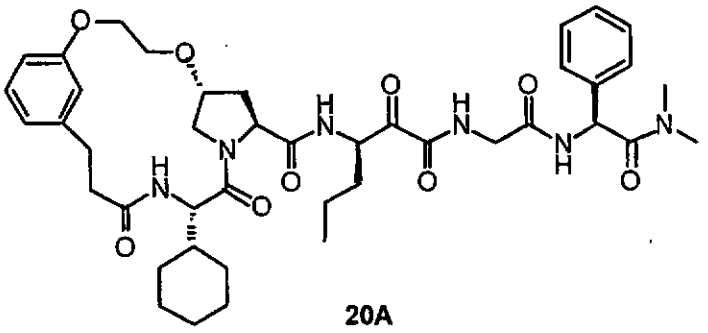


The expected product **20e** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step.

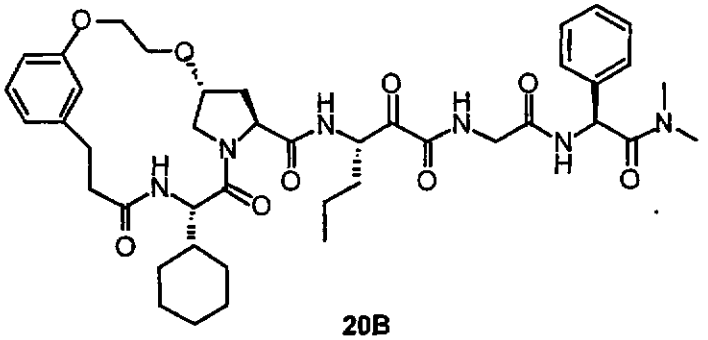
Step F:



20e



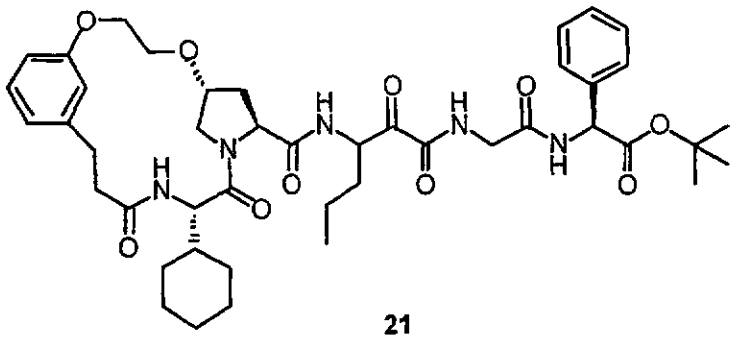
20A



20B

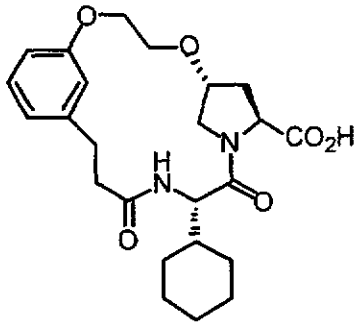
The desired products **20A** and **20B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 100/0 to 98/2 dichloromethane/methanol afforded separate isomers **20A** and **20B**, and some mixture. Combined yield = 50% (for 2 steps). HRMS (FAB) Calcd for $C_{42}H_{57}N_6O_9$: 789.4187 $(M+H)^+$. Found: 789.4179 (**20A**) and 789.4187 (**20B**).

Example 21: Preparation of Compound of Formula 21:



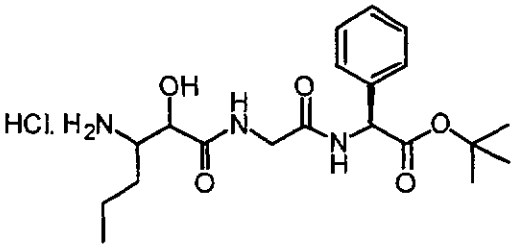
21

Step A:

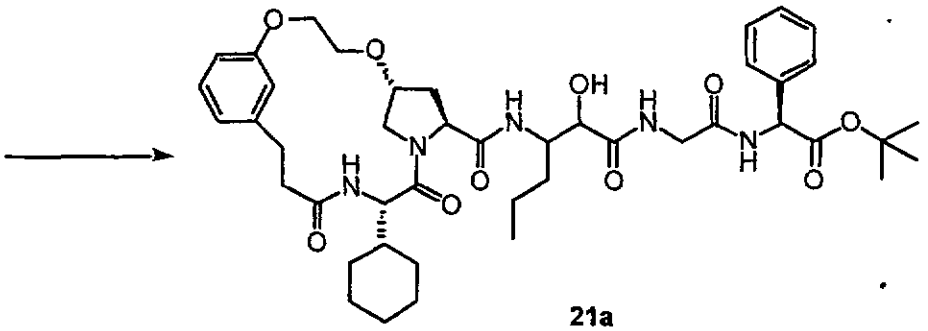


20d

+



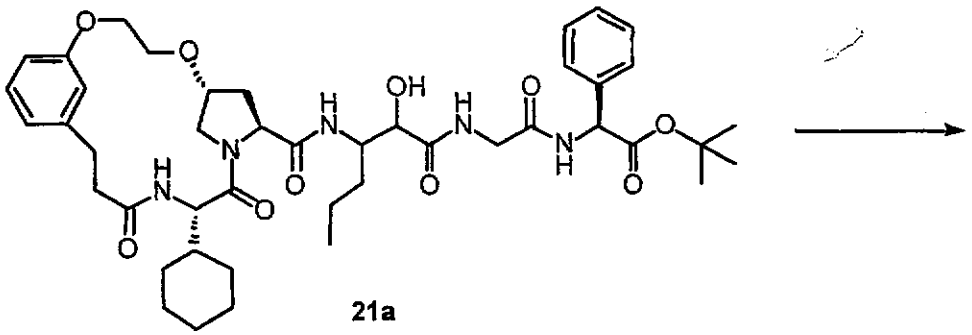
B



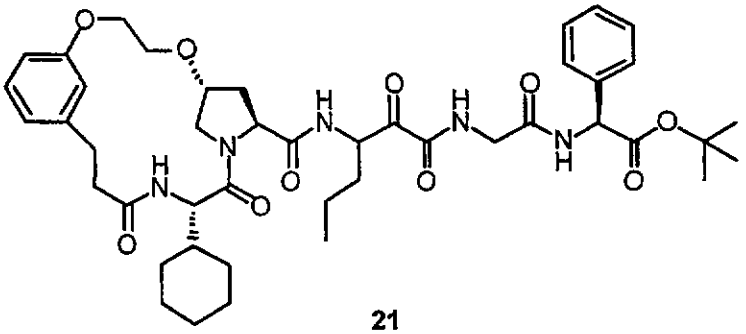
21a

The expected product **21a** was synthesized as described earlier for the Example 2, Step A. The material after work-up was of sufficient purity to be carried forward to the next step.

Step B:



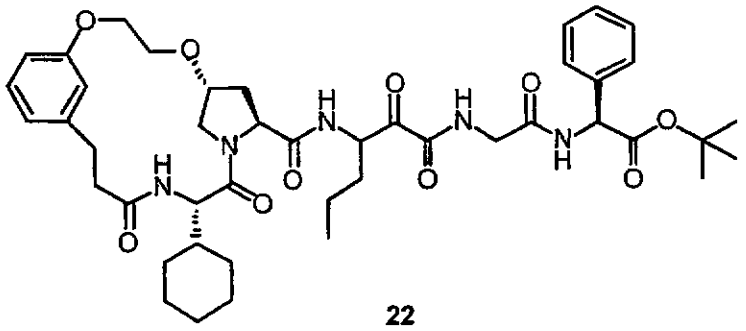
21a



21

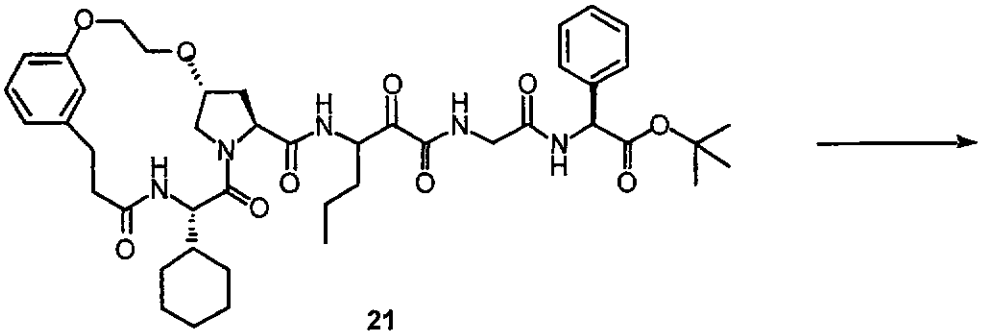
The desired product **21** was obtained by the oxidation protocol described previously for Example 2, Step B. Purification by flash column chromatography using 100/0 to 98/2 dichloromethane/methanol afforded **21** in 38% yield. HRMS (FAB) Calcd for $C_{44}H_{60}N_5O_{10}$: 818.4340 $(M+H)^+$. Found: 818.4329.

Example 22: Preparation of Compound of Formula 22:

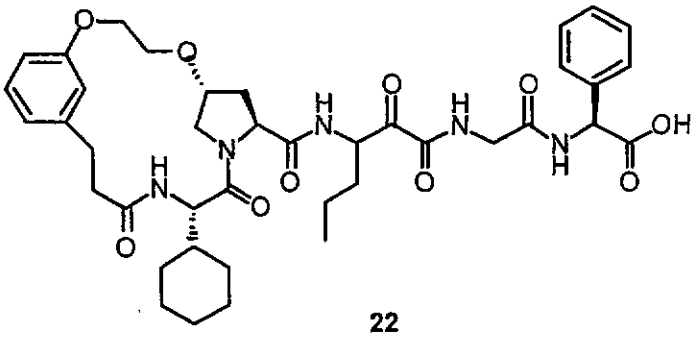


22

Step A:



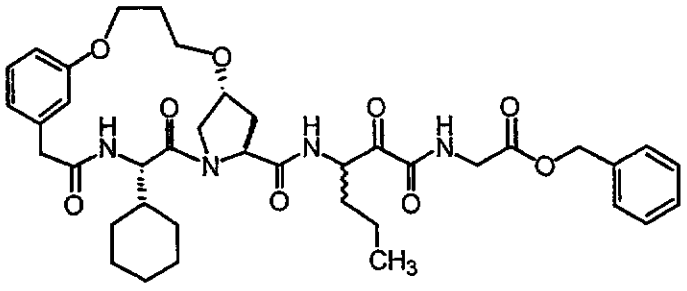
21



22

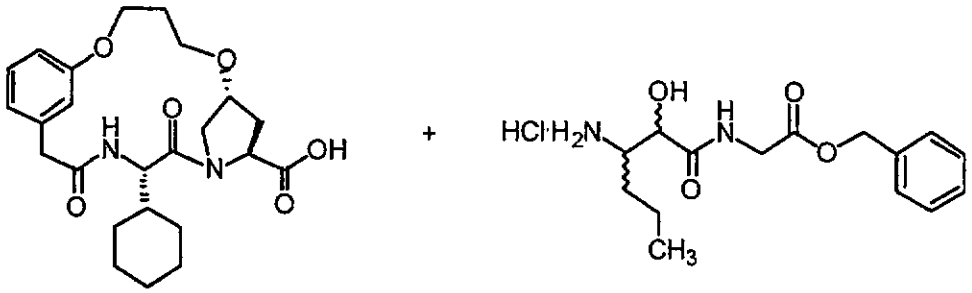
The expected product **22** was synthesized as described earlier for the Example 3, Step A, in quantitative yield. HRMS (FAB) Calcd for $C_{40}H_{52}N_5O_{10}$: 762.3714 $(M+H)^+$. Found: 762.3722.

Example 23: Preparation of Compound of Formula 23:

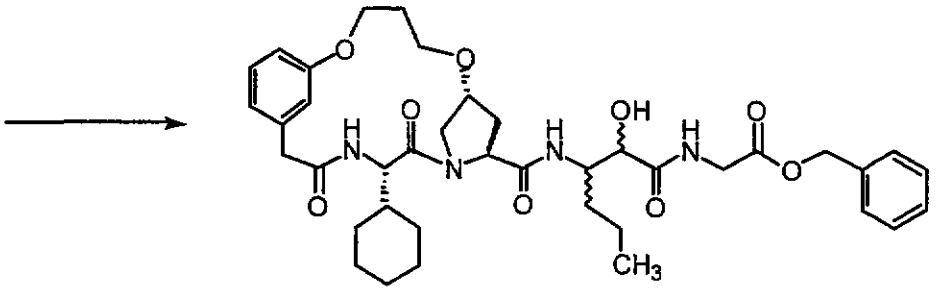


23

Step A:



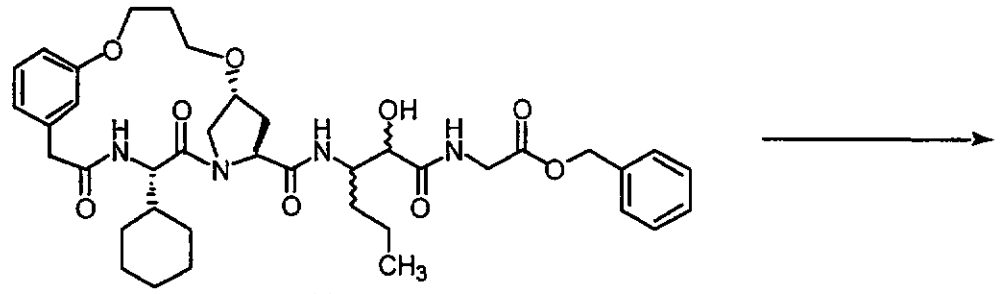
1l D



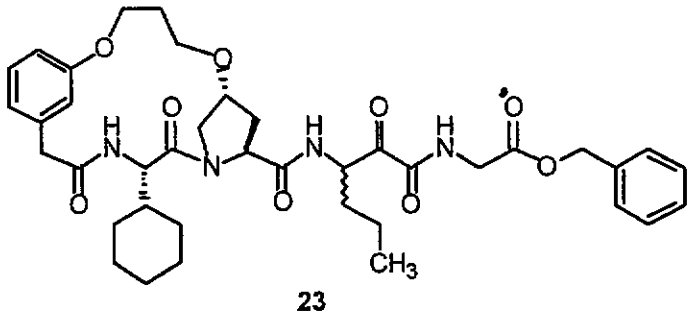
23a

The desired compound **23a** was prepared in 58 % yield from **1l** and D according to the method of Example 1, Step J.

Step B:



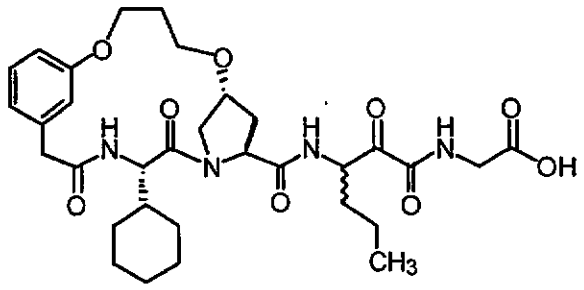
23a



23

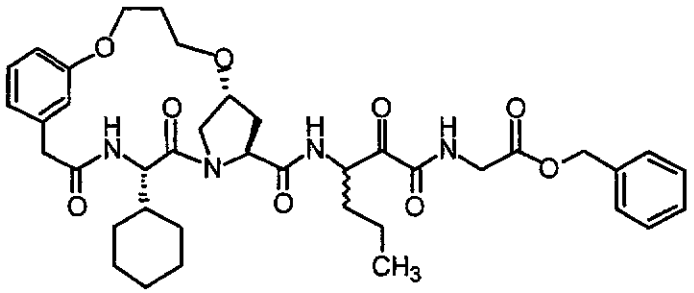
The desired compound **23** was prepared in 79 % yield from **23a** according to the method of Example 1, Step K.

Example 24: Preparation of Compound of Formula 24:

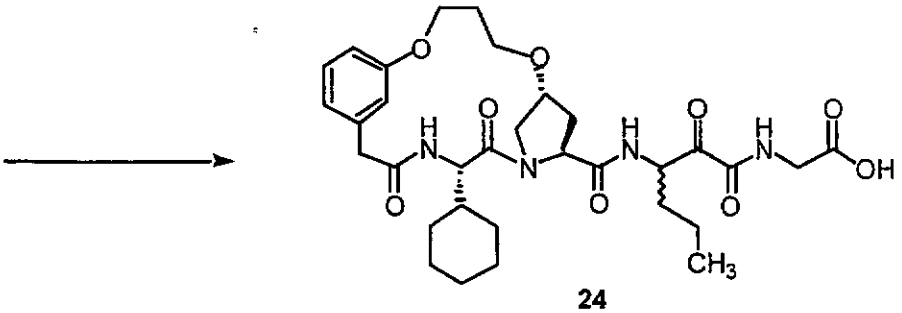


24

Step A:



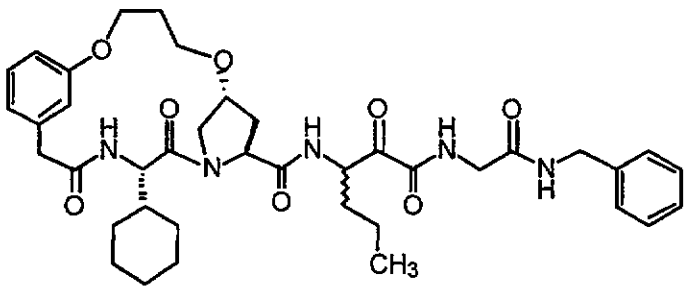
23



24

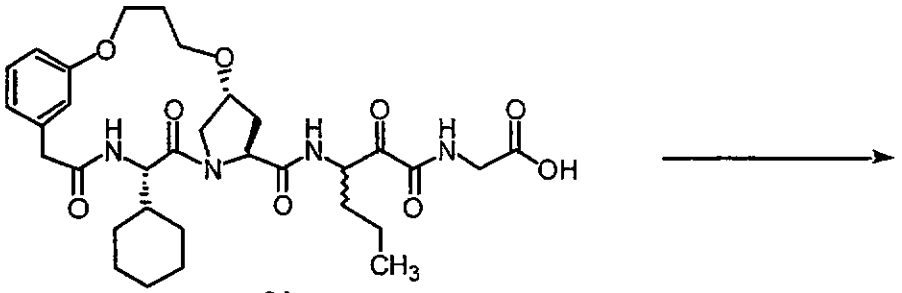
The solution of the benzyl ester **23** (80 mg, 0.11 mmol) in ethanol (30 mL) and methanol (15 mL) was stirred at rt. for 3 h under hydrogen in the presence of palladium on carbon (50 mg). The reaction progress was monitored by TLC. After careful filtration through a celite pad, solvents were then removed *in vacuo* to give a white solid (67 mg, quant.).

Example 25: Preparation of Compound of Formula 25:

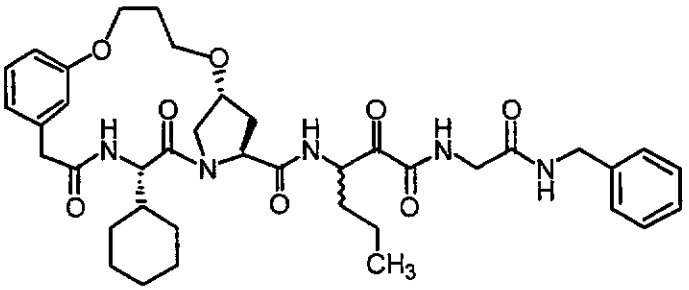


25

Step A:



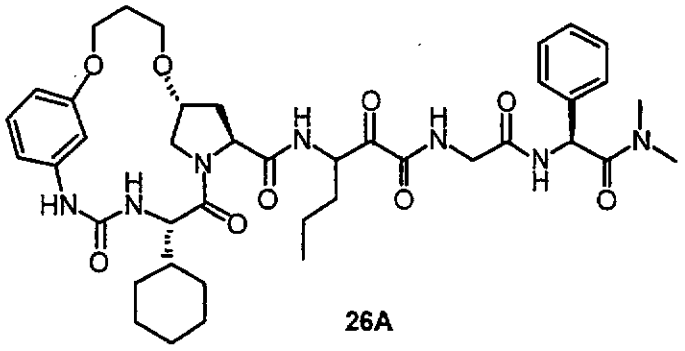
24



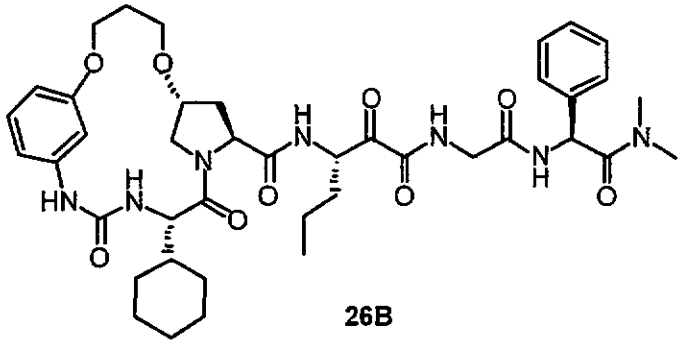
25

The desired compound **25** was prepared in 53 % yield from **24** according to the method of Example 1, Step J, except substituting benzyl amine for amine **A**.

Example 26: Preparation of Compounds of Formulas 26A and 26B:

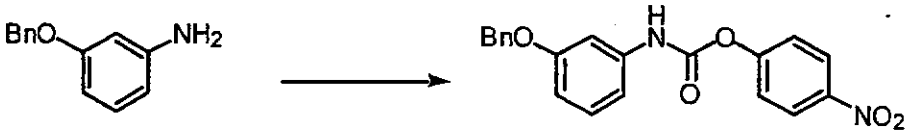


26A



26B

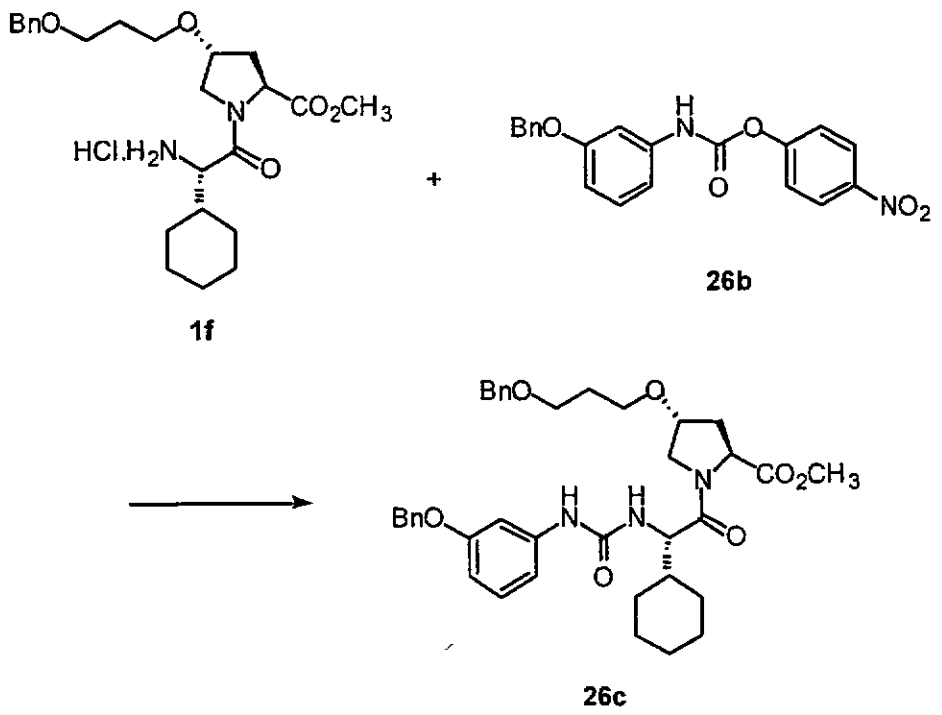
Step A:



26a **26b**

To a cold (0°C) solution of **26a** (4.0 g, 20 mmol) in THF/MeCN (35/5 mL) was added 4-nitrophenyl chloroformate (4.86 g, 24 mmol) and then pyridine (1.9 mL, 24 mmol). The reaction mixture was warmed to ambient temperature over 4.5 hrs. Reaction was monitored till consumption of **26a** (needed to add some more of other two reagents). The reaction was quenched by adding water, the organics were separated, washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford the product **26b**. This material was sufficiently pure for further studies.

Step B:



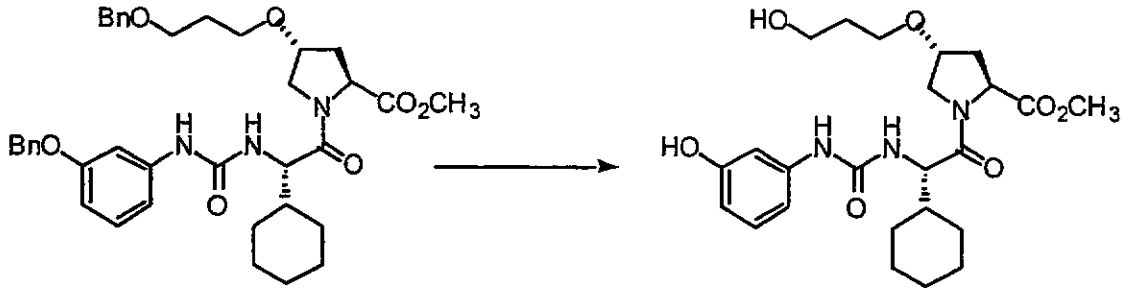
1f

26b

26c

To a solution of **1f** (2.3 g, 5.1 mmol) in dichloromethane/DMF (25/5 mL) at 0°C was added **26b** (2.24 g, 6.1 mmol) followed by triethylamine (0.86 mL, 6.1 mmol). Few crystals of imidazole were added and the reaction mixture stored at -8°C for 16 hrs. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, 10% aqueous citric acid solution, dried (Na_2SO_4), and evaporated *in vacuo*. The crude material was purified by flash column chromatography using 100/0 to 70/30 dichloromethane/ethyl acetate to provide **26c** (1.2 g, 38% yield). HRMS (FAB) Calcd for $C_{38}H_{48}N_3O_7$: 658.3492 $(M+H)^+$. Found: 658.3483.

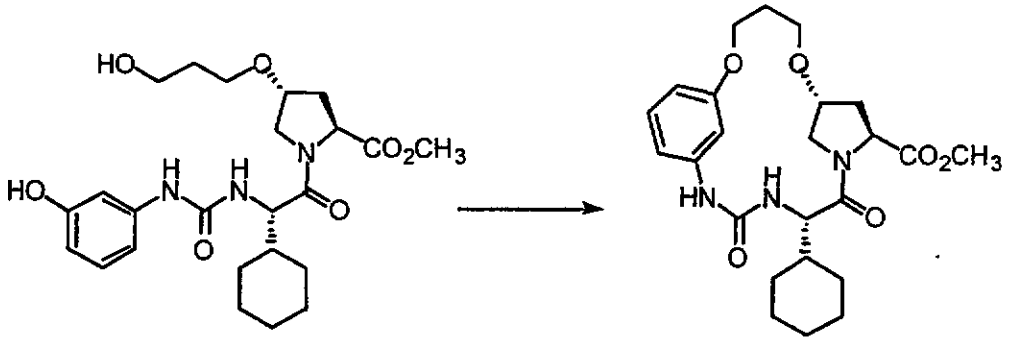
Step C:



26c 26d

The desired product **26d** was obtained by the method described for Example 1, Step G. The crude material was carried to the next step as it was. HRMS (FAB) Calcd for $C_{24}H_{36}N_3O_7$: 478.2553 $(M+H)^+$. Found: 478.2547.

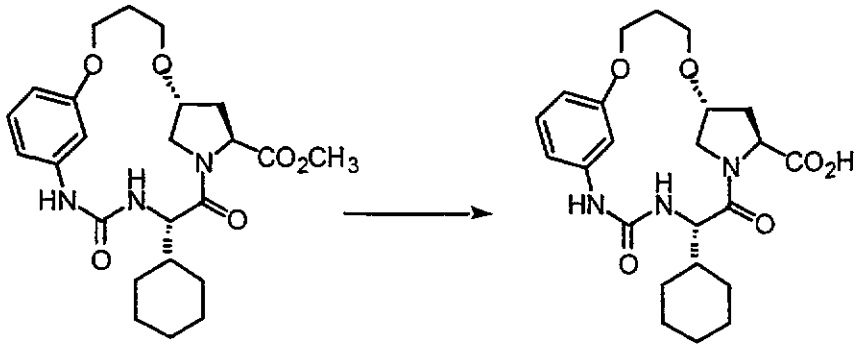
Step D:



26d 26e

The desired product **26e** was obtained by the method described for Example 1, Step H. Purification by column chromatography using 99/1 dichloromethane/methanol afforded **26e** along with triphenylphosphine oxide. This mixture was taken to the next step.

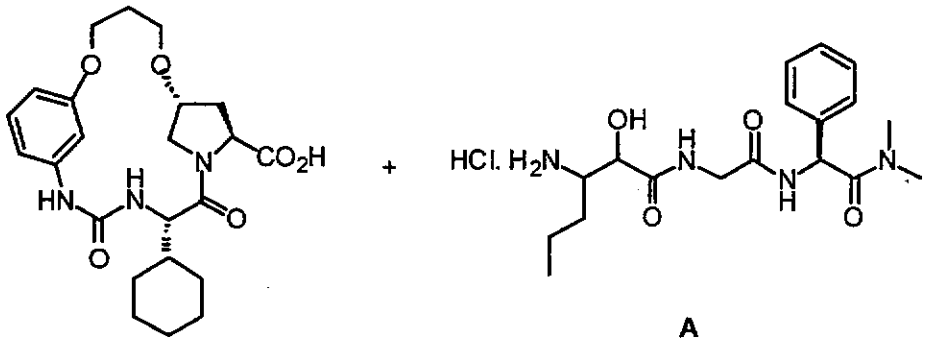
Step E:



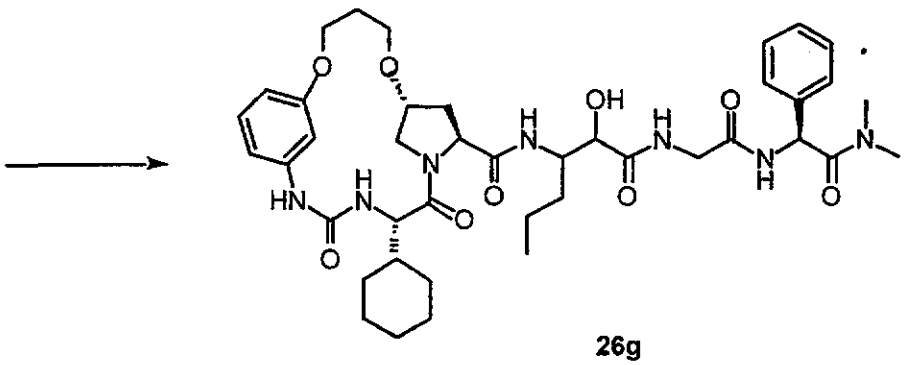
26e 26f

The desired product **26f** was obtained by the method described for Example 1, Step I. HRMS (FAB) Calcd for $C_{23}H_{32}N_3O_6$: 446.2291 $(M+H)^+$. Found: 446.2290.

Step F:



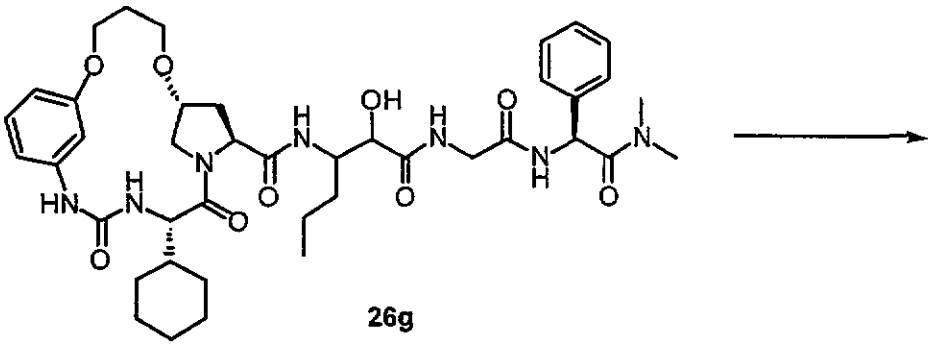
26f A



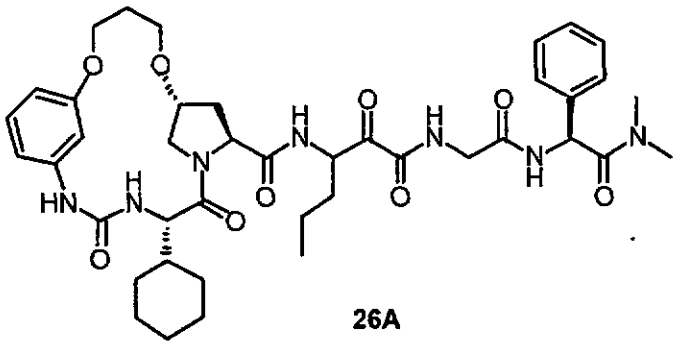
26g

The desired product **26g** was obtained by the method described for Example 1, Step J. The crude material was purified by flash column chromatography using 98/2 dichloromethane/methanol to provide **26g** in 31% yield (3 steps). HRMS (FAB) Calcd for $C_{41}H_{58}N_7O_9$: 792.4296 $(M+H)^+$. Found: 792.4284.

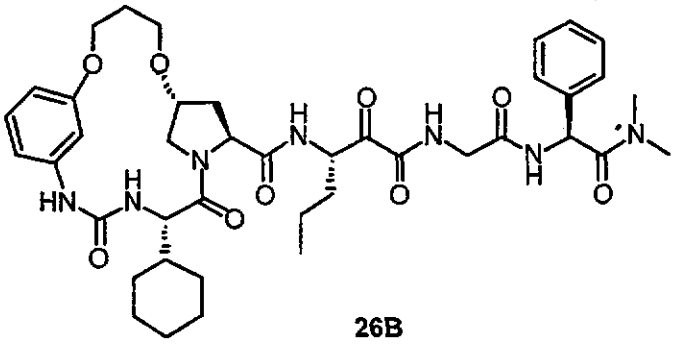
Step G



26g



26A

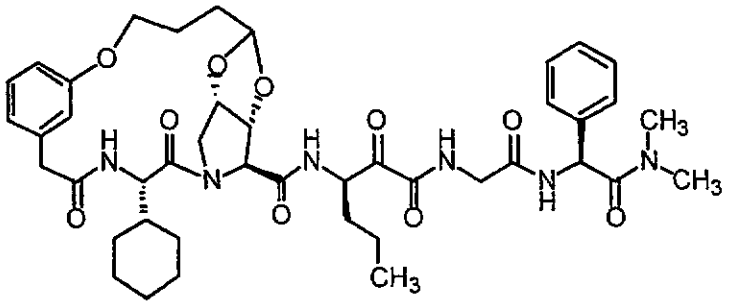


26B

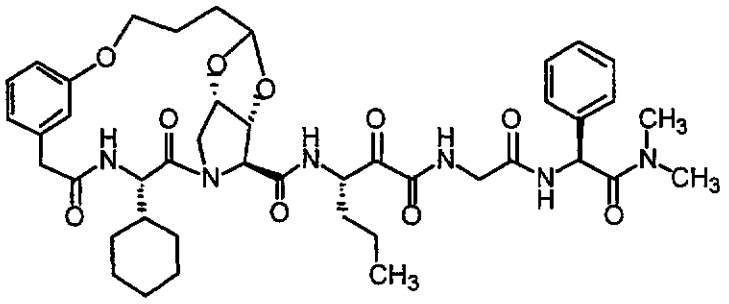
The desired products **26A** and **26B** were obtained by the method described for Example 1, Step K. Purification by column chromatography

using 99/1 to 95/5 dichloromethane/methanol provided **26A** (as a mixture) and **26B** (pure lower R_f isomer). Combined yield = 25%.

Example 27: Preparation of Compound 27:

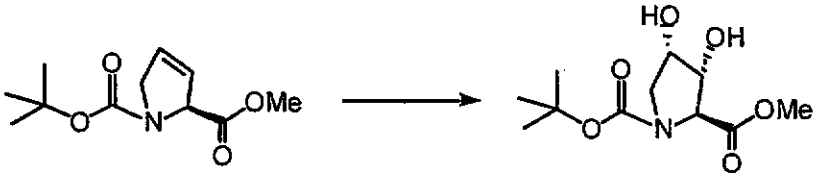


27A



27B

Step A

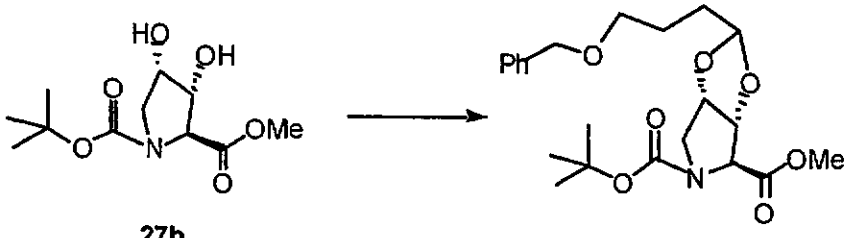


27a **27b**

To the mixture of Boc-3,4-didehydroproline-OMe (**27a**, 5.30 g, 23.4 mmol), *N*-methylmorpholine-*N*-oxide (4.75 g, 35.1 mmol) in acetone (10 mL) and water (15 mL) at rt. was added an Osmium tetroxide solution in tert-butanol (2.5% w/w, 3.5 mL, 0.344 mmol). To this cloudy solution was added THF until the mixture became almost homogeneous. After stirred at rt. overnight, saturated aqueous sodium thiosulfate solution (30 mL) was added and 10 min later, followed by addition of EtOAc (300 mL) and brine (80 mL). After layers were separated, aqueous solution was extracted with EtOAc

(2X100 mL). Organic solutions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give a dark liquid. Flash chromatography (4 to 8 % MeOH/CH_2Cl_2) afforded **27b** (4.73 g, 18.1 mmol, 77 %) as an oil.

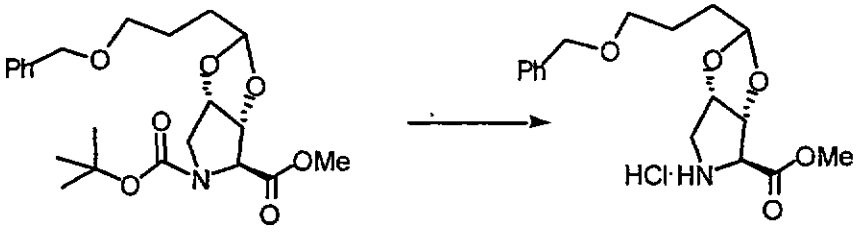
Step B



27b **27c**

To a suspension of the diol **27b** (1.6 g, 6.12 mmol) magnesium sulfate (4.0 g, 33.2 mmol) and 3-benzyloxypropionaldehyde (2.32 g, 13.0 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0°C was added *p*-toluenesulfonic acid (150 mg, 1.01 mmol). The resulting mixture was stirred vigorously and allowed to warm to rt. along with the ice-bath overnight (18 h). Saturated sodium bicarbonate solution (60 mL), water (30 mL) and CH2Cl2 (100 mL) were added and the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (2 X 100 mL) and combined organic solution was dried (MgSO4), filtered and concentrated in vacuo to give a colorless oil. Flash chromatography (5 to 15 % EtOAc/CH_2Cl_2) afforded **27c** (2.35 g, 5.57 mmol, 91 %) as an oil.

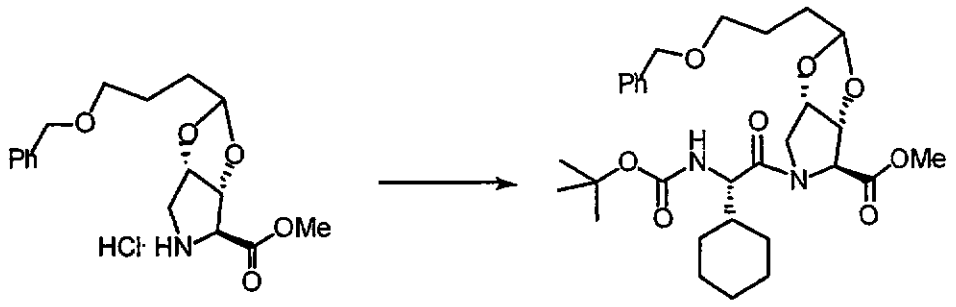
Step C



27c **27d**

The desired compound **27d** was prepared from **27c** according to the method of Example 1, Step C. It was used in the next reaction without further purification.

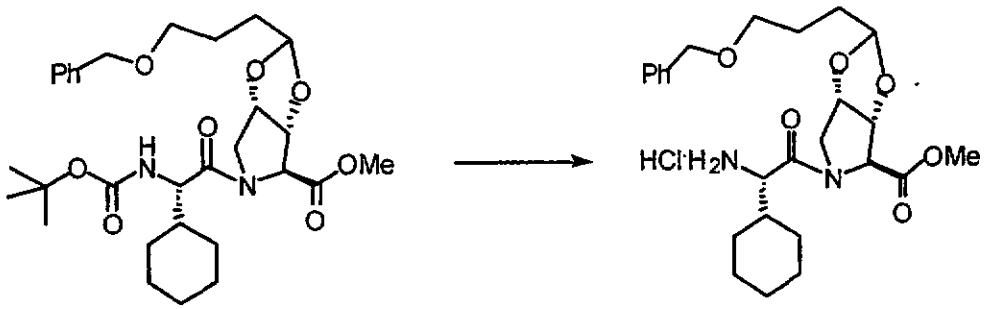
Step D



27d **27e**

The desired compound was prepared from **27d** according to the method of Example 1, Step D. Flash chromatography (8 to 20 % EtOAc/CH_2Cl_2) afforded **27e**.

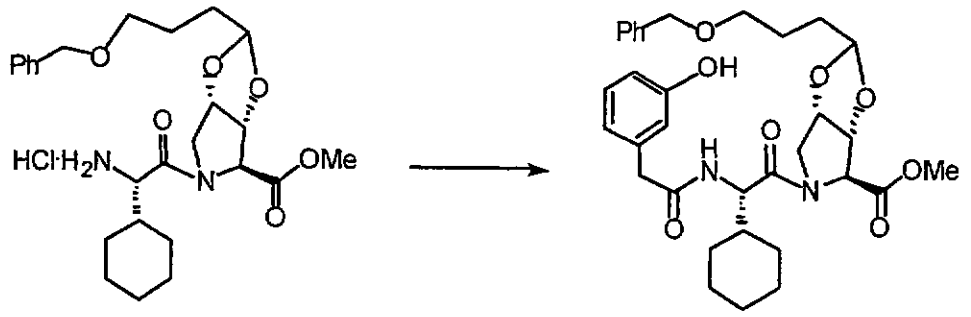
Step E



27e **27f**

The desired compound **27f** was prepared from **27e** according to the method of Example 1, Step E. It was used in the next reaction without further purification.

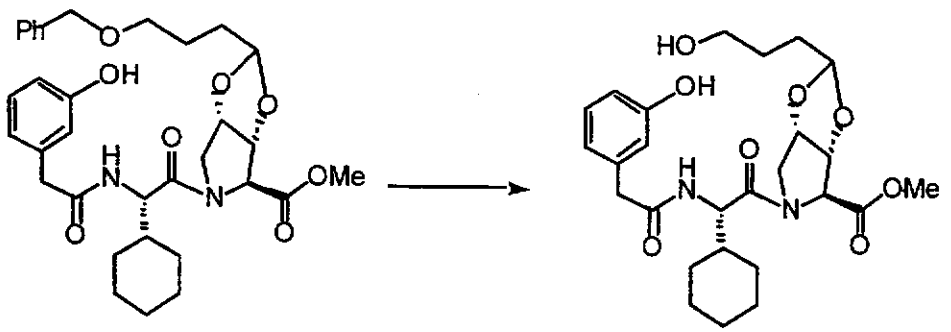
Step F



27f 27g

The desired compound was prepared from **27f** according to the method of Example 1, Step F. Flash chromatography (8 to 20 % EtOAc/CH_2Cl_2) afforded **27g** (36%, 4 steps). HRMS *m/z* 595.3014 [calcd for $C_{33}H_{42}N_2O_8$, 595.3019].

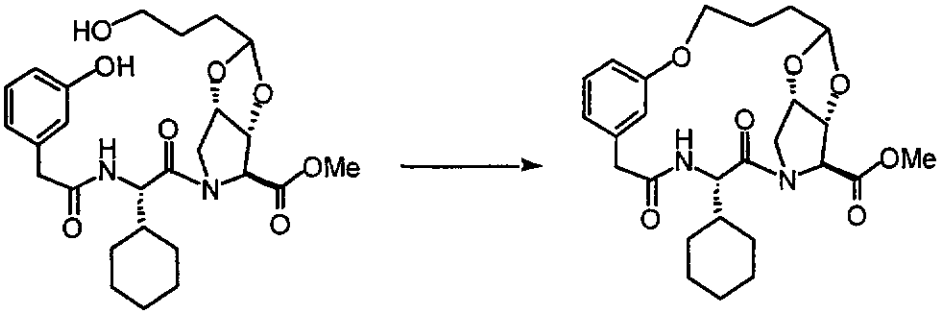
Step G



27g 27h

The desired compound was prepared quantitatively from **27g** according to the method of Example 1, Step G. Flash chromatography (3 to 5 % MeOH/CH_2Cl_2) afforded **27h** as a white solid. HRMS *m/z* 595.2553 [calcd for $C_{26}H_{36}N_2O_8$, 595.2550].

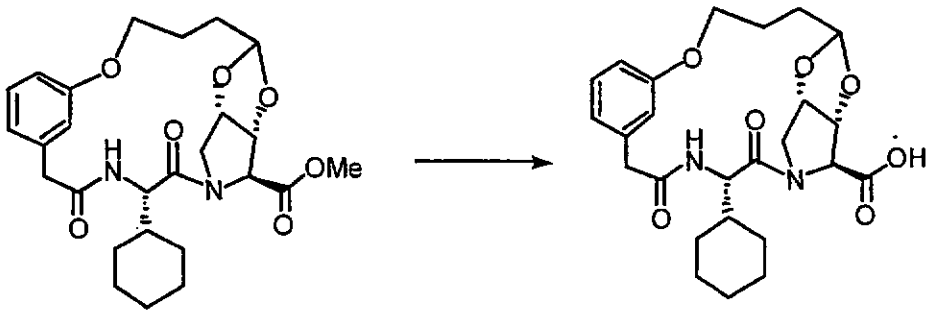
Step H



27h 27i

The desired compound was prepared from **27h** according to the method of Example 1, Step H. Flash chromatography (3 to 5 % MeOH/CH_2Cl_2) afforded **27i** as a mixture with triphenylphosphine oxide which was hydrolyzed.

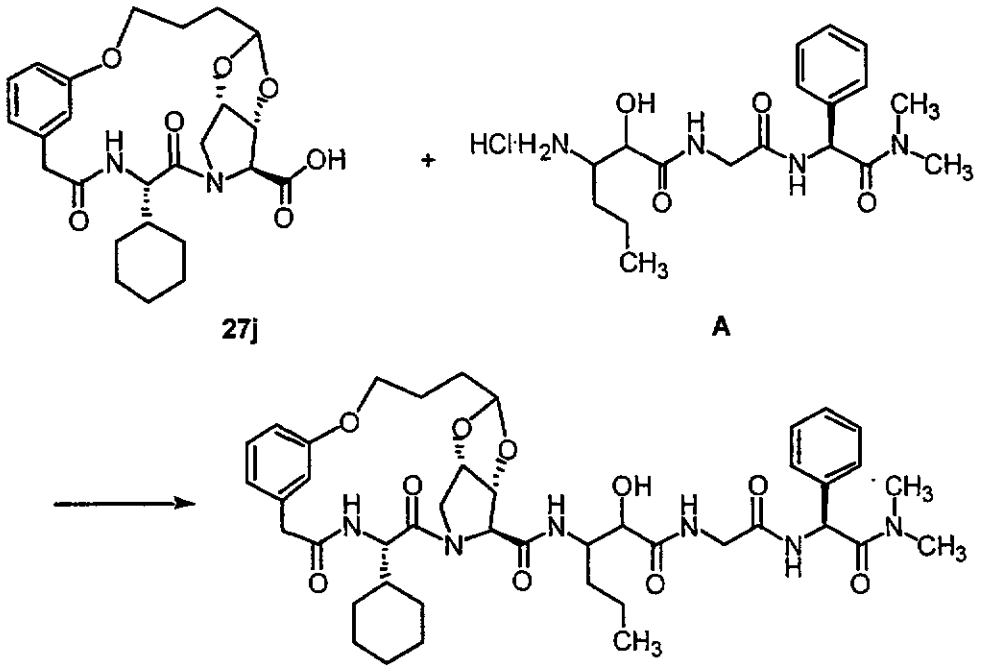
Step I



27i 27j

The desired compound was prepared (72%, 2 steps) from **27i** according to the method of Example 1, Step I.

Step J

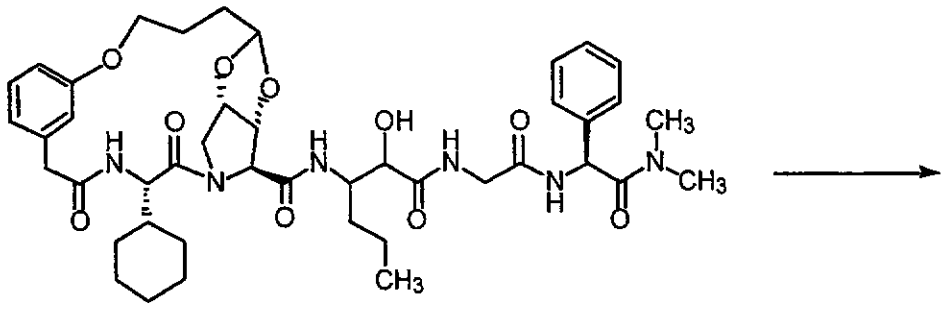


27j A

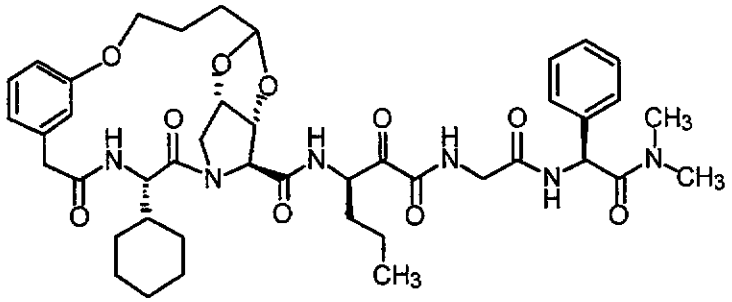
27k

The desired compound was prepared from **27j** according to the method of Example 1, Step J. Flash chromatography (3 to 6 % MeOH/CH_2Cl_2) afforded **27k** (69%) as a mixture of diastereomers.

Step K

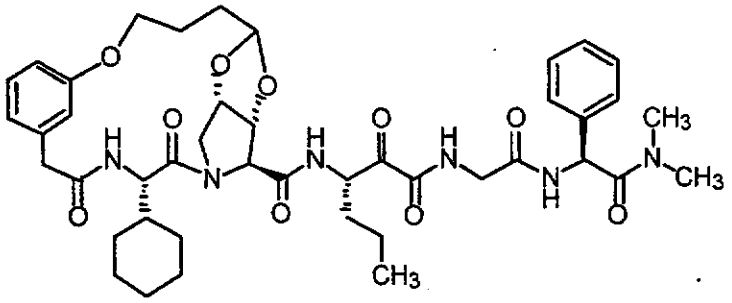


27k



27A

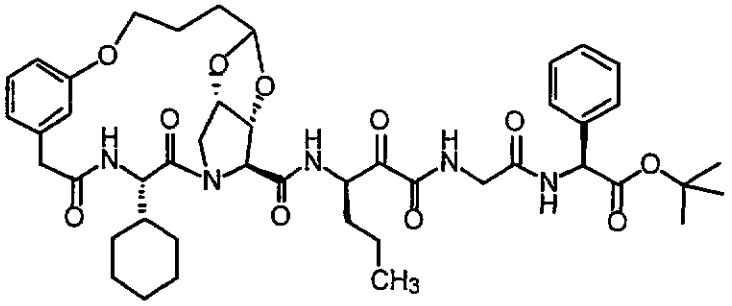
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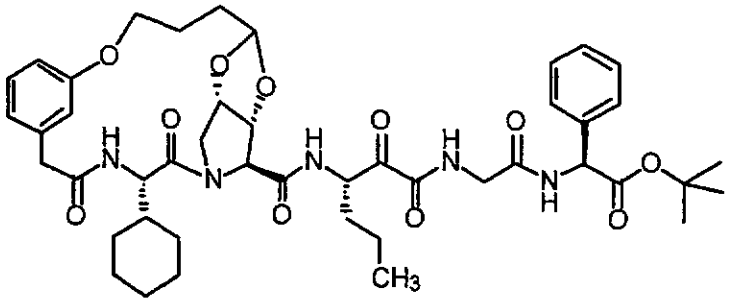
27B

The desired compound was prepared from **27k** according to the method of Example 1, Step K. Flash chromatography (2 to 5 % $MeOH/CH_2Cl_2$) afforded pure **27A** and **27B**.

Example 28: Preparation of Compound 28:

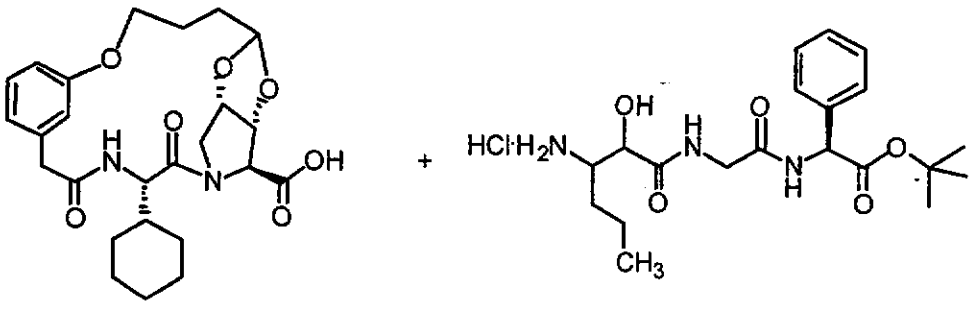


28A

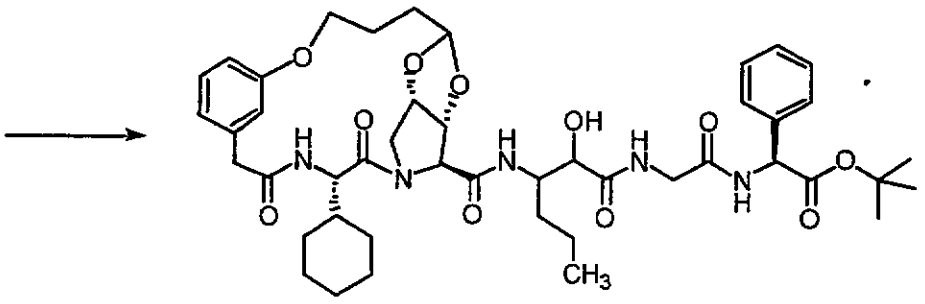


28B

Step A



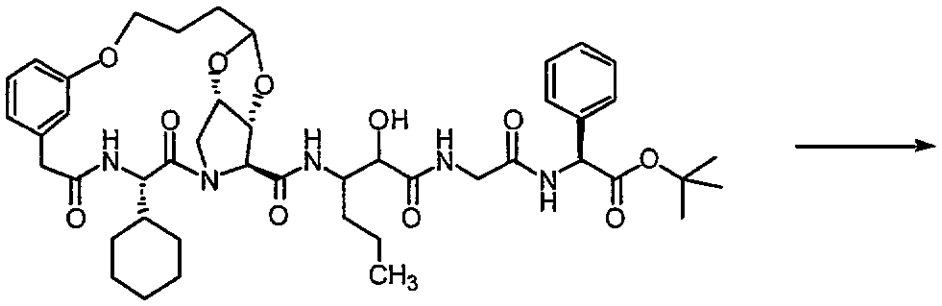
27j B



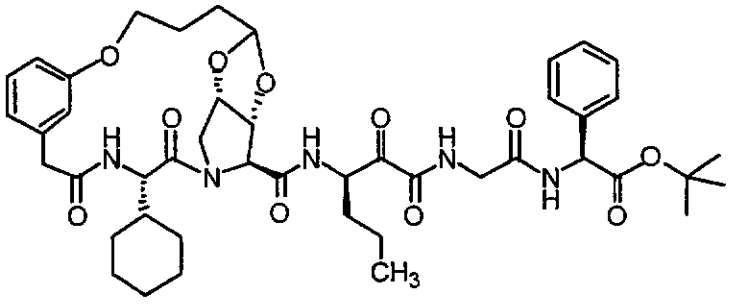
28a

The desired compound was prepared from **27j** according to the method of Example 2, Step A. Flash chromatography (3 to 6 % MeOH/CH_2Cl_2) afforded **28a** (50%) as a mixture of inseparable diastereomers.

Step B

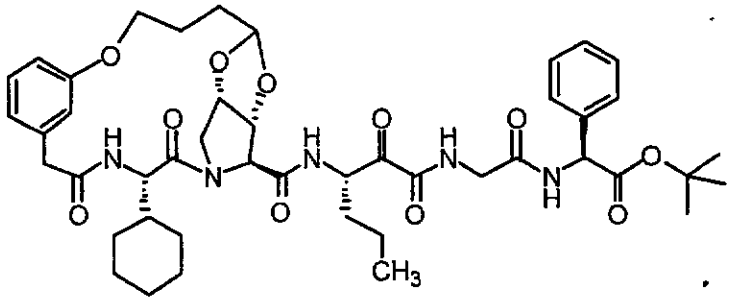


28a



28A

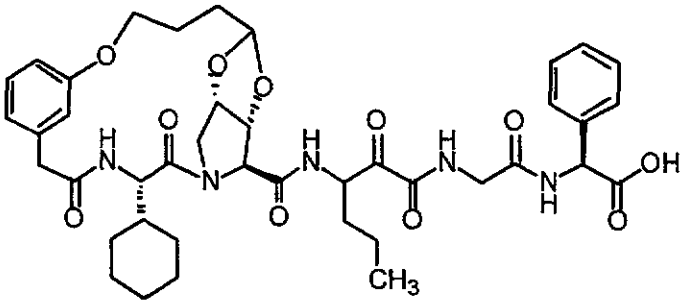
+



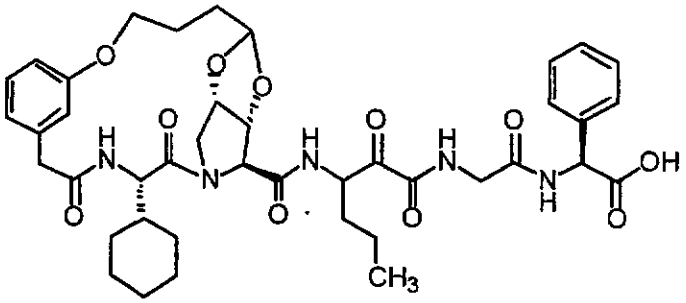
28B

The desired compound was prepared from **28a** according to the method of Example 2, Step B. Flash chromatography (2 to 5 % MeOH/CH_2Cl_2) afforded **28A** and **28B**.

Example 29: Preparation of Compound 29:

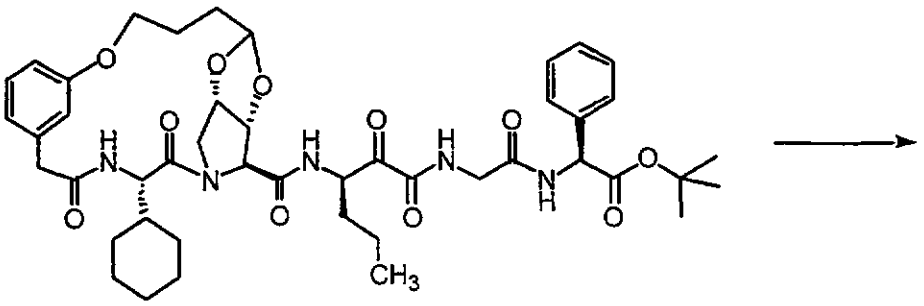


29A

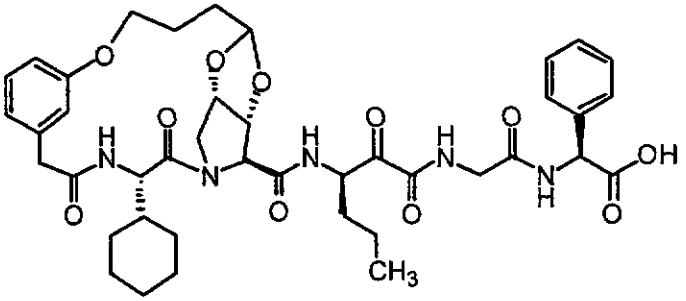


29B

Step A



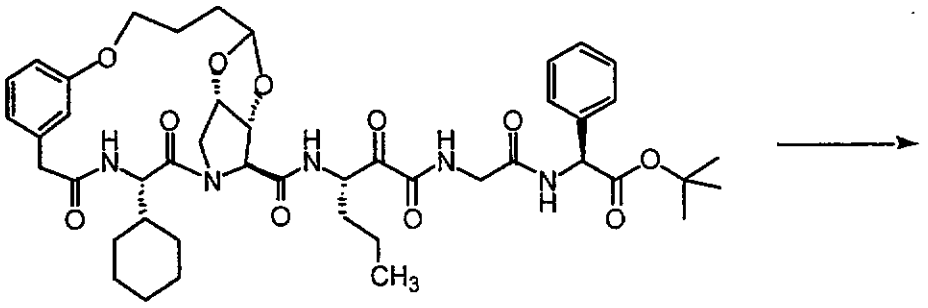
28A



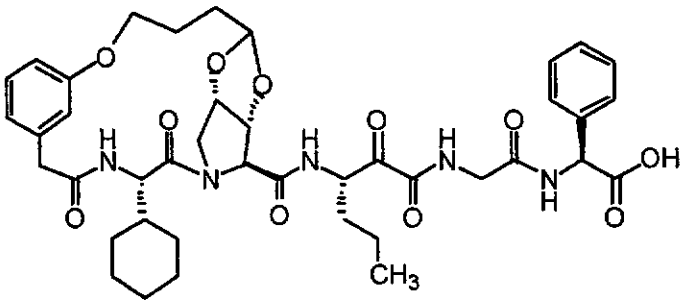
29A

The desired compound **29A** was prepared from **28A** according to the method of Example 3, Step A.

Step B



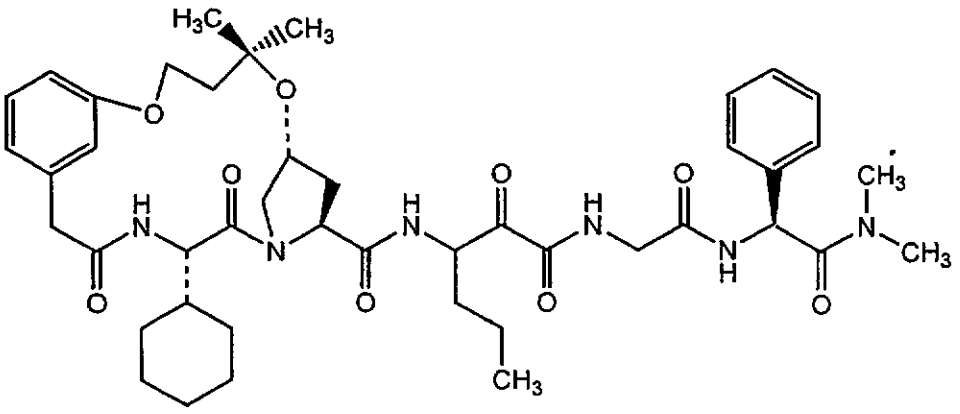
28B



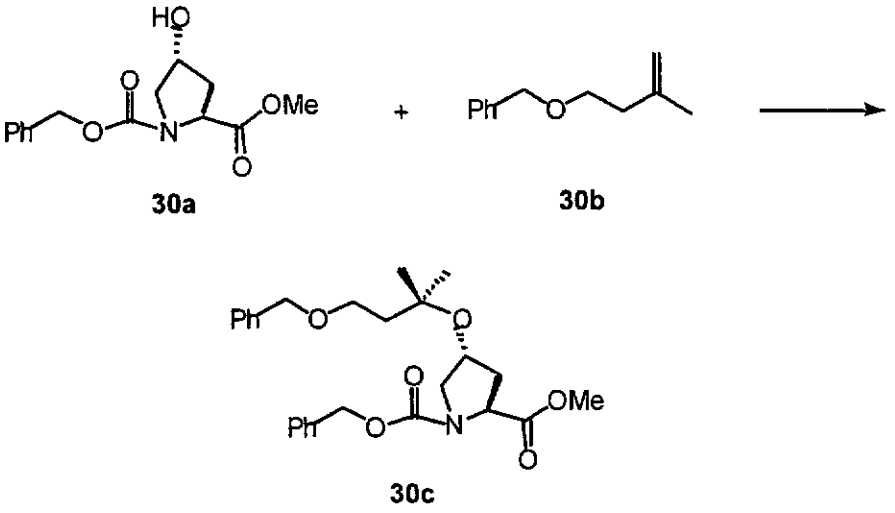
29B

The desired compound **29B** was prepared from **28B** according to the method of Example 3, Step A.

Example 30: Preparation of Compound 30:



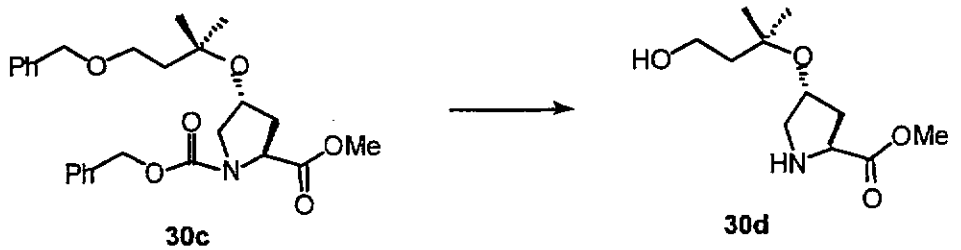
Step A:



30a 30b 30c

To a solution of the Cbz-HYP-OMe (**30a**) (3.0 g, 10.7 mmol) and 4-benzyloxy-2-methyl-1-butene **30b** (5.30 g, 30.0 mmol) in anhydrous CH_2Cl_2 (80 mL) at 0°C was added trifluoroboron diethyl etherate (0.25 mL, 1.97 mmol). The resulting mixture was stirred at rt. overnight (18 h). Saturated sodium bicarbonate solution (30 mL), brine (50 mL) and EtOAc (300 mL) were added and the layers were separated. The aqueous solution was extracted with EtOAc
(2 X 100 mL) and the combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Flash chromatography (5 to 20 % EtOAc/CH_2Cl_2) afforded **30c** (2.00 g, 4.39 mmol, 41 %) as an oil.

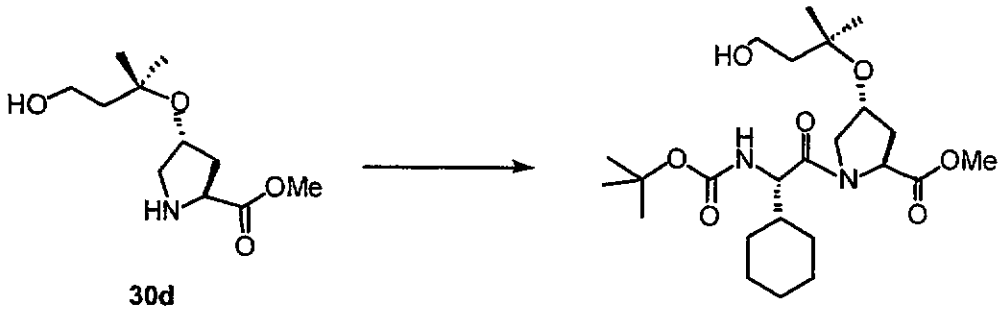
Step B:



30c 30d

The desired compound **30d** was prepared from **30c** quantitatively according to the procedure of Example 1, Step G.

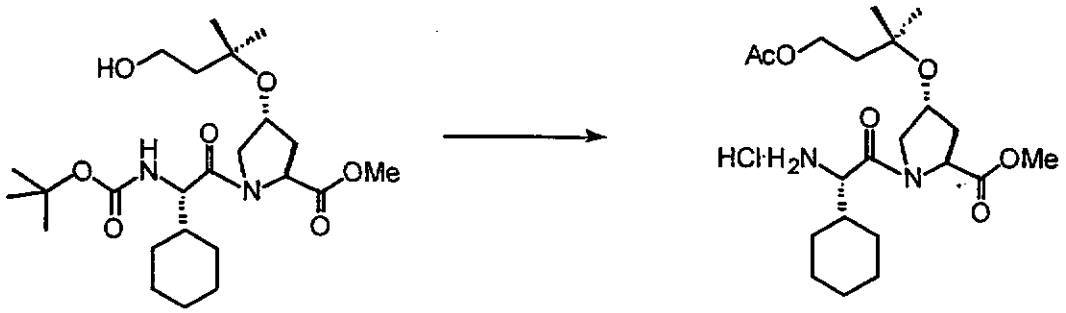
Step C:



30d **30e**

The desired compound **30e** was prepared from **30d** and Boc-cyclohexylglycine-OH according to the procedure of Example 1, Step D. Flash chromatography (3 to 5 % MeOH/CH_2Cl_2) afforded **30e** (61%).

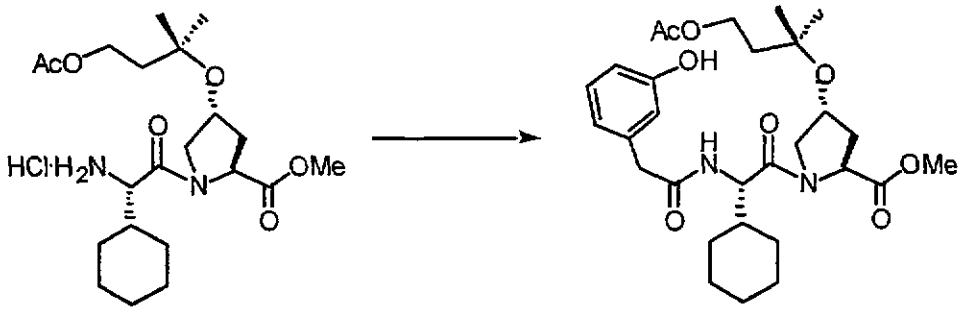
Step D:



30e **30f**

The solution of **30e** and 2 N HCl in dioxane and EtOAc (1:1) was stirred at rt. for 3 h, after which it was concentrated in vacuo. The product was used in the next reaction without further purification.

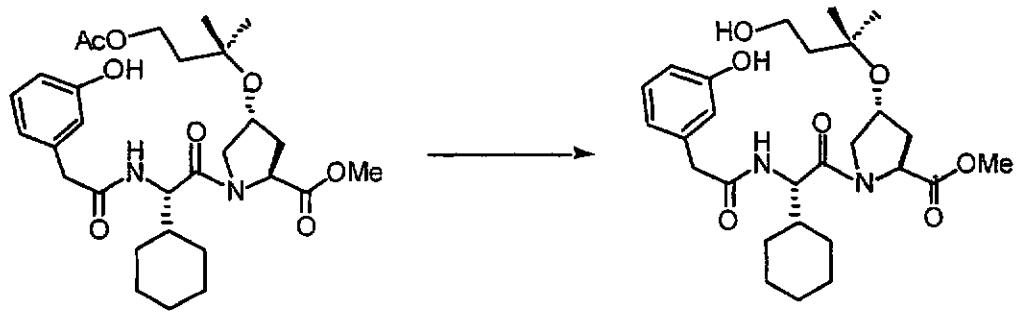
Step E:



30f 30g

The desired compound **30g** was prepared from **30f** according to the procedure of Example 1, Step F. Flash chromatography (2 to 5 % MeOH/CH_2Cl_2) afforded **30g** (48%, 2 steps).

Step F:

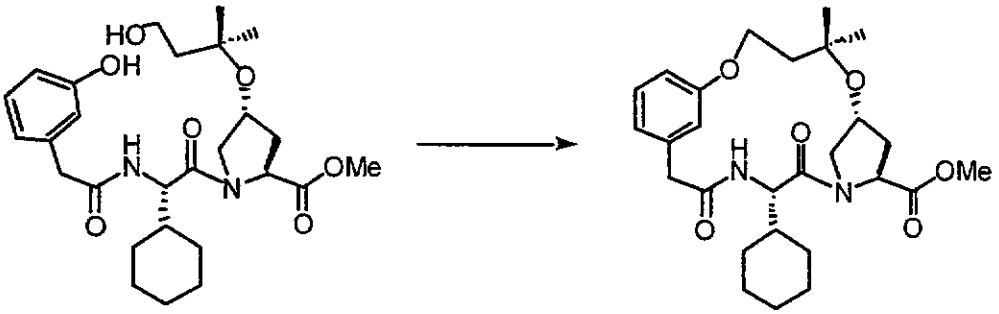


30g 30h

The mixture of **30g** (700 mg, 1.28 mmol) and potassium carbonate (530 mg, 3.84 mmol) in anhydrous methanol (80 mL) was vigorously stirred at rt. The reaction progress was monitored by TLC. After 3 h, it was concentrated in vacuo before EtOAc (200 mL) and water (100 mL) were added and layers were separated. The aqueous solution was extracted with EtOAc (2 X 100 mL). The organic solutions were combined, dried ($MgSO_4$),

filtered and concentrated in vacuo. The product was used in the next reaction without further purification.

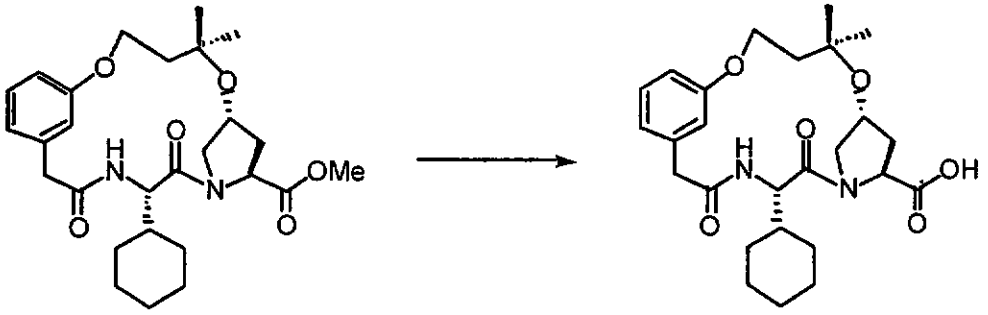
Step G:



30h **30i**

The desired compound **30i** was prepared from **30h** according to the procedure of Example 1, Step H.

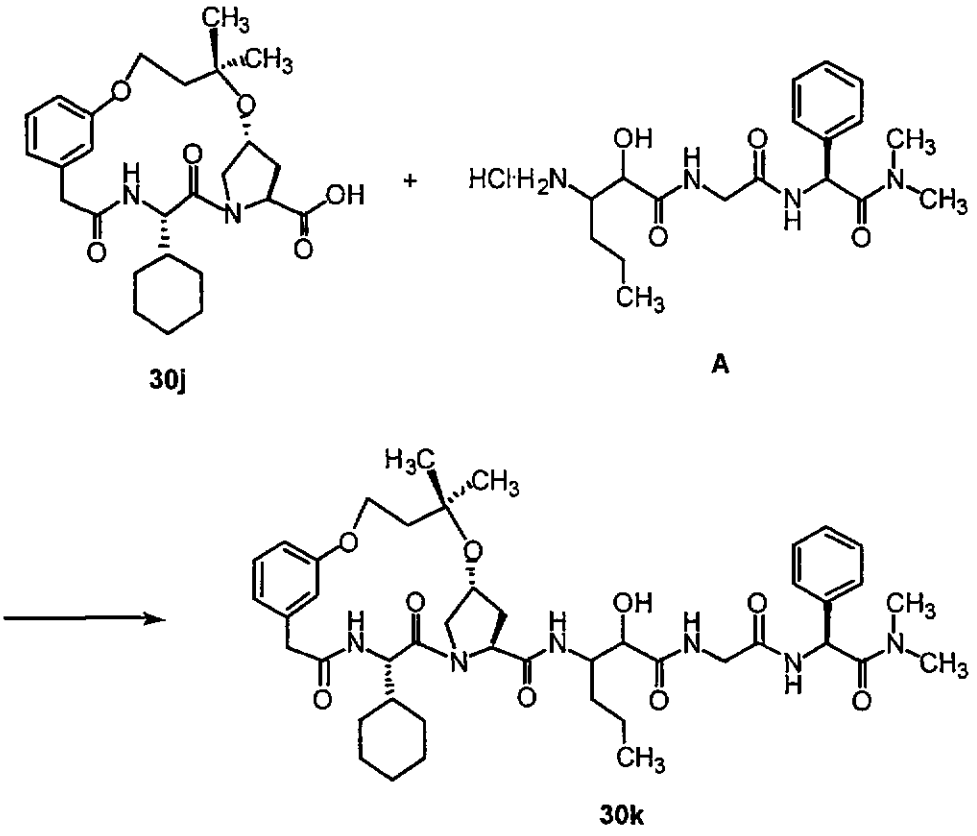
Step H:



30i **30j**

The desired compound **30j** was prepared from **30i** according to the procedure of Example 1, Step I (23 %, 3 steps).

Step I:

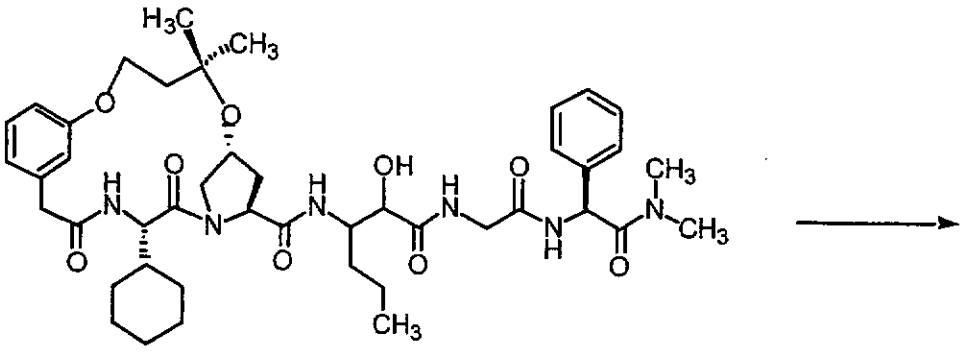


30j A

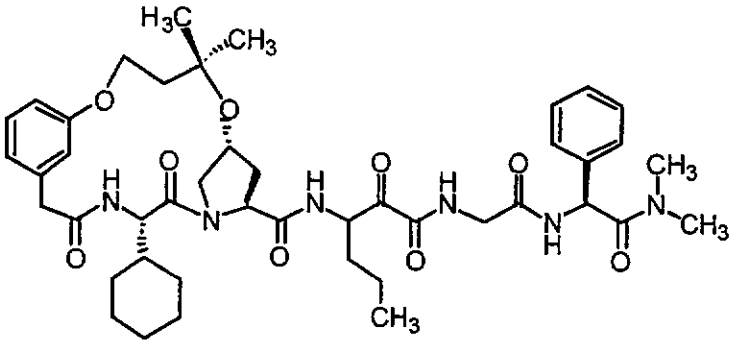
30k

The desired compound was prepared from **30j** according to the procedure of Example 1, Step J . Flash chromatography (3 to 6 % MeOH/CH_2Cl_2) afforded **30k** (58%).

Step J:



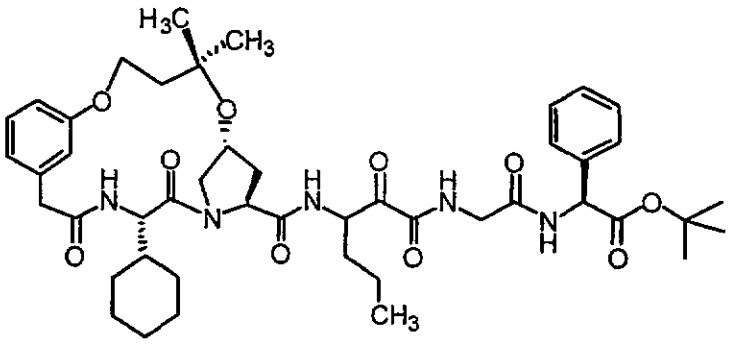
30k



30

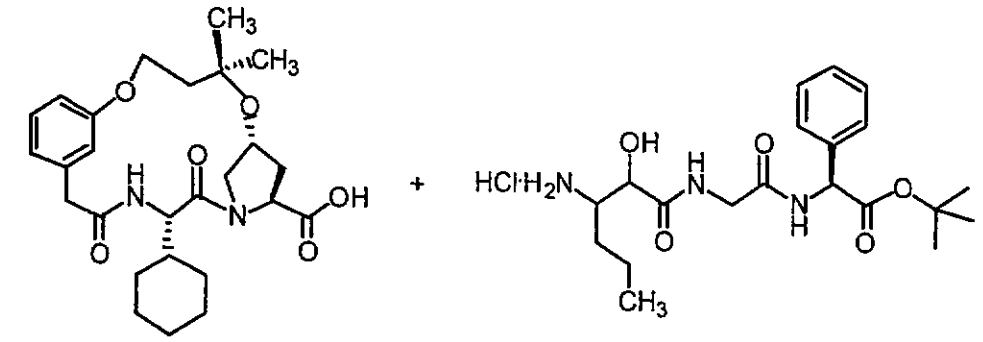
The desired compound **30** was prepared from **30k** according to the procedure of Example 1, Step K. Flash chromatography (3 to 5 % MeOH/CH_2Cl_2) afforded **30** as a mixture of inseparable diastereomers.

Example 31: Preparation of Compound 31:



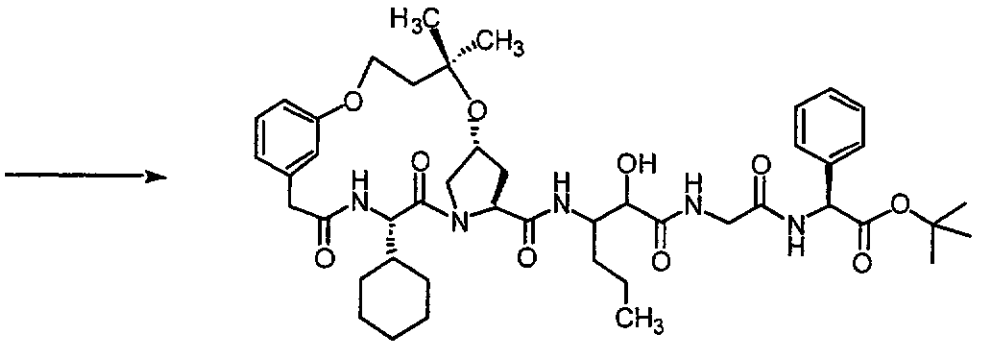
31

Step A



30j

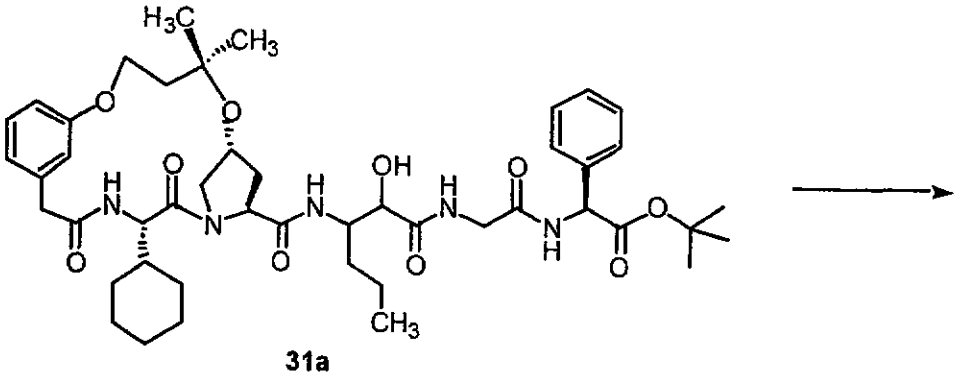
B



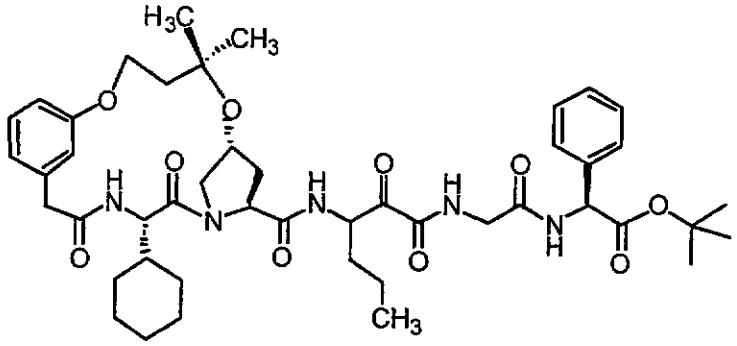
31a

The desired compound was prepared from **30j** and **B** according to the procedure of Example 1, Step J. Flash chromatography (2 to 5 % MeOH/CH_2Cl_2) afforded **31a** (73 %).

Step B



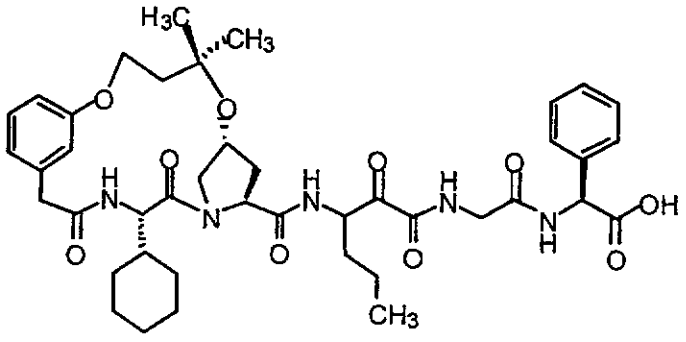
31a



31

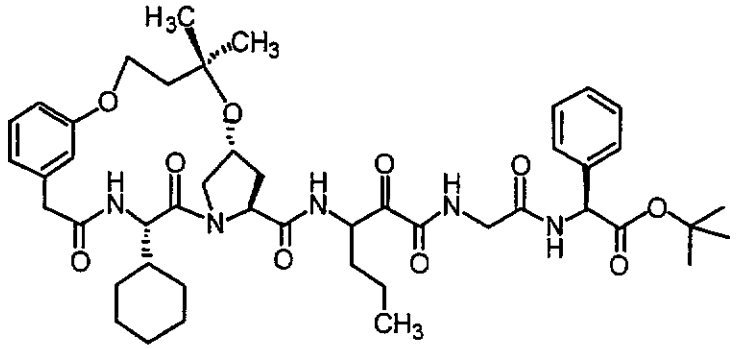
The desired compound was prepared from **31a** according to the procedure of Example 1, Step K. Flash chromatography (2 to 5 % MeOH/CH_2Cl_2) afforded **31** as a mixture of inseparable diastereomers.

Example 32: Preparation of Compound 32:

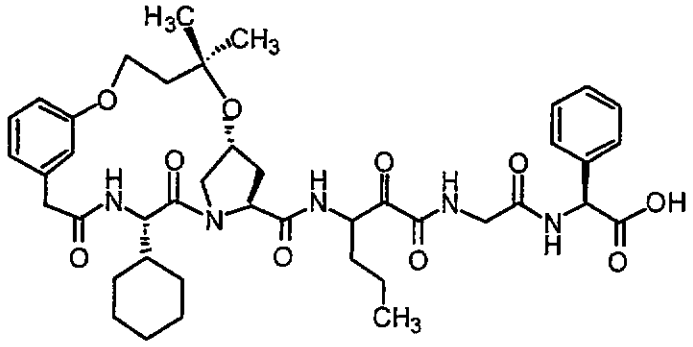


32

Step A



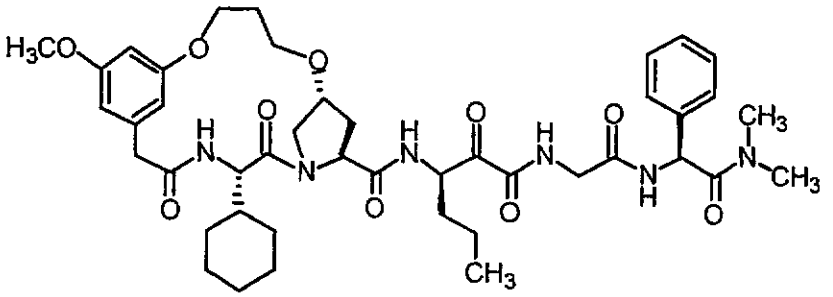
31



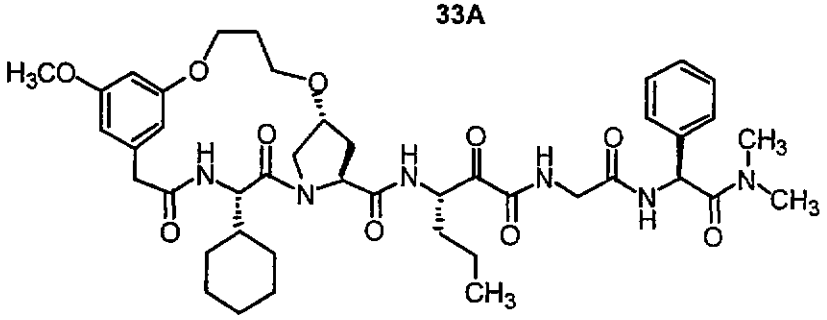
32

The desired compound **32** can be prepared from **31** according to the procedure of Example 3, Step A.

Example 33 : Preparation of Compound 33:



33A



33B

Step A

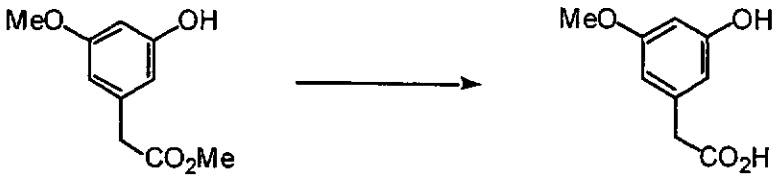


33a

33b

The suspension of methyl 3,5-dihydroxyphenylacetate (**33a**) (5.0 g, 27.4 mmol) methyl iodide (4.6 g, 32.9 mmol), potassium carbonate (5.69 g, 41.2 mmol) in DMF (30 mL) was heated to 55°C and stirred overnight. After cooling to rt., saturated aqueous sodium bicarbonate solution (100 mL) and EtOAc (200 mL) were added and layers were separated. The aqueous solution was extracted with EtOAc (2x100 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (2 to 5 % MeOH/CH_2Cl_2) afforded **33b** (1.11g, 29 %) as a white liquid.

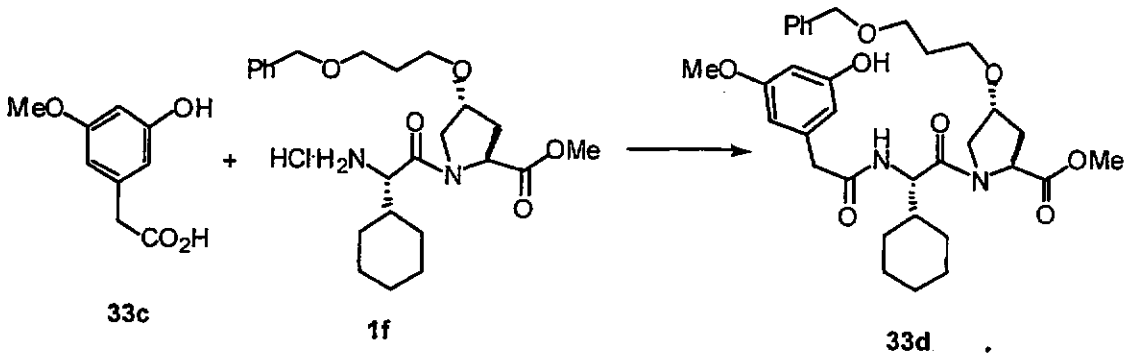
Step B



33b **33c**

An aqueous lithium hydroxide solution (0.342 g in 10 mL H_2O) was added to a solution of the methyl ester **33b** in THF (10 mL) and methanol (10 mL) at rt. The progress of the reaction was monitored by TLC. After 4 hr., the volatiles were removed in vacuo, EtOAc (150 mL) and water (30 mL) were added and the aqueous solution was acidified to pH = 1 and saturated with solid sodium chloride. After separation of the layers, the aqueous layer was extracted with EtOAc (2 X 150 mL). Organic solutions were combined, dried with sodium sulfate, filtered and concentrated in vacuo to afford **33c** (1.6 g).

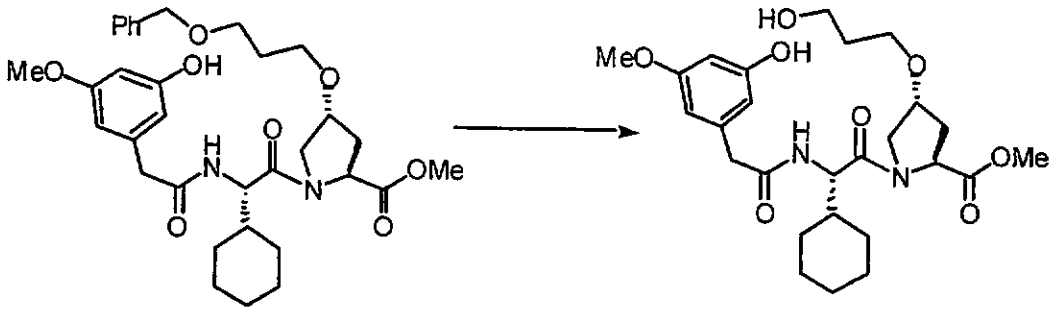
Step C:



33c **1f** **33d**

The desired compound **33d** was prepared from **33c** and **1f** according to the procedure of Example 1, Step F. Flash chromatography (2 to 5 % $MeOH/CH_2Cl_2$) afforded **33d** in 90% yield.

Step D:

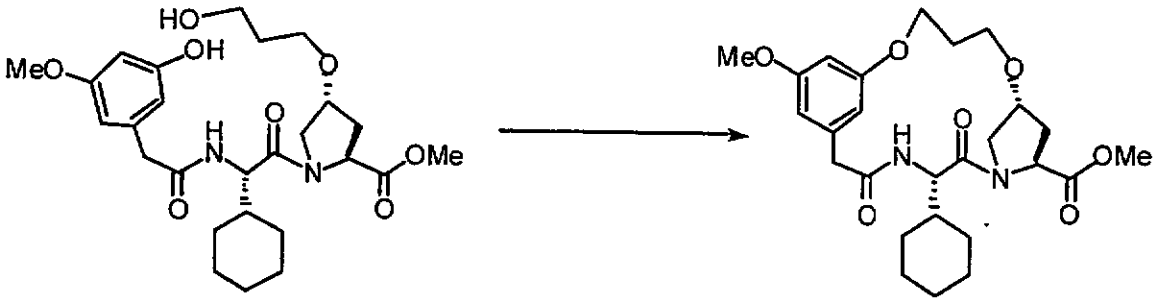


33d

33e

The desired compound **33e** was prepared from **33d** according to the procedure of Example 1, Step G. Flash chromatography (2 to 5 % $MeOH/CH_2Cl_2$) afforded **33e** in 56% yield.

Step E:

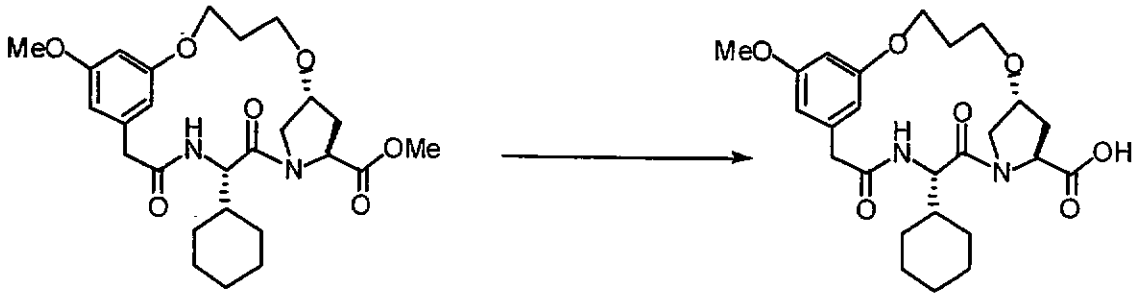


33e

33f

The desired compound **33f** was prepared from **33e** according to the procedure of Example 1, Step H. Flash chromatography (2 to 5 % $MeOH/CH_2Cl_2$) afforded **33e** as a mixture with triphenylphosphine oxide which was used in the next reaction without further purification.

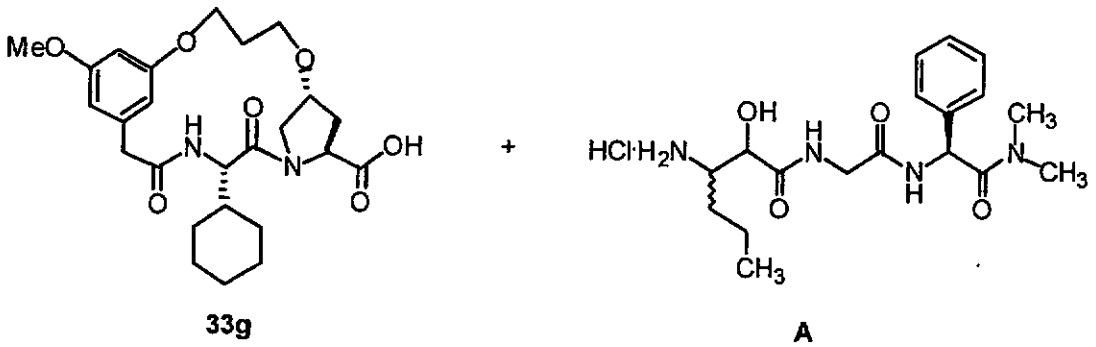
Step F:



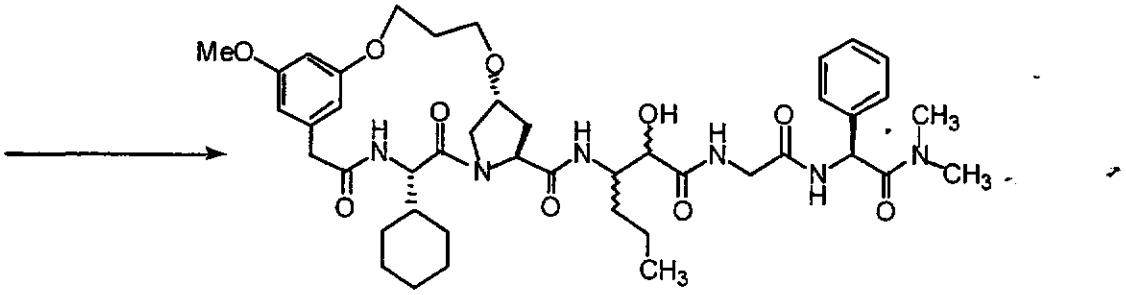
33f 33g

The desired compound **33g** was prepared from **33f** in 45% yield (2 steps) according to the procedure of Example 1, Step I.

Step G:



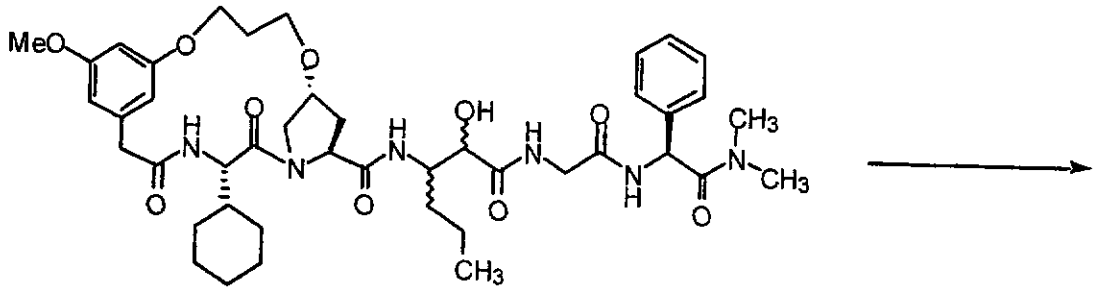
33g A



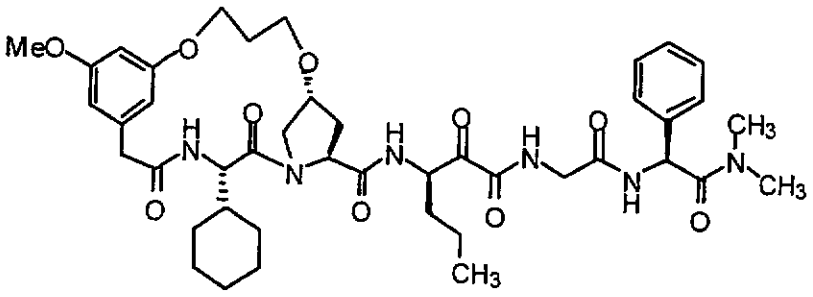
33h

The desired compound **33h** is prepared from **33g** and **A** according to the procedure of Example 1, Step J.

Step H:

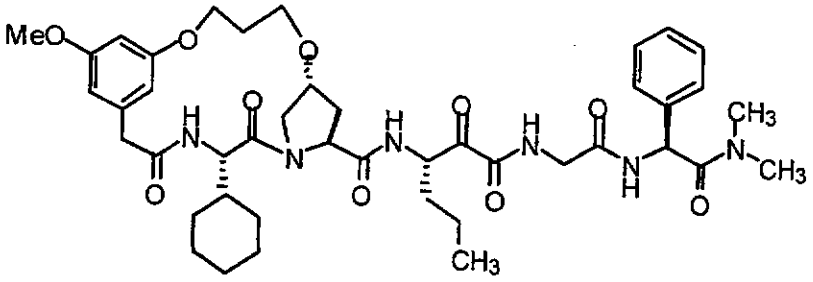


33h



33A

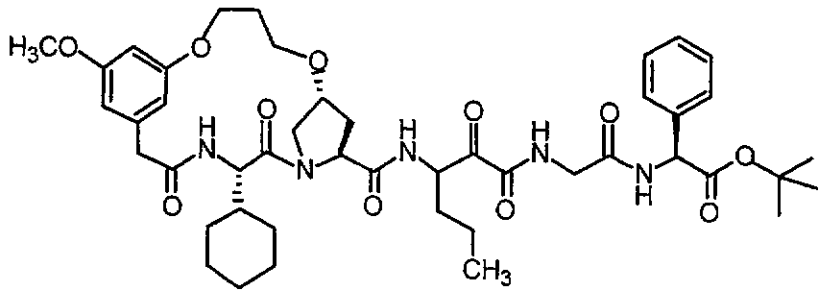
+



33B

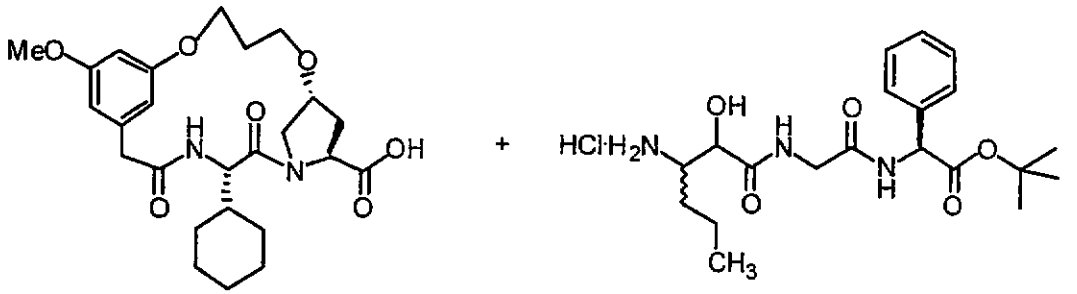
The desired compounds are prepared from **33h** according to the procedure of Example 1, Step K.

Example 34: : Preparation of Compound 34:



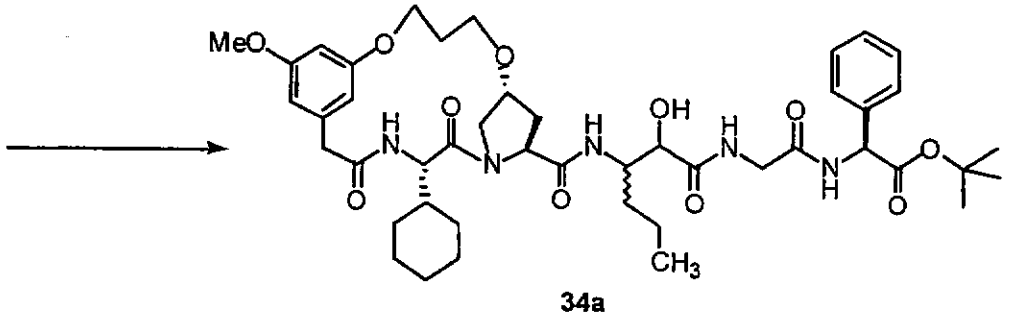
34

Step A:



33g

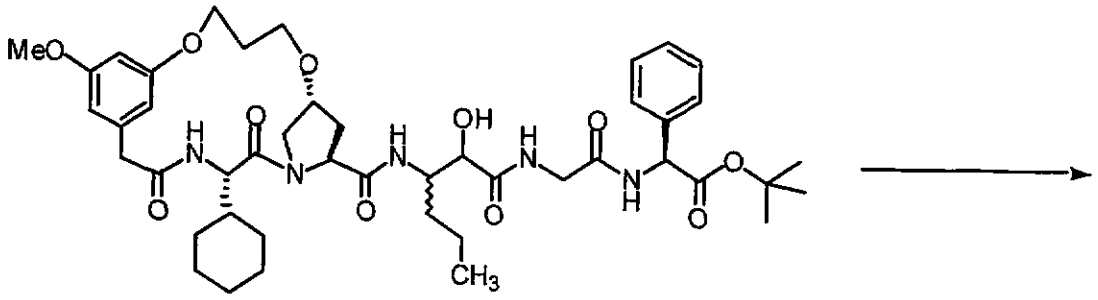
B



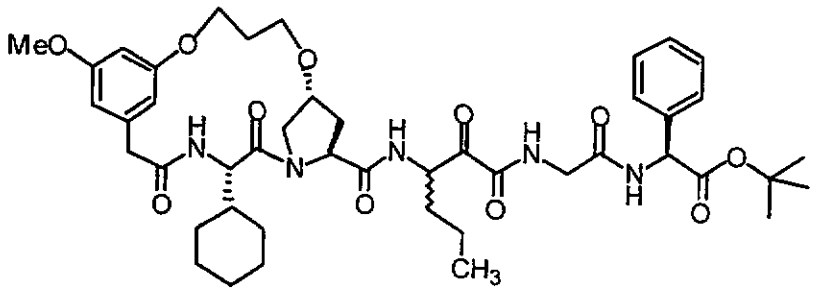
34a

The desired compound **34a** is prepared according to the method of Example 1, Step J, except substituting amine **B** for amine **A**. The product is obtained as a mixture of inseparable diastereomers.

Step B:



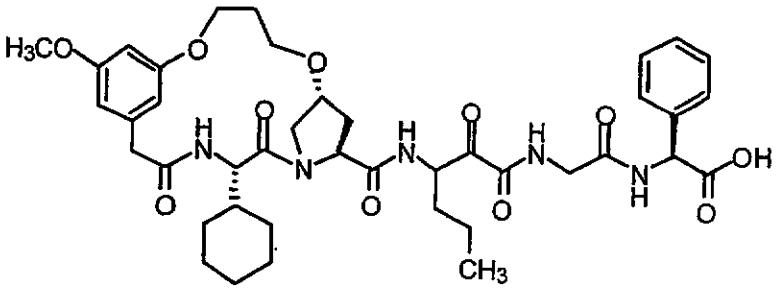
34a



34

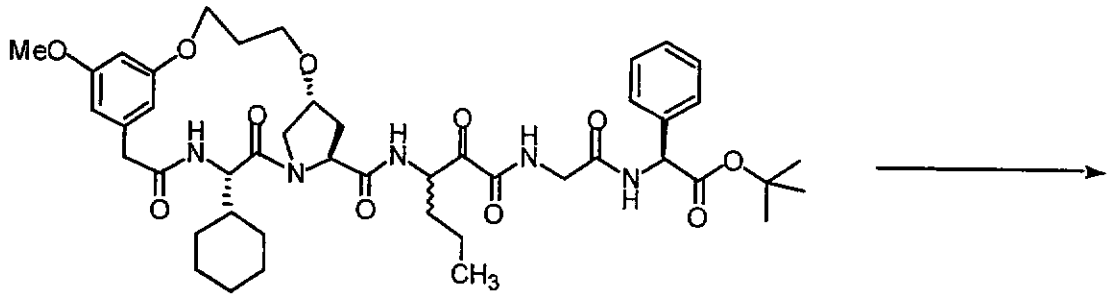
The desired compound is prepared from **34a** according to the method of Example 1, Step K.

Example 35: : Preparation of Compound 35:

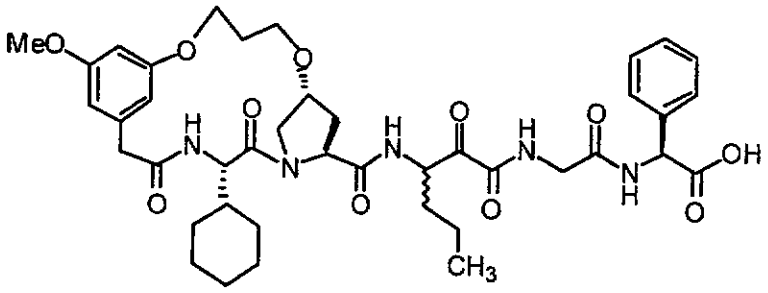


35

Step A:



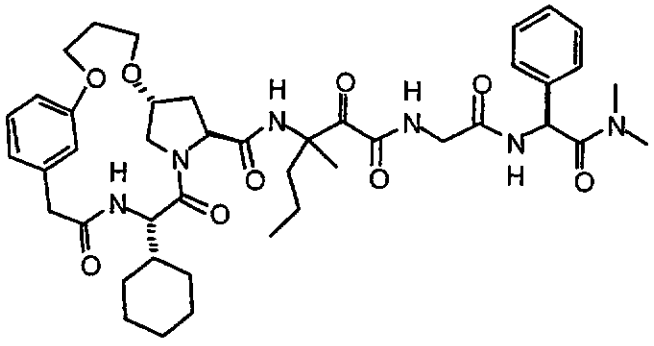
34



35

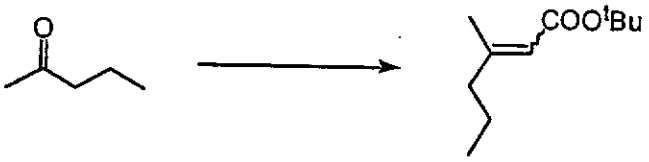
The desired compound **35** is prepared from **34** according to the method of Example 3, Step A.

Example 36 : Preparation of Compound 36:



36

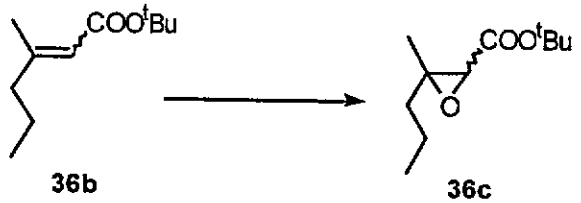
Step A



36a **36b**

A solution of *tert*-butyl phosphonoacetate (15.1 g, 50.0 mmol) in dry THF was cooled to 0°C and treated with NaH (60%, 2.5 g, 62.5 mmol, 1.25 equiv.) and stirred for 20 min. The reaction mixture was treated with 2-pentanone (4.3 g, 50 mmol) and stirred at rt. for 24 h. The reaction mixture was diluted with aq. $NaHCO_3$ and extracted into ether (3x100 mL). The combined ether layer were extracted with brine, dried ($MgSO_4$), concentrated in vacuo and distilled to yield 8.2 g (88%) of **36b** (stereochemical ratio 2:1).

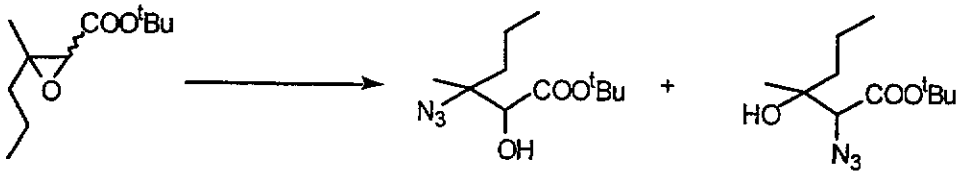
Step B



36b **36c**

A solution of **36b** (5.0 g, 27.1 mmol) was dissolved in dichloroethane and treated with 4,4'-thiobis-(2-*tert*-butyl-5-methylphenol) (100 mg) and MCPBA (60-80%, 7.76 g, 27.1 mmol) and heated at reflux for 4 h. The reaction mixture was concentrated in vacuo and the residue was diluted with ether (200 mL) The ether layer was washed twice with satd aq $Na_2S_2O_3$, aq. NaOH and brine (100 ml). The reaction mixture was concentrated in vacuo to yield 4.2 g (77%) of **36c** which was used as it is in the next step.

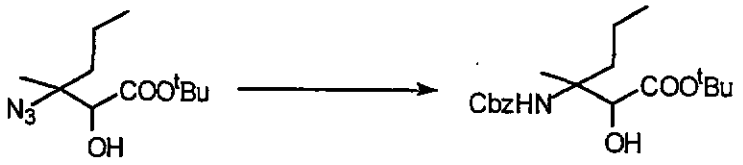
Step C



36c **36d** **36 d'**

A solution of epoxide (4.0 g, 18.4 mmol) in dry ethanol (100 mL) was treated with NaN_3 (12 g, 184 mmol) and NH_4Cl (9.6 g. 184 mmol) and heated at reflux for 36 h. The reaction mixture was diluted with water and the reaction mixture was extracted with ether (300 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by SiO_2 chromatography (EtOAc/Hex 1:19) to yield 1.1 g (28%) of **36d** and 731 mg (18%) of **36d'** as a colorless liquid.

Step D



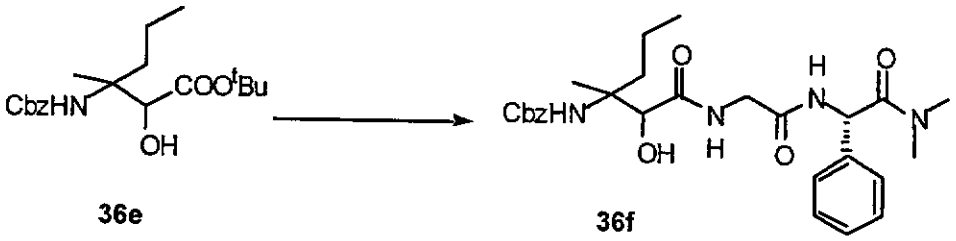
36d **36e**

A solution of azide **36d** (2.1 g, 8.7 mmol) was dissolved in CH_3OH (100 mL) and treated with Pd/C (50 mg) and hydrogenated (40 psi) for 24 h. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated in vacuo. The residue was used for next reaction without further purification.

A solution of Cbz-Cl (1.48 g, 8.7 mmol, 1.23 mL) was added dropwise to a mixture of amine and Et_3N (878 mg, 1.25 mL) at -78 °C in CH_2Cl_2 (30 mL). The reaction mixture was warmed to rt. and concentrated in vacuo. The

residue was chromatographed on SiO_2 (EtOAc/Hex 8:2) to **36e** (450 mg, 15%) as a colorless solid.

Step E

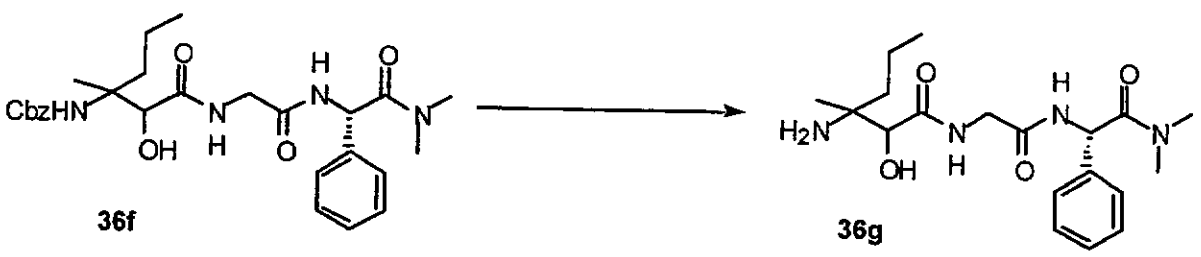


36e **36f**

A solution of **36e** (450 mg, 1.29 mmol) in CH_2Cl_2/TFA (10 mL, 1:1) was stirred at rt. for 4 h. The reaction mixture was concentrated in vacuo to obtain the acid (250 mg) which was used in the next step without further purification.

The acid obtained by hydrolysis of **36e** was dissolved in CH_2Cl_2 (10 mL) at -20 °C and treated with H-Glycyl-Phenylglycycl-$N(CH_3)_2$ (281 mg, 0.93 mmol), HOOBt (208 mg, 1.27 mmol, 1.25 equiv.) EDCI (244 mg, 1.27 mmol) and NMM (343 mg, 3.4 mmol, 490 µL). The reaction mixture was stored in the freezer for 24 h and diluted with aq. HCl (1M, 50 mL). The reaction mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were extracted with aq. HCl (1M, 100 mL), aq. $NaHCO_3$ (1M, 100 mL), brine (100 ml), dried ($MgSO_4$), filtered and concentrated in vacuo and chromatographed on SiO_2 (acetone/Hexanes 1:3) to yield **36f** (330 mg, 75%) as a colorless solid.

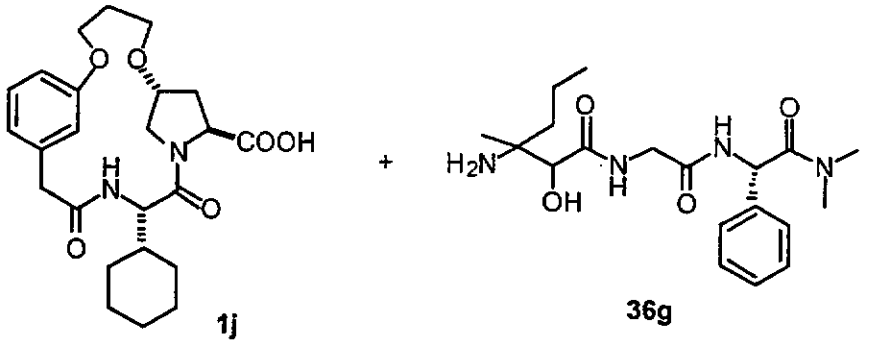
Step F



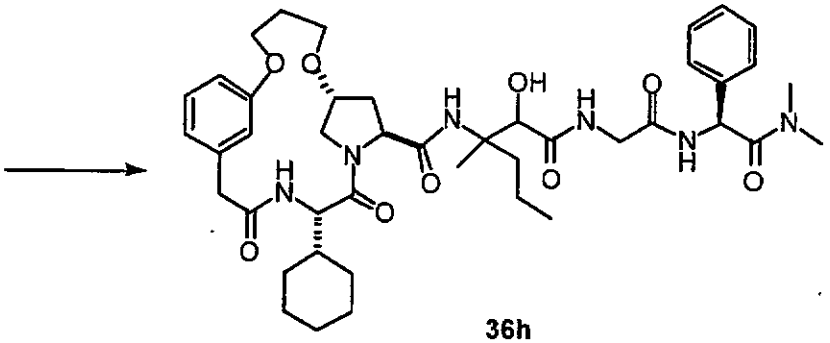
36f **36g**

A solution of **36f** is dissolved in CH_3OH (20 mL) and treated with Pd/C (10 mol%, 20 mg). The reaction mixture will be hydrogenated at 40 psi for 12 h. The reaction mixture is filtered through a plug of Celite and the filtrate is concentrated in *vacuo* and directly used in the next step.

Step G



1j + **36g**

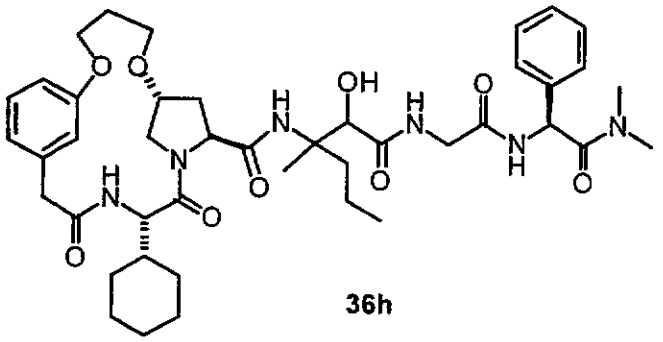


36h

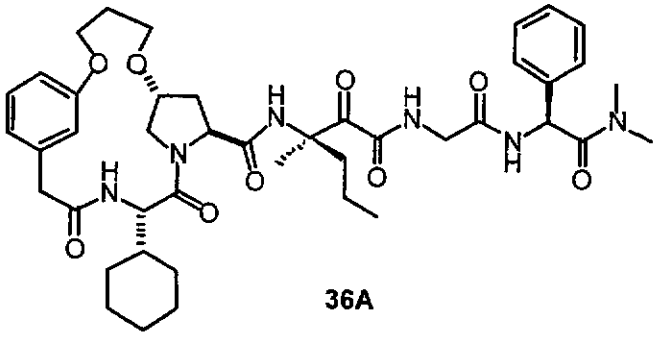
The expected product **36h** is synthesized as described earlier for the Example 1, Step J. The coupled material will be used directly for the next step to synthesize **36A** and **36 B.**

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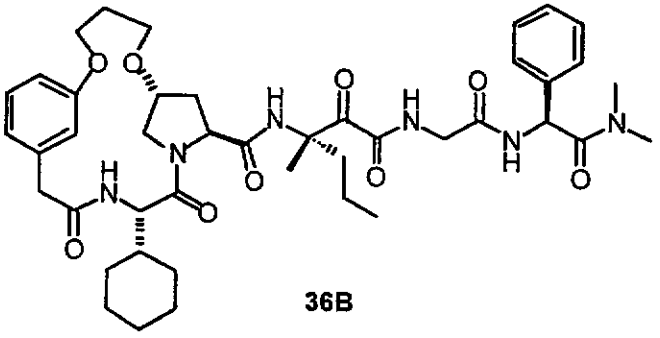
Step H



36h



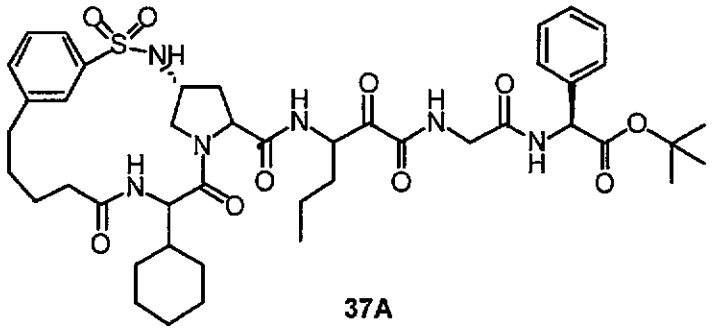
36A



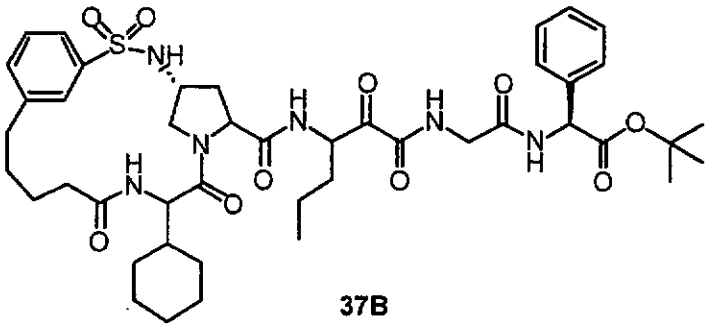
36B

The desired products **36A** and **36B** are obtained by the oxidation protocol described previously for Example 1, Step K.

Example 37: Preparation of Compound 37:

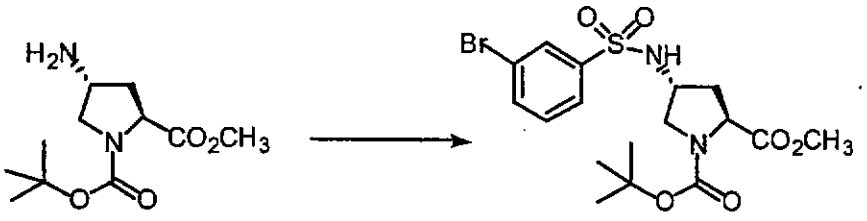


37A



37B

Step A

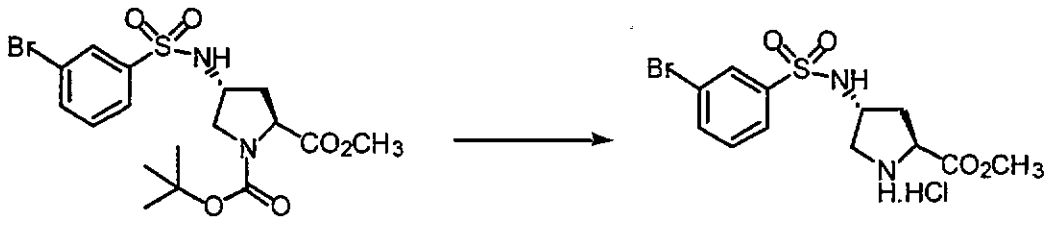


F 37a

To a cold (0°C) solution of **F** (2.3g g, 9.43 mmol) in dichloromethane (20 mL) was added triethylamine (3.97 mL, 28.28 mmol), DMAP (few crystals) and 3-bromobenzenesulfonyl chloride (3.61 g, 14.14 mmol). The reaction mixture was left standing in the refrigerator (0°-5°C) overnight. The reaction mixture was washed with saturated $NaHCO_3$, and 10% citric acid solution. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using 95/5 to 90/10 dichloromethane/EtOAc

to afford 2.7 g (62% yield) of **37a**. HRMS (FAB) Calcd for $C_{17}H_{24}N_2O_6SBr$: 465.0518 $(M+H)^+$. Found: 465.0497.

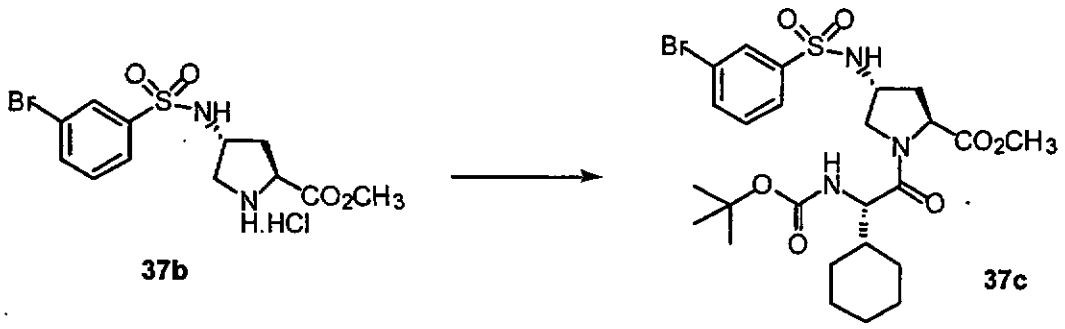
Step B



37a **37b**

The desired product **37b** was obtained by the method described for Example 1, Step C. The crude material was used in the next step without purification.

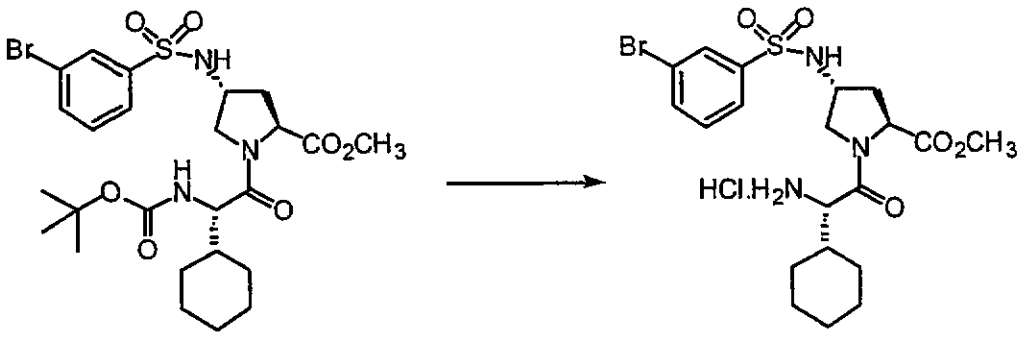
Step C



37b **37c**

The desired product **37c** was obtained by the method described for Example 1, Step D in 97% yield. The material after workup was pure enough to be carried forward.

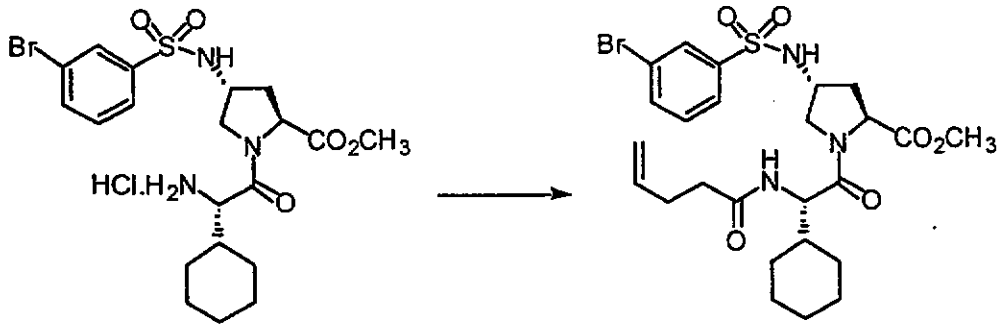
Step D



37c 37d

The desired product **37d** was obtained by the method described for Example 1, Step E. The crude material was used in the next step without purification.

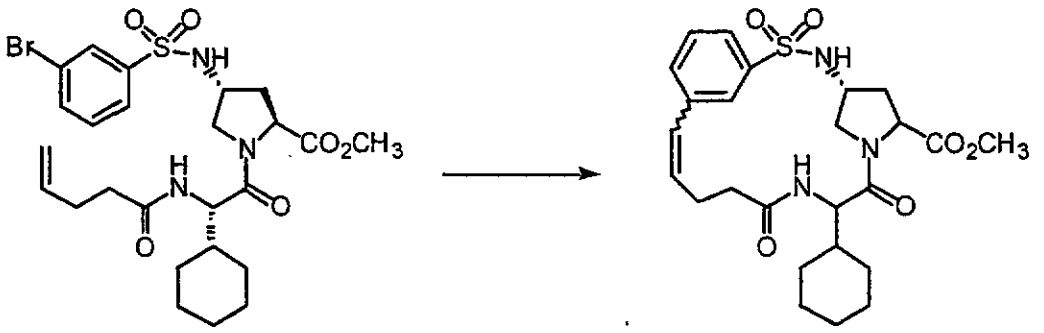
Step E



37d 37e

The desired product **37e** was obtained by the method described for Example 1, Step F using pentenoic acid as the coupling partner. Purification of the residue by column chromatography using 90/10 to 80/20 dichloromethane/EtOAc provided 35% yield of **37e**. HRMS (FAB) Calcd for $C_{25}H_{35}N_3O_6SBr$: 586.1409 $(M+H)^+$. Found: 586.1423.

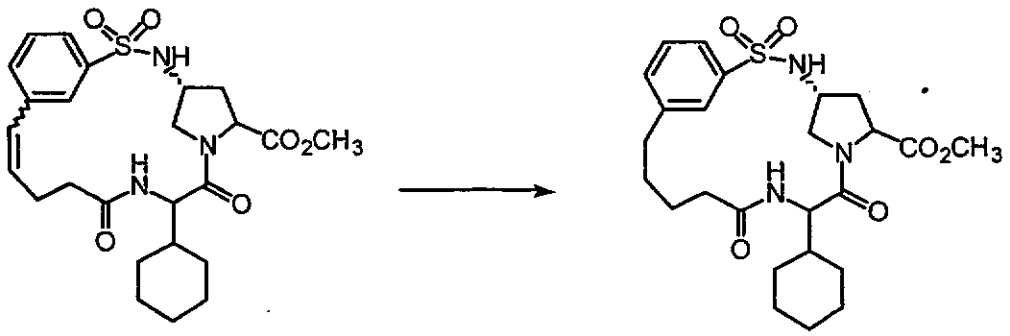
Step F



37e 37f

To a stirred solution of **37e** (660 mg, 1.13 mmol) in DMF (10 mL) under nitrogen atmosphere was added triethylamine (3.61 mL, 32.77 mmol), potassium carbonate (780 mg, 5.65 mmol), tetrabutylammonium bromide (730 mg, 2.26 mmol), and palladium (II) acetate (33 mg, 0.15 mmol). the mixture was heated at 100°C for 2 hrs. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with 5% phosphoric acid solution. The organic layer was separated, dried (Na_2SO_4) and concentrated to provide 280 mg (49% yield) of **37f** as a mixture of diastereomers. This material was pure enough to be carried to the next step. HRMS (FAB) Calcd for $C_{25}H_{34}N_3O_6S$: 504.2168 $(M+H)^+$. Found: 504.2155.

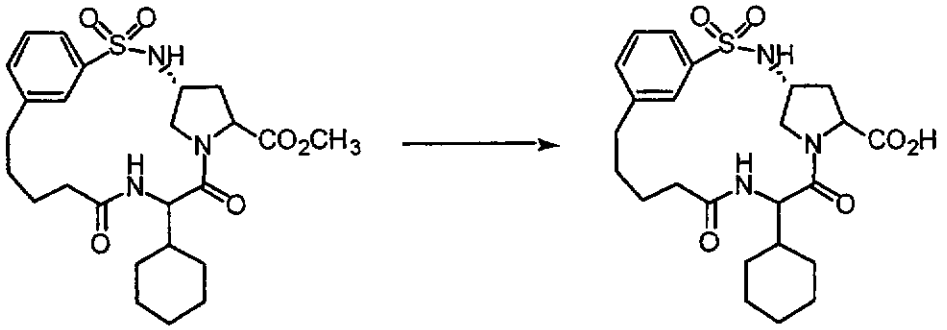
Step G



37f 37g

The desired product **37g** was obtained by the hydrogenation procedure described for Example 1, Step G in 73% yield. The material was sufficiently pure for further studies. HRMS (FAB) Calcd for $C_{25}H_{36}N_3O_6S$: 506.2325 $(M+H)^+$. Found: 506.2314.

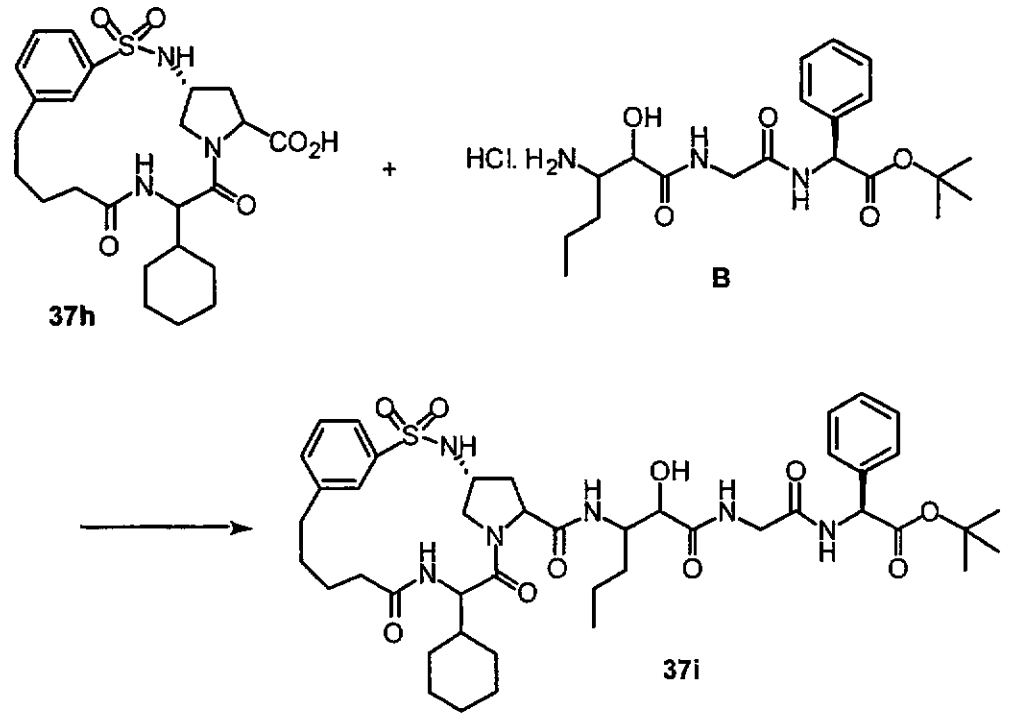
Step H



37g **37h**

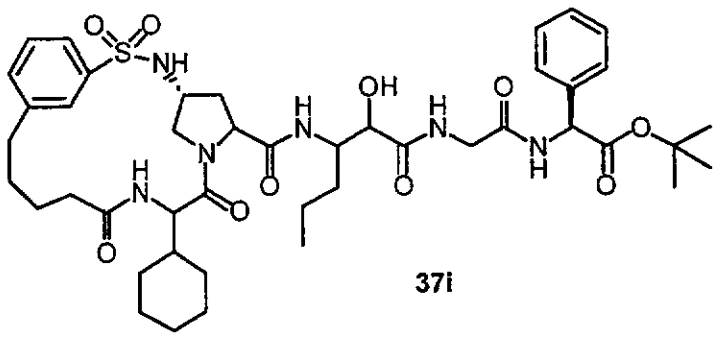
The desired product **37h** was obtained by the procedure described for Example 1, Step H in 84% yield. HRMS (FAB) Calcd for $C_{24}H_{34}N_3O_6S$: 492.2168 $(M+H)^+$. Found: 492.2175.

Step I

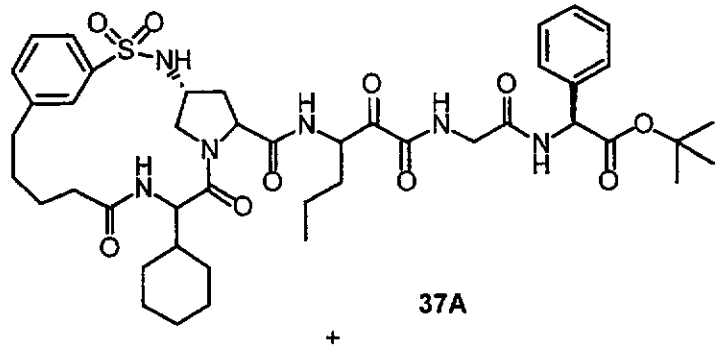


The expected product **37i** was obtained by the procedure described for Example 2, Step A in 90% yield. The crude material was sufficiently pure for further studies. HRMS (FAB) Calcd for $C_{44}H_{63}N_6O_{10}S$: 867.4326 $(M+H)^+$. Found: 867.4342.

Step J

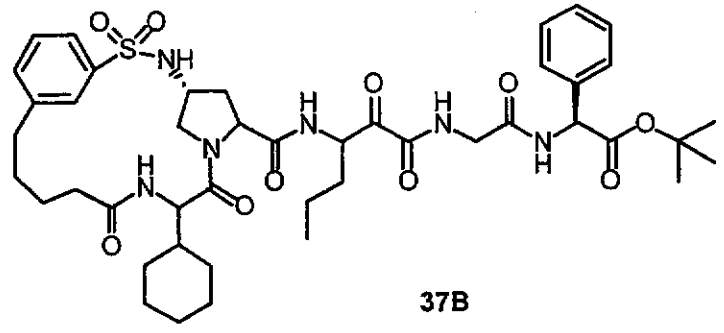


37I



37A

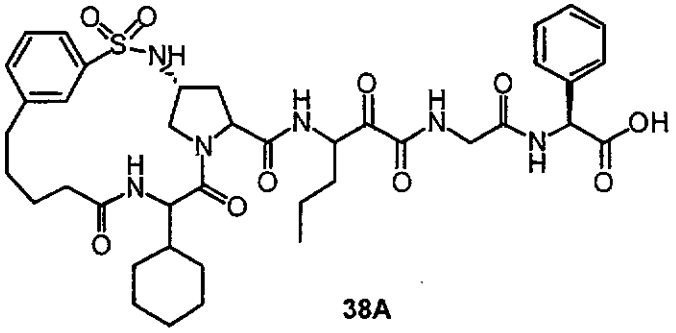
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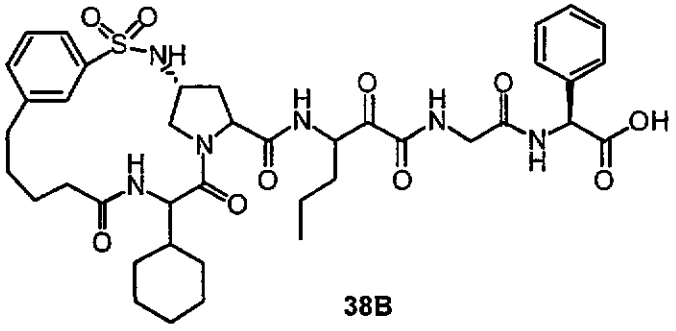
37B

The desired materials **37A** and **37B** were synthesized by the oxidation protocol described for Example 2, Step B. Purification of the residue using 98/2 to 96/4 dichloromethane/MeOH afforded **37A** (61%, less polar) and **37B** (15%, more polar) as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{44}H_{61}N_6O_{10}S$: 865.4170 $(M+H)^+$. Found: 865.4190 (**37A**), 865.4181 (**37B**).

Example 38: Preparation of Compound 38:

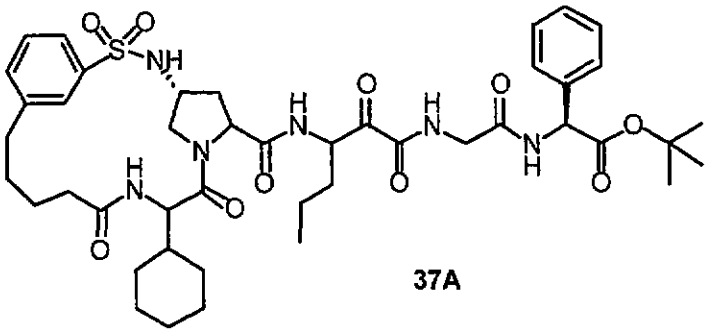


38A

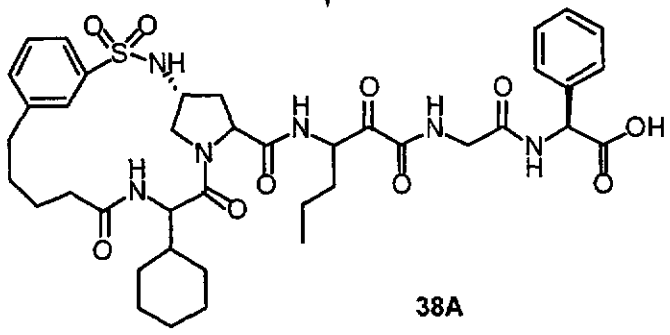


38B

Step A



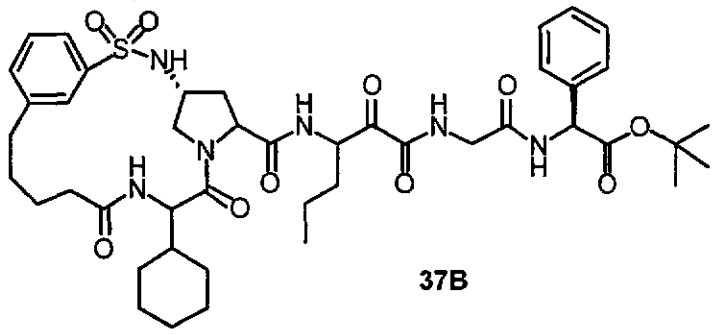
37A



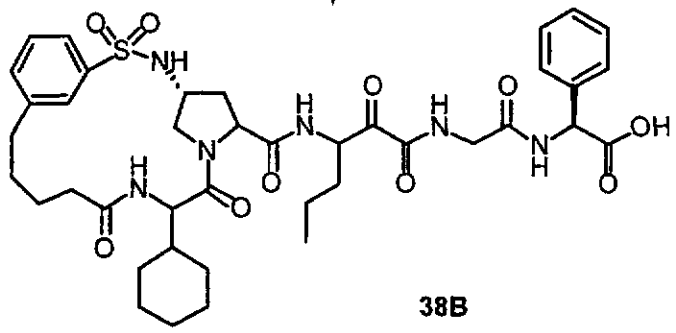
38A

The desired material **38A** was synthesized as described for Example 3, Step A in 91% yield.

Step B



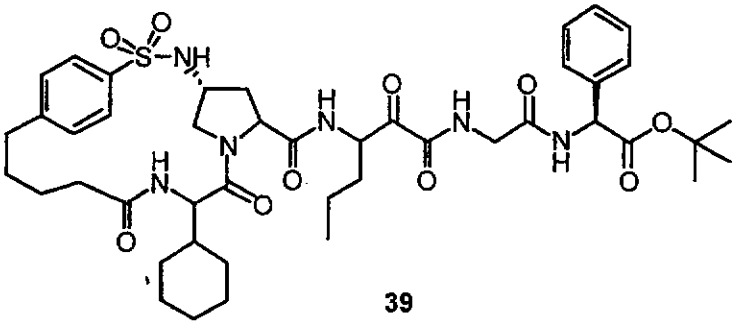
37B



38B

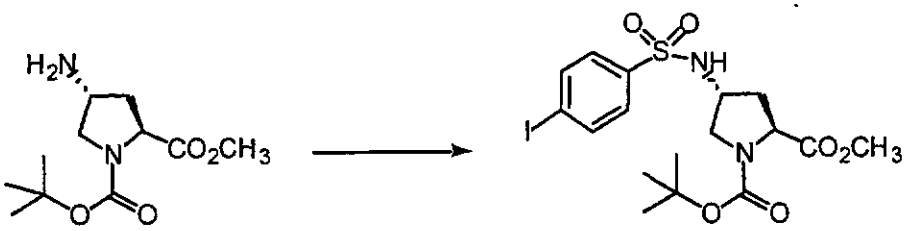
The desired material **38B** was synthesized as described for Example 3, Step A in 83% yield. HRMS (FAB) Calcd for $C_{40}H_{53}N_6O_{10}S$: .809.3544 $(M+H)^+$. Found: 809.3547.

Example 39: Preparation of Compound 39:



39

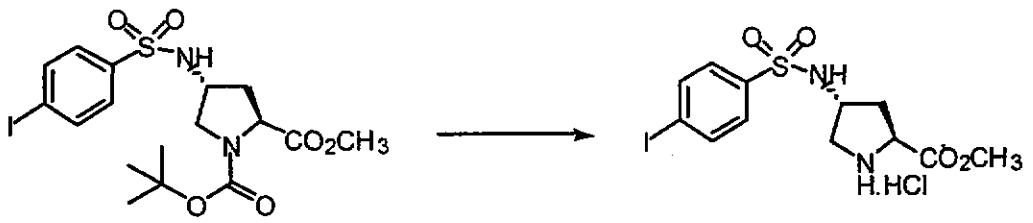
Step A



F 39a

The desired product **39a** was obtained by the method described for Example 37, Step A using pipsyl chloride instead of 3-bromobenzenesulfonyl chloride. Purification of the residue by column chromatography using 95/5 to 90/10 dichloromethane/EtOAc provided 75% yield of **39a**. HRMS (FAB) Calcd for $C_{17}H_{24}N_2O_6SI$: 511.0400 $(M+H)^+$. Found: 511.0386.

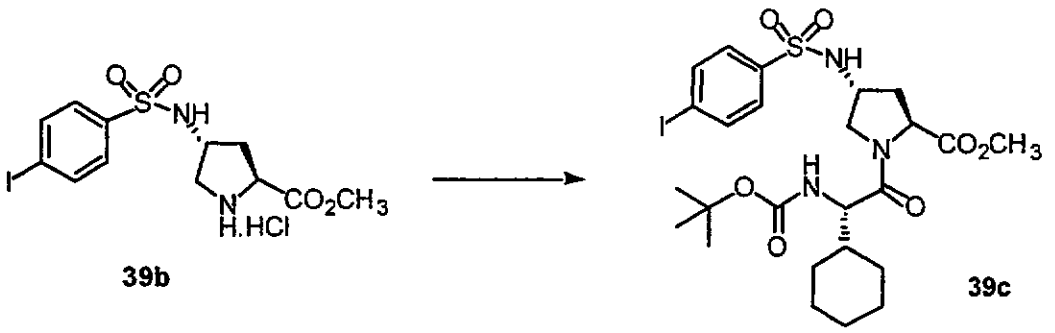
Step B



39a 39b

The desired product **39b** was obtained by the method described for Example 1, Step C. The crude material was used in the next step without purification.

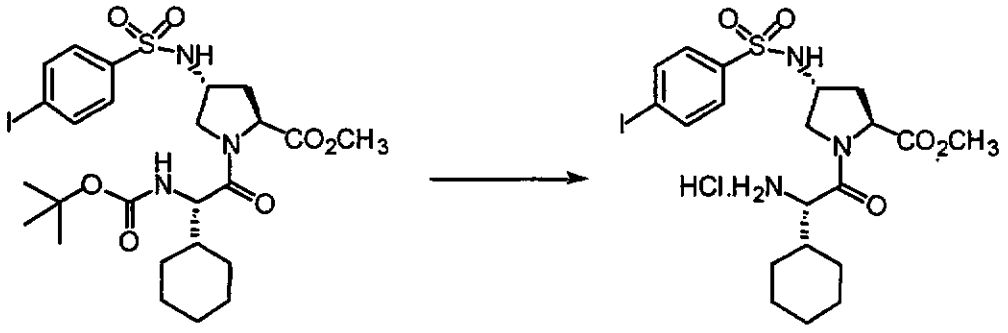
Step C



39b 39c

The desired product **39c** was obtained by the method described for Example 1, Step D. Purification of the residue by column chromatography using 90/10 to 80/20 dichloromethane/EtOAc provided 68% yield of **39c**. HRMS (FAB) Calcd for $C_{25}H_{37}N_3O_7SI$: 650.1397 $(M+H)^+$. Found: 650.1398.

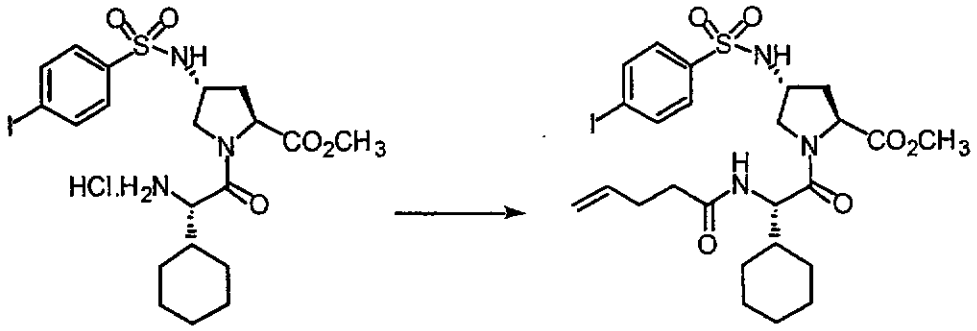
Step D



39c 39d

The desired product **39d** was obtained by the method described for Example 1, Step E. The crude material was used in the next step without purification.

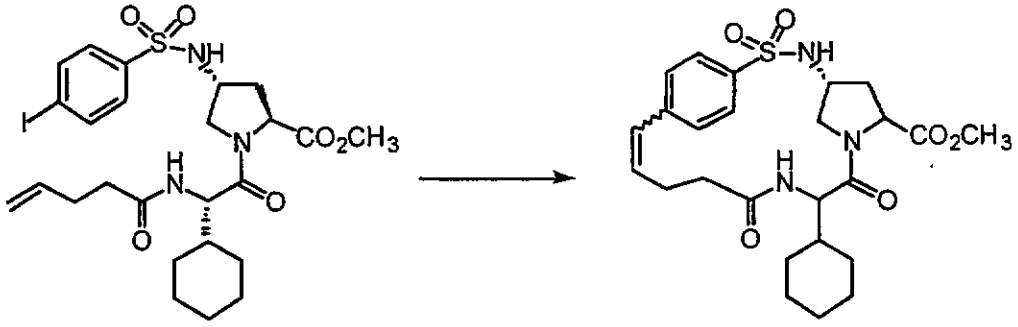
Step E



39d 39e

The desired product **39e** was obtained by the method described for Example 1, Step F using pentenoic acid as the coupling partner. Purification of the residue by column chromatography using 98/2 dichloromethane/MeOH provided 76% yield of **39e**.

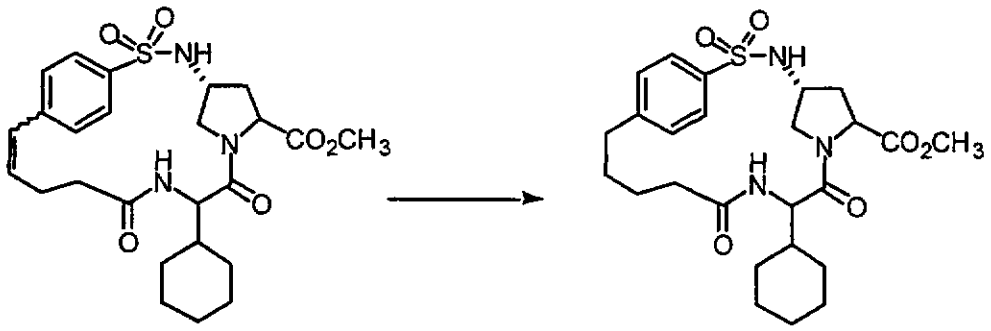
Step F



39e 39f

The desired product **39f** was obtained by the method described for Example 37, Step F. Purification of the residue by column chromatography using 98/2 dichloromethane/MeOH provided 28% yield of **39f** as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{25}H_{34}N_3O_6S$: 504.2168 $(M+H)^+$. Found: 504.2160.

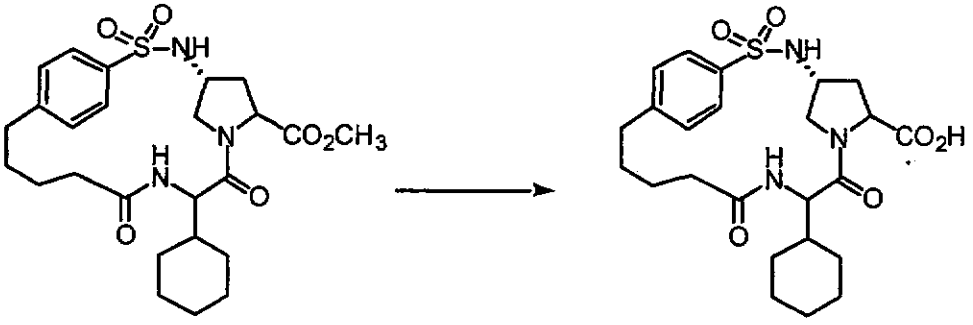
Step G



39f 39g

The desired product **39g** was obtained by the hydrogenation procedure described for Example 1, Step G in 84% yield. The material was sufficiently pure for further studies. HRMS (FAB) Calcd for $C_{25}H_{36}N_3O_6S$: 506.2325 $(M+H)^+$. Found: 506.2314.

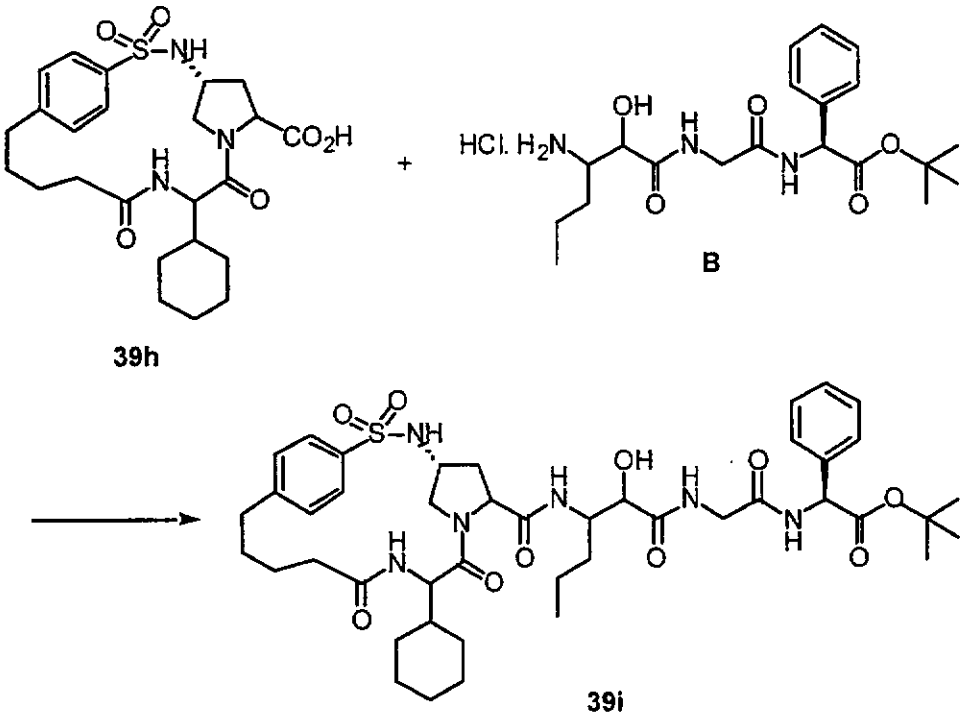
Step H



39g 39h

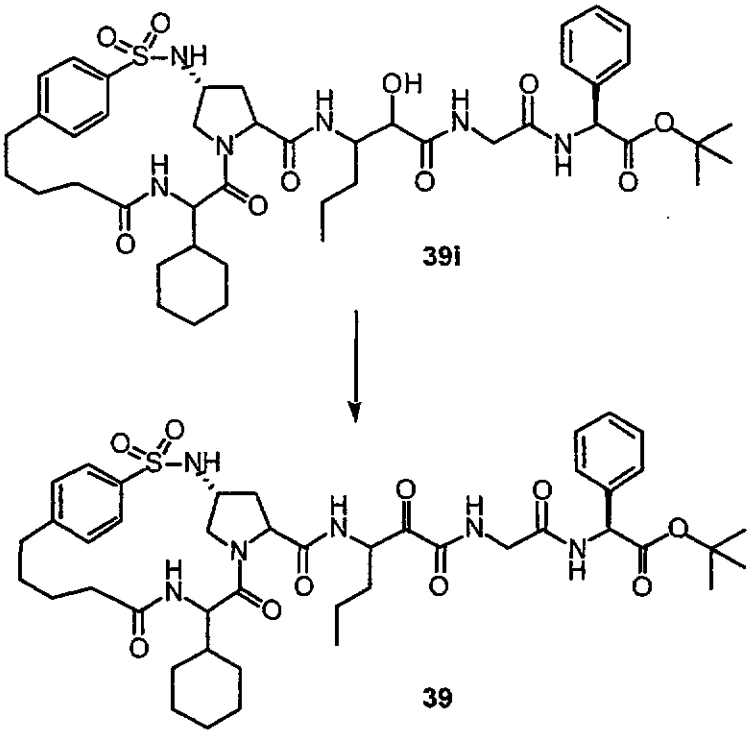
The desired product **39h** was obtained by the procedure described for Example 1, Step H in quantitative yield. HRMS (FAB) Calcd for $C_{24}H_{34}N_3O_6S$: 492.2168 $(M+H)^+$. Found: 492.2175.

Step I



The expected product **39i** was obtained by the method described for Example 2, Step A in 36% yield. The crude material was sufficiently pure for further studies. HRMS (FAB) Calcd for $C_{44}H_{63}N_6O_{10}S$: 867.4326 $(M+H)^+$. Found: 867.4342.

Step J

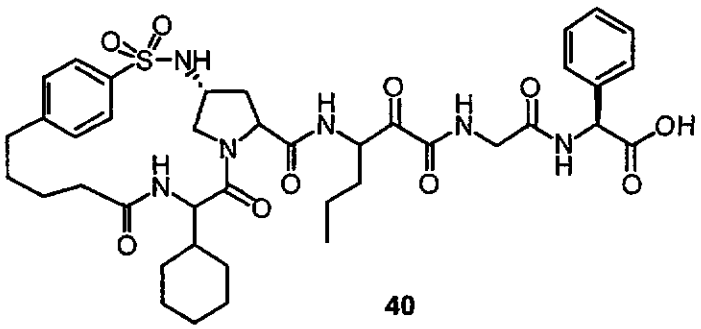


39i

39

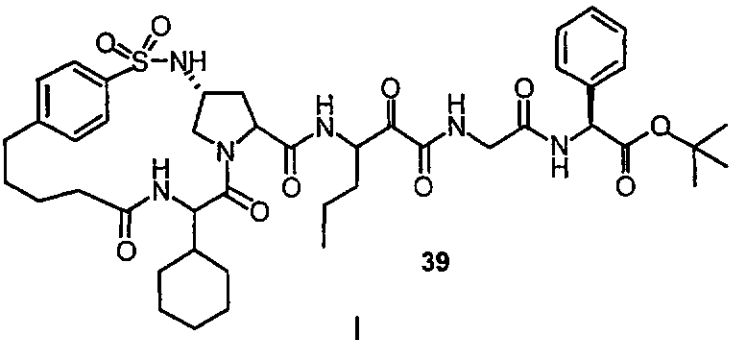
The desired material **39** was obtained by the oxidation protocol described for Example 2, Step B. Purification of the residue using 98/2 dichloromethane/MeOH afforded **39** in 24% yield as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{44}H_{61}N_6O_{10}S$: 865.4170 $(M+H)^+$. Found: 865.4181.

Example 40: Preparation of Compound 40:

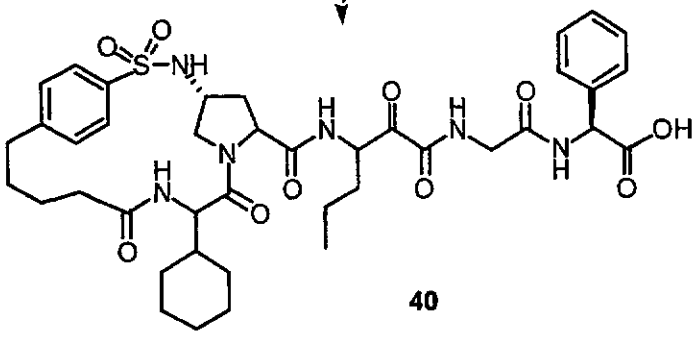


40

Step A



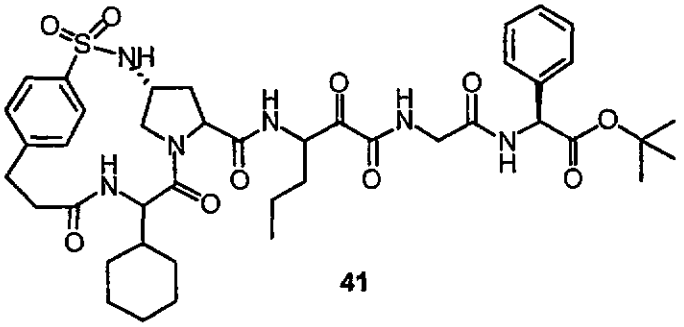
39



40

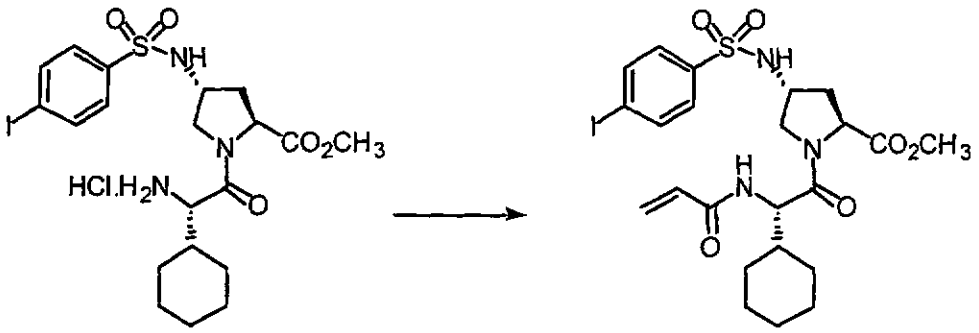
The desired material **40** was obtained by the procedure described for Example 3, Step A in 93% yield as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{40}H_{53}N_6O_{10}S$: 809.3544 $(M+H)^+$. Found: 809.3544.

Example 41: Preparation of Compound 41:



41

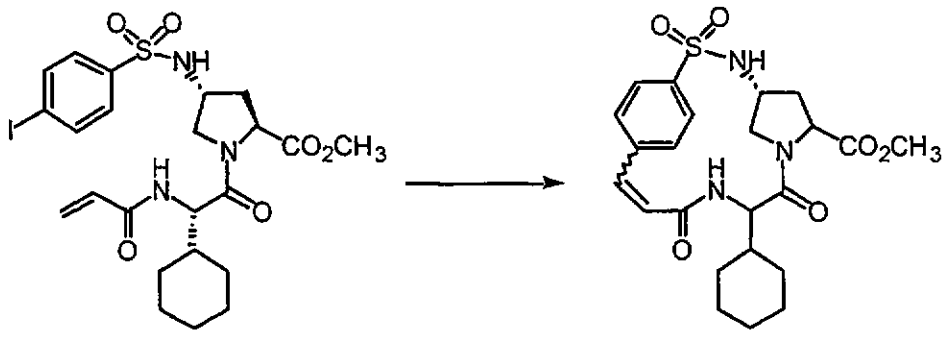
Step A



39d 41a

To a 25 mL addition funnel was added benzene (5 mL), DMF (0.32 mL, 4.1 mmol), and thionyl chloride (0.33 mL, 4.5 mmol). After 5 minutes two layers appeared. The lower layer was separated and added slowly to a cooled (0-5°C) solution of acrylic acid (0.19 mL, 2.8 mmol) in dichloromethane. The mixture was maintained at that temperature for 10 minutes. Then triethylamine (0.77 mL, 5.5 mmol) was added followed by **39d** (1.13 g, 2.1 mmol). The reaction mixture was warmed to ambient temperature over 5 hrs and quenched with saturated $NaHCO_3$. The organic layer was separated, washed with 5% H_3PO_4 solution and brine. The dichloromethane layer was dried (Na_2SO_4), and concentrated. The crude material was purified by flash column chromatography using 98/2 dichloromethane/MeOH to provide 870 mg of **41a** (67% yield). HRMS (FAB) Calcd for $C_{23}H_{31}N_3O_6SI$: 604.0978 $(M+H)^+$. Found: 604.0964.

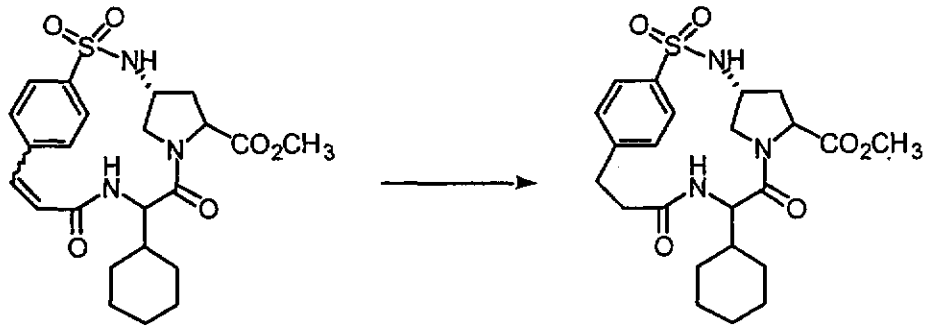
Step B



41a 41b

The desired product **41b** was obtained by the method described for Example 37, Step F. The residue was purified using 97/3 dichloromethane/MeOH to afford **41b** in 26% yield. HRMS (FAB) Calcd for $C_{23}H_{30}N_3O_6S$: 476.1855 $(M+H)^+$. Found: 476.1858.

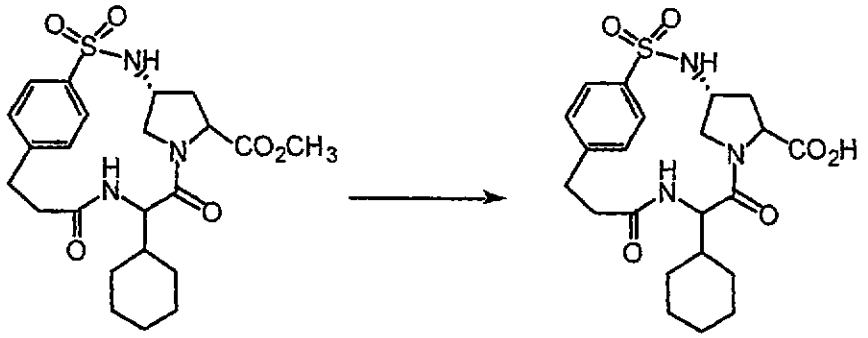
Step C



41b 41c

The desired product **41c** was obtained by the hydrogenation method described for Example 1, Step D in 75% yield. The material was sufficiently pure for further studies.

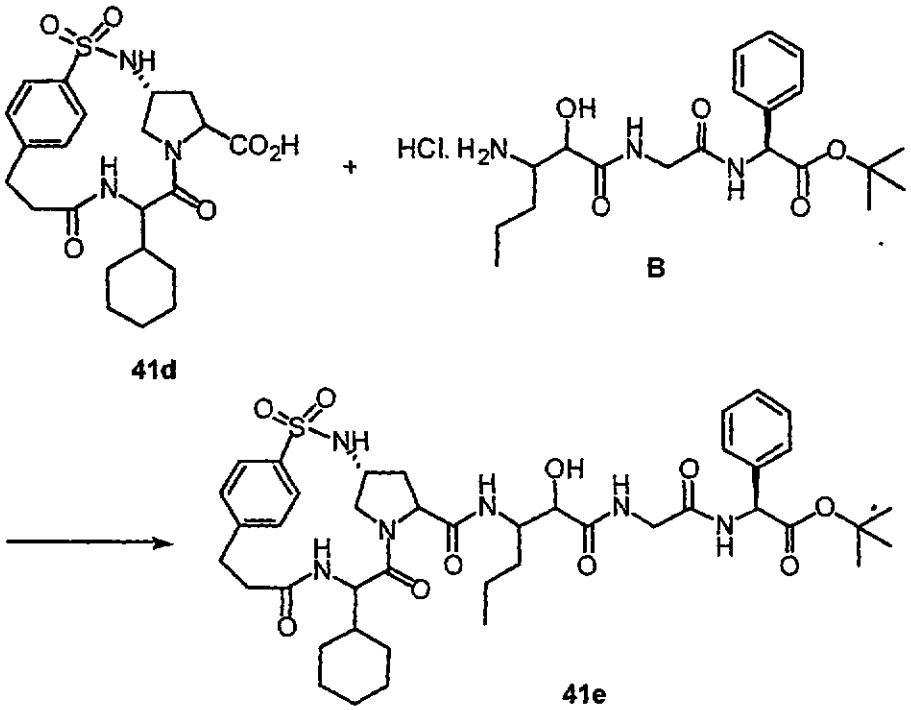
Step D



41c 41d

The desired product **41d** was obtained by the method described for Example 1, Step E. The crude material was used in the next step without purification.

Step E

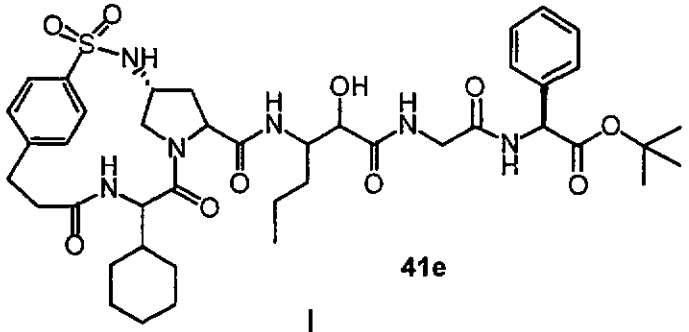


41d B

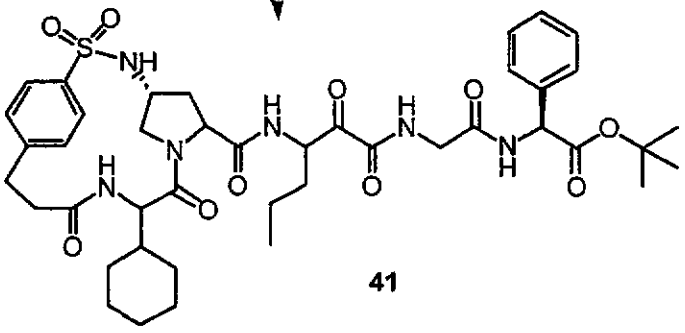
41e

The expected product **41e** was obtained by the method described for Example 2, Step A in 63% yield. The crude material was sufficiently pure for further studies.

Step F



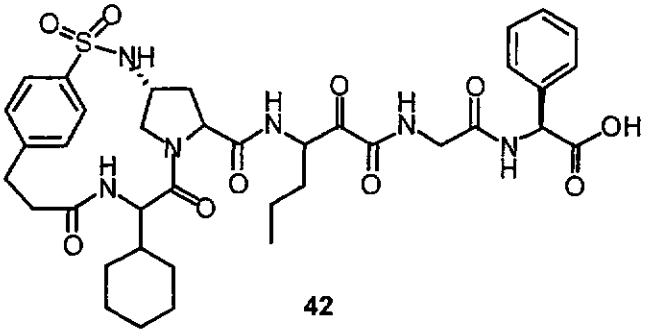
41e



41

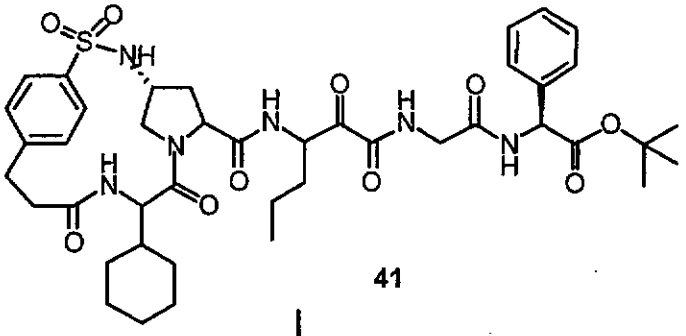
The desired material **41** was obtained by the oxidation protocol described for Example 2, Step B. Purification of the residue using 98/2 to 95/5 dichloromethane/MeOH afforded **41** in 52% yield as a mixture of diastereomers.

Example 42: Preparation of Compound 42:

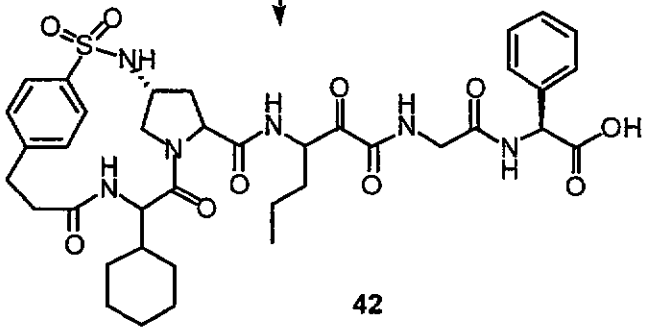


42

Step A



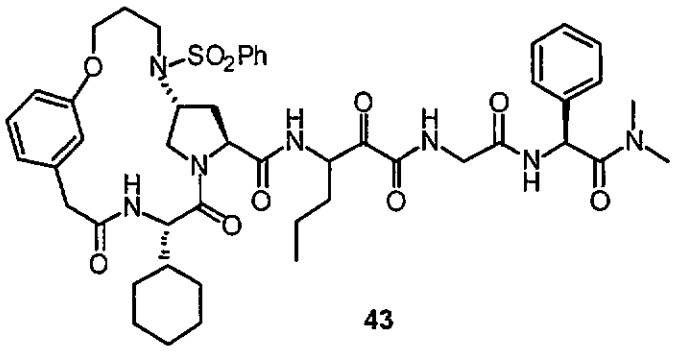
41



42

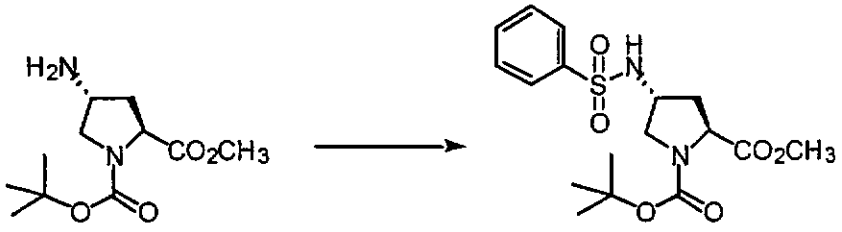
The desired material **42** was obtained by the procedure described for Example 3, Step A in quantitative yield as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{38}H_{49}N_6O_{10}S$: 781.3231 $(M+H)^+$. Found: 781.3233.

Example 43: Preparation of Compound 43:



43

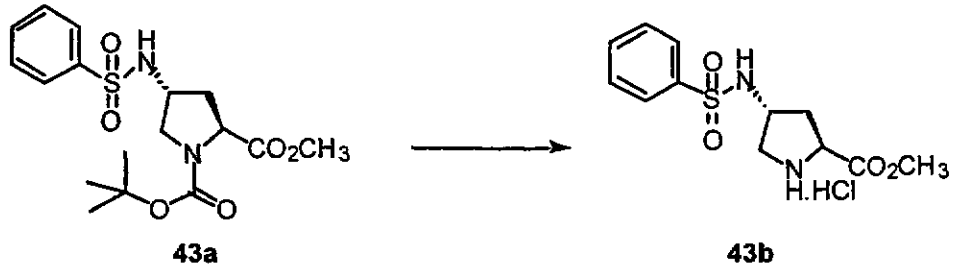
Step A



F 43a

To a cold (0°C) solution of **F** (5.4 g, 22.1 mmol) in dichloromethane (50 mL) was added triethylamine (6.8 mL, 48.6 mmol), DMAP (few crystals) and benzenesulfonyl chloride (3.29 g, 24.1 mmol). The reaction mixture was left standing in the refrigerator (0-5°C) overnight. The reaction mixture was washed with saturated $NaHCO_3$, and 10% citric acid solution. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using 95/5 dichloromethane/EtOAc to afford 5.0 g (59% yield) of **43a**.

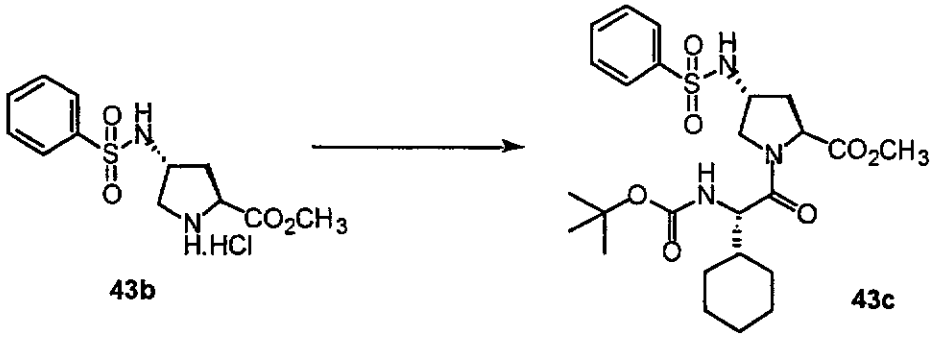
Step B



43a 43b

The desired product **43b** was obtained by the method described for Example 1, Step C. The crude material was used in the next step without purification.

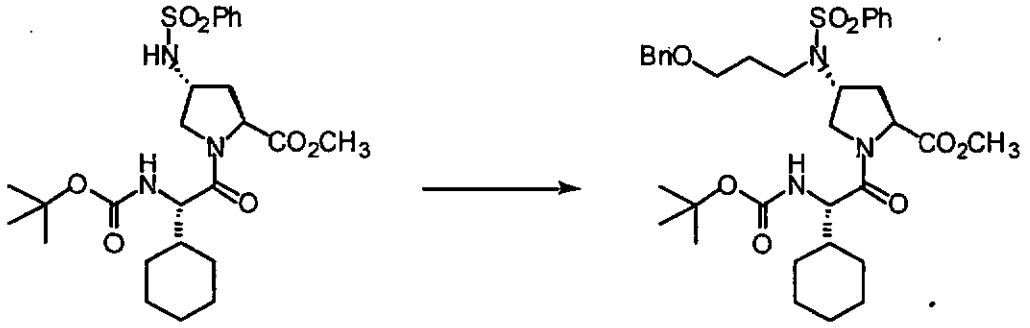
Step C



43b **43c**

The desired product **43c** was obtained by the method described for Example 1, Step D. Purification of the residue by column chromatography using 99/1 dichloromethane/MeOH provided 60% yield of **43c**.

Step D

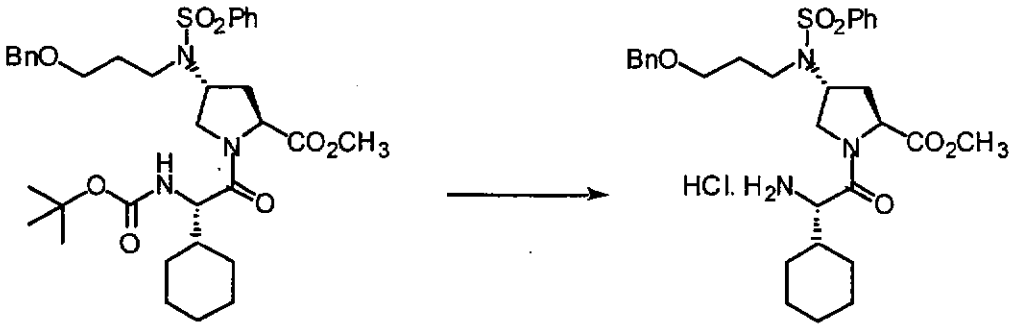


43c **43d**

Argon gas was bubbled into a cold (0°C) solution of **43c** (1.72 g, 3.28 mmol) in dichloromethane (40 mL) for 20-30 min. ADDP (2.5 g, 9.84 mmol) was added followed by triphenylphosphine (2.6 g, 9.84 mmol) and 3-benzyloxypropanol (0.57 mL, 3.61 mmol). The reaction was warmed to ambient temperature and left standing for 2 days. Concentrated the reaction

mixture and added Et_2O (50 mL). The precipitated solid material was filtered off. Repeated this operation twice to remove most of the side products. The filtrate was concentrated and purified by flash chromatography using 90/10 to 85/15 dichloromethane/EtOAc to provide 330 mg of **43d**. The recovered starting materials, along with some triphenylphosphine oxide, was resubjected to the above described conditions to provide additional 420 mg of **43d**. Combined yield = 34%. HRMS (FAB) Calcd for $C_{35}H_{50}N_3O_8S$: 672.3319 $(M+H)^+$. Found: 672.3330.

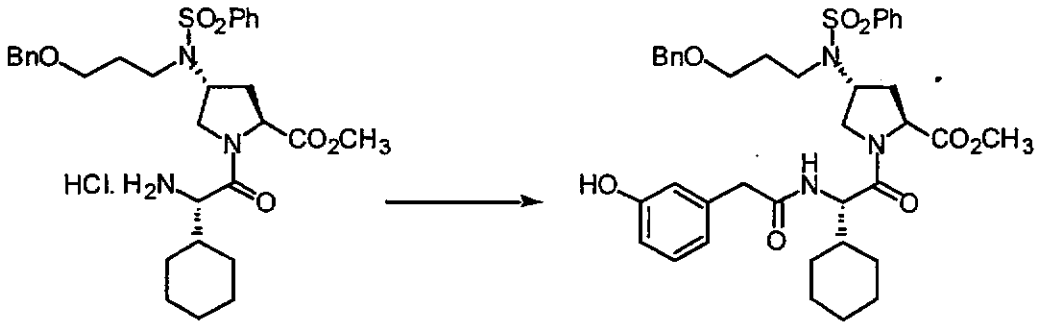
Step E



43d **43e**

The desired product **43e** was obtained by the method described for Example 1, Step E. The crude product was carried to the next step.

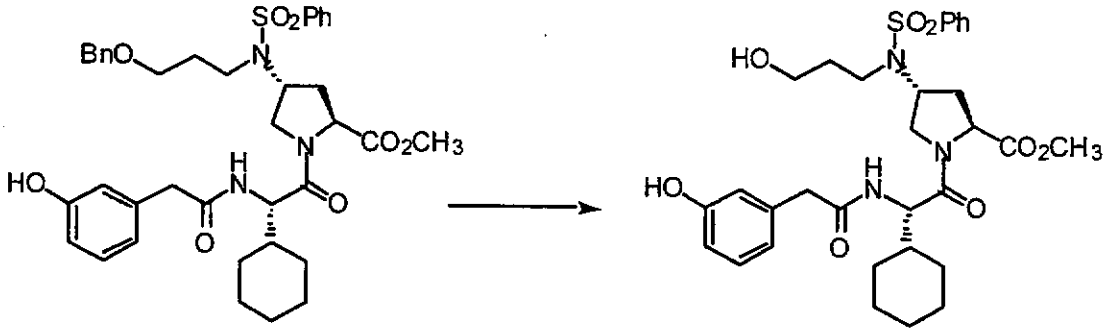
Step F



43e **43f**

The desired compound **43f** was prepared by the protocol described for Example 1, step F. Purification by flash chromatography was carried out with 60/40 to 50/50 dichloromethane/EtOAc to provide **43f** in quantitative yield. HRMS (FAB) Calcd for $C_{38}H_{48}N_3O_8S$: 706.3162 $(M+H)^+$. Found: 706.3157.

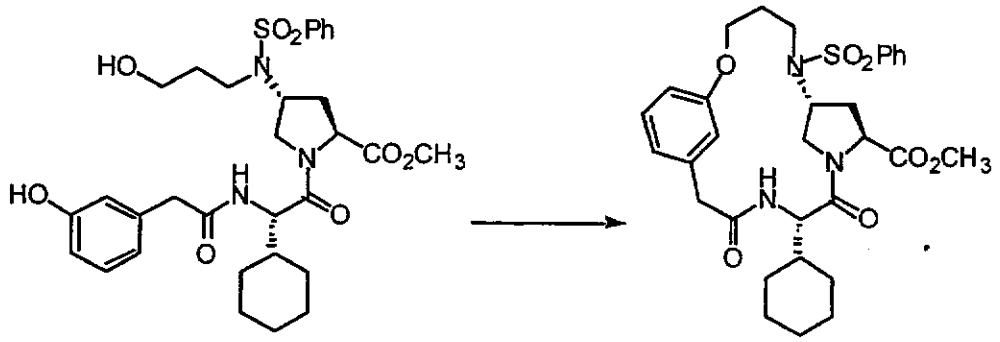
Step G



43f **43g**

The desired product **43g** was obtained by the procedure described for Example 1, Step G. The material was sufficiently pure for further studies.

Step H

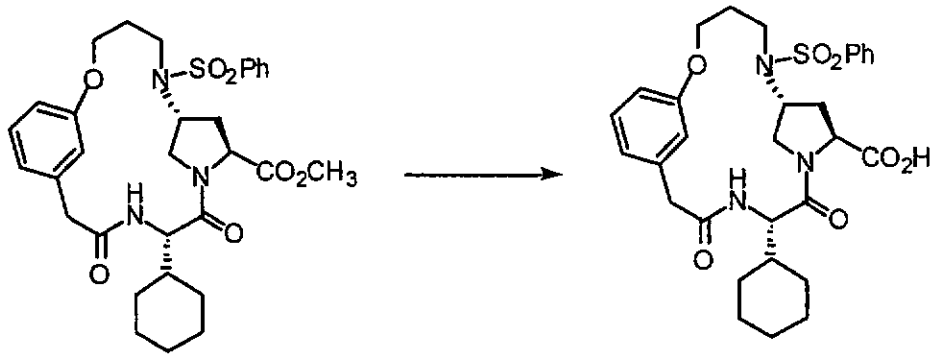


43g **43h**

The desired product **43h** was obtained by the procedure described for Example 1, Step H. After completion of reaction, the solvent was evaporated. Et_2O (50 mL) was added and the solids were filtered off. The filtrate was

concentrated and Et2O/EtOAc (50mL/50 mL) was added. The precipitated solids were filtered off and the filtrate was concentrated. The residue was purified by flash chromatography using 85/15 to 80/20 dichloromethane/EtOAc to afford pure **43h** in 20% yield. HRMS (FAB) Calcd for $C_{31}H_{40}N_3O_7S$: 598.2587 $(M+H)^+$. Found: 598.2581.

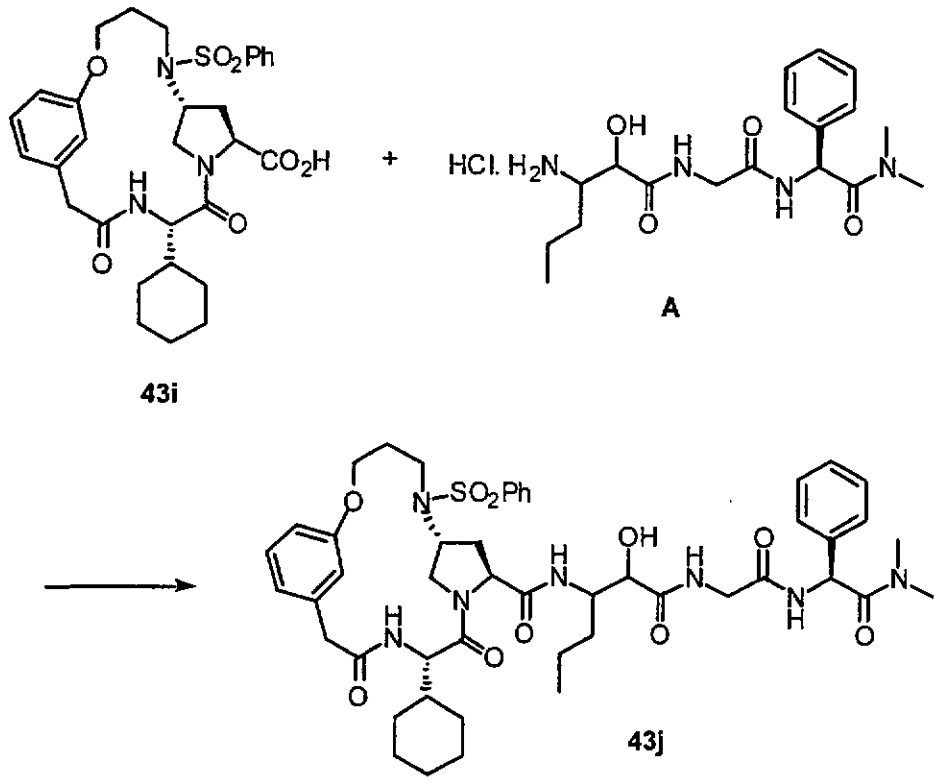
Step I



43h **43i**

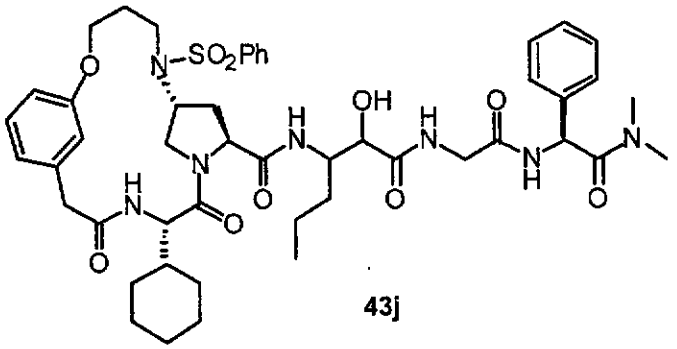
The expected product **43i** was obtained by the procedure described for Example 1, Step I in 92% yield.

Step J

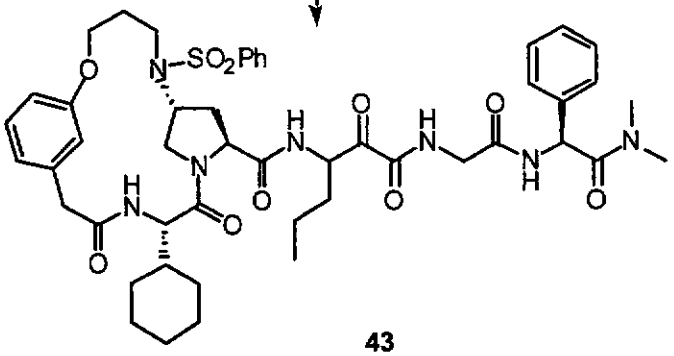


The desired material **43j** was synthesized as described for Example **1**, Step J. The crude product was of sufficient purity to be carried forward.

Step K



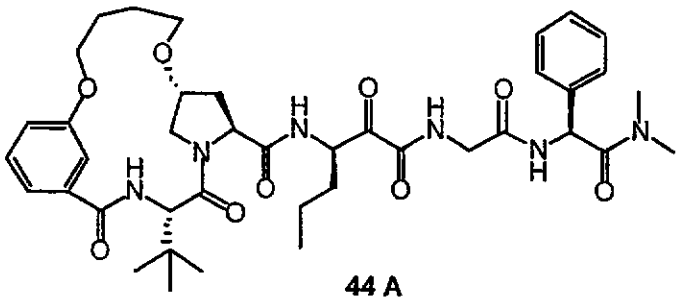
43j



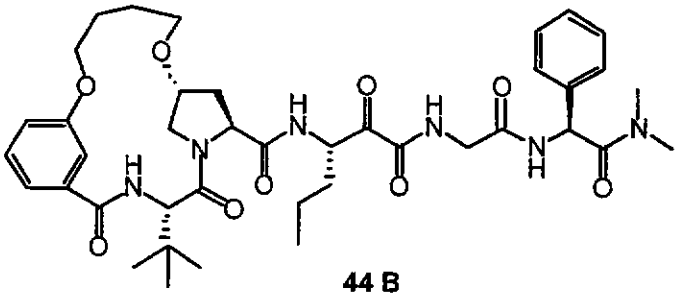
43

The expected product **43** was obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 97/3 dichloromethane/MeOH afforded **43** as a mixture of diastereomers. Combined yield = 60% (for 2 steps). HRMS (FAB) Calcd for $C_{48}H_{62}N_7O_{10}S$: 928.4279 $(M+H)^+$. Found: 928.4290.

Example 44: Preparation of Compound 44:

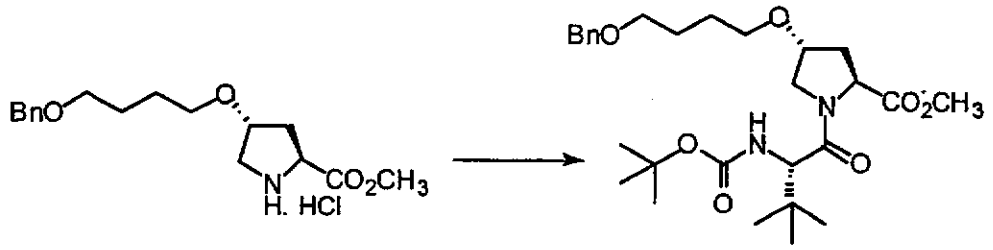


44 A



44 B

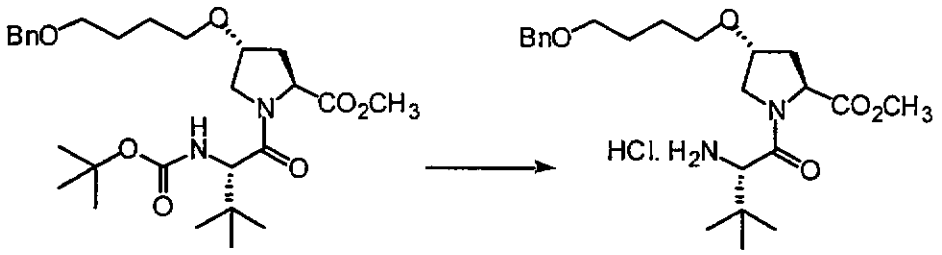
Step A



4c **44a**

The desired product **44a** was obtained by the method described for Example 1, Step D using N-boc-tert-butylglycine as the coupling partner. The material after work-up was sufficiently pure to be carried to the next step.

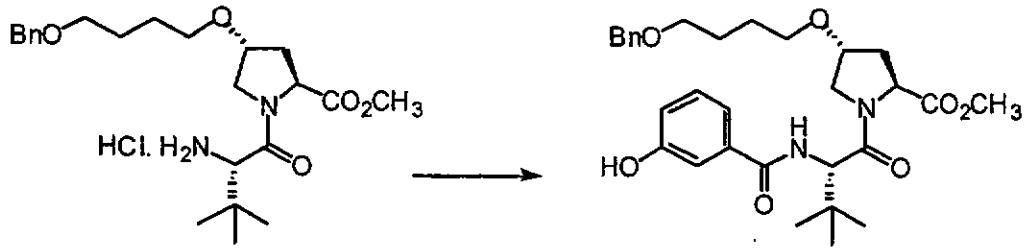
Step B



44a **44b**

The desired product **44b** was obtained by the method described for Example 1, Step E. The crude material was carried forward without purification.

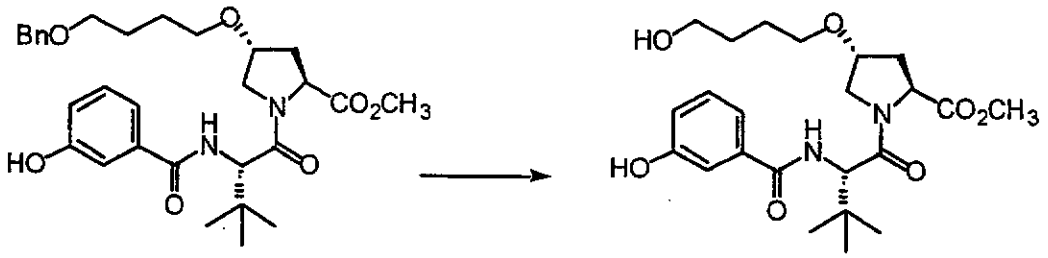
Step C



44b **44c**

The desired product was obtained by the method described for Example 1, Step F, using 3-hydroxybenzoic acid. The material was purified by flash column chromatography using 85/15 to 65/35 dichloromethane/ethyl acetate to provide **44c** in 81% yield.

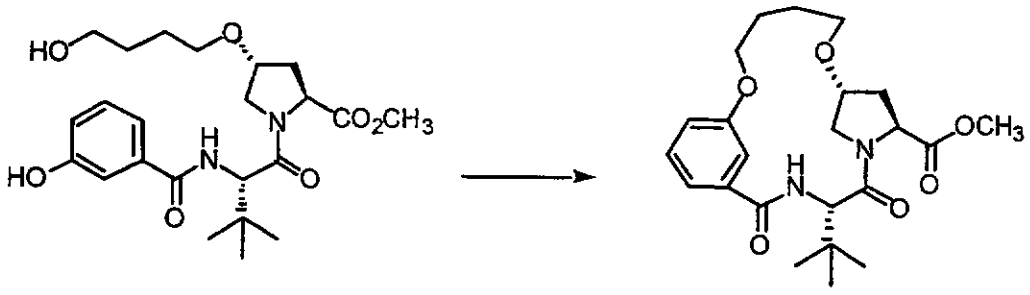
Step D



44c 44d

The desired product **44d** was obtained by the method described for Example 1, Step G. The residue after workup was sufficiently pure for further manipulation.

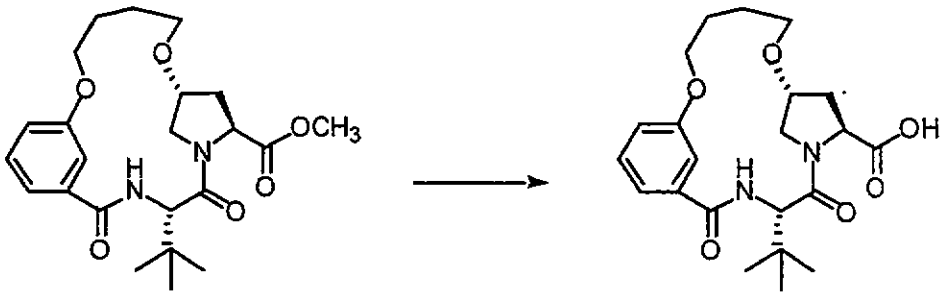
Step E



44d 44e

The desired product **44e** was obtained by the method described for Example 1, Step H. The crude residue after concentration was taken in hexanes/EtOAc (1/1) and the solid material was filtered off. This operation was performed again to remove some of the side products. Purification by column chromatography using 80/20 dichloromethane/EtOAc afforded **44e** along with triphenylphosphine oxide. This mixture was taken to the next step

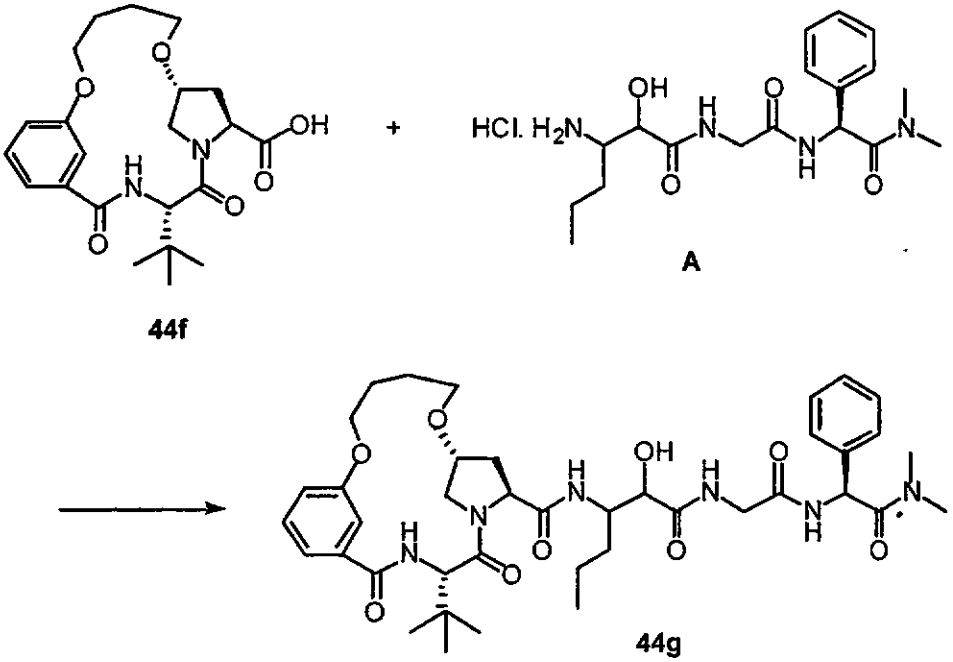
Step F



44e 44f

The desired product **44f** was obtained by the method described for Example 1, Step I. Yield of **44f** (for 2 steps) = 11%.

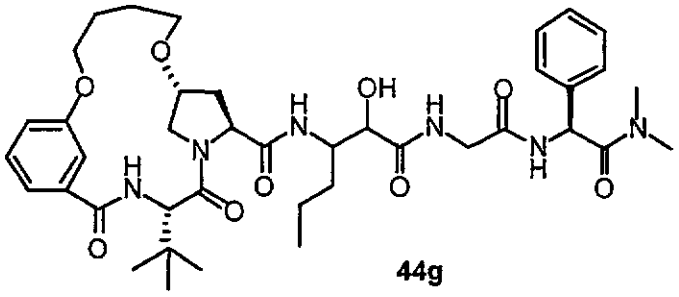
Step G



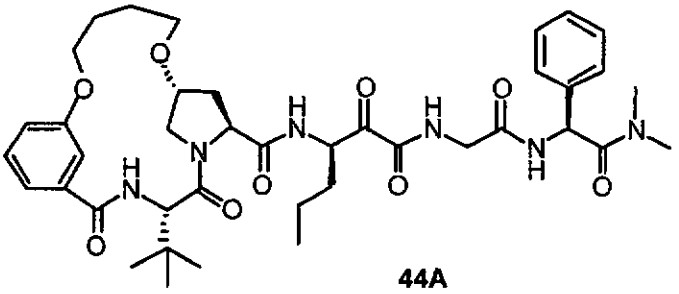
44f A 44g

The expected product **44g** was synthesized as described earlier for the Example 1, Step J. The material after work-up was carried forward to the next step.

Step H

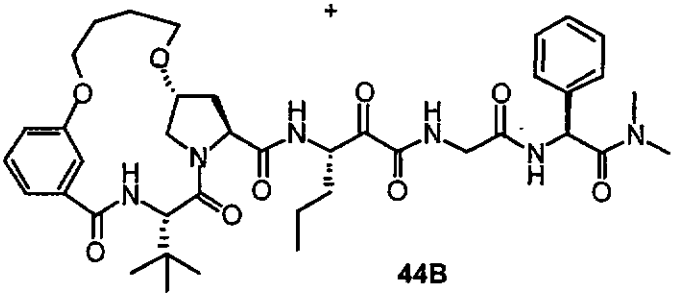


44g



44A

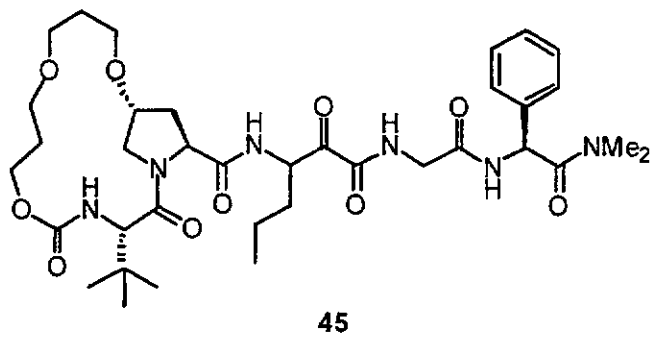
+



44B

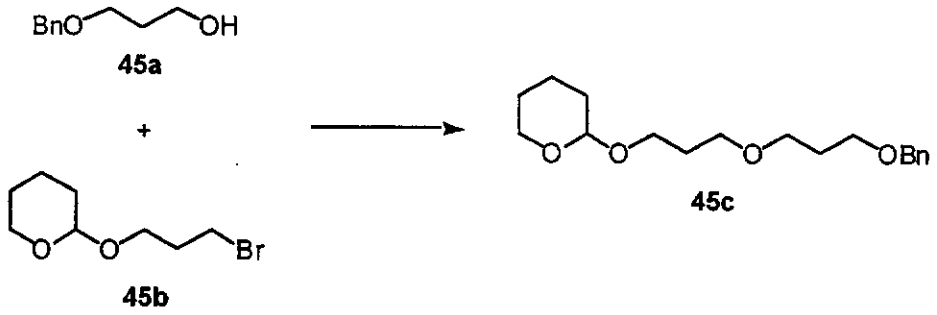
The desired products **44A** and **44B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 97/3 to 96/4 dichloromethane/methanol afforded equal amount of separate isomers **44A** and **44B**. Combined yield = 58% (for 2 steps).

Example 45: Preparation of Compound 45:



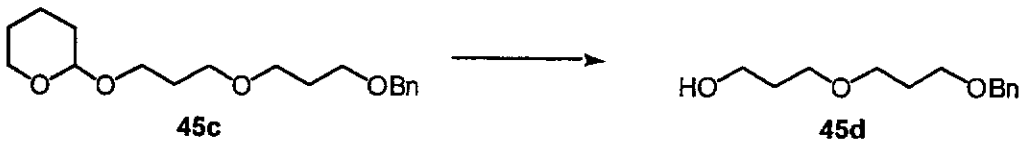
45

Step A



Alkylation of **45a** with **45b** was carried out using the procedure described for Example 1 Step A. The crude product was purified using 85/0/15 to 85/5/10 hexanes/EtOAc/dichloromethane to provide **45c** in 37% yield. HRMS (FAB) Calcd for $C_{18}H_{29}O_4$: 309.2066 $(M+H)^+$. Found: 309.2060.

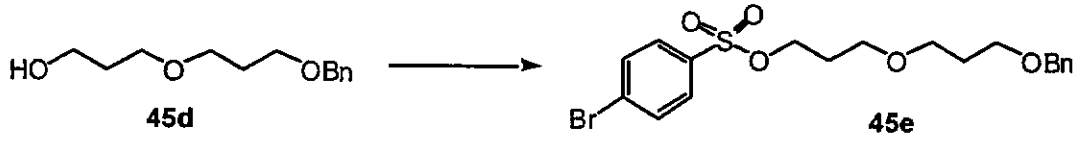
Step B



To a solution of **45c** (4.8 g, 15.5 mmol) in MeOH (30 mL) was added pyridinium *p*-toluenesulfonate (780 mg, 3.1 mmol) and refluxed for 3 hrs when

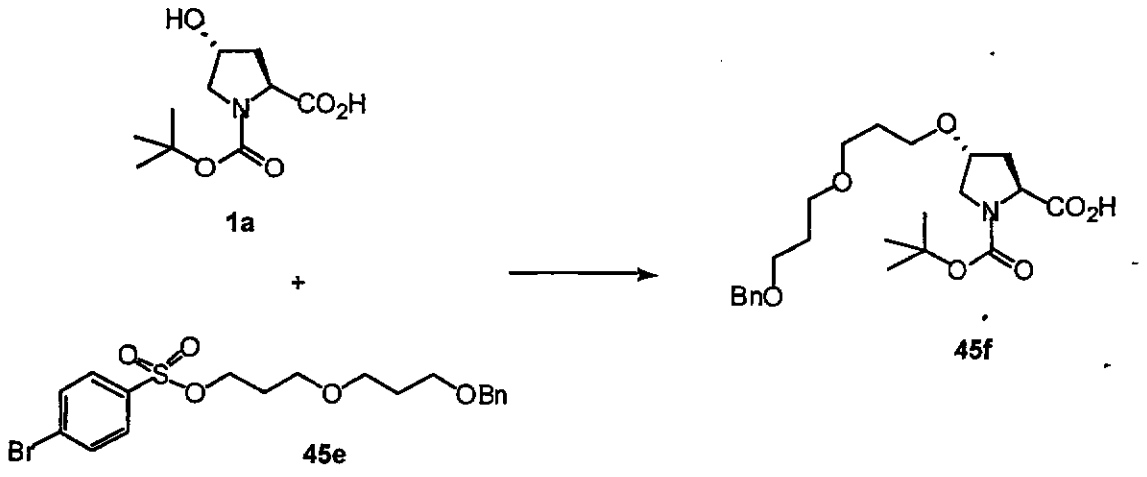
all the starting material was consumed. The reaction mixture was concentrated. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, dried (Na2SO4) and the organic layer was concentrated to afford 3.2 g of **45d** (92% yield). This material was sufficiently pure for further studies. HRMS (FAB) Calcd for $C_{13}H_{21}O_3$: 225.1491 $(M+H)^+$. Found: 225.1486.

Step C



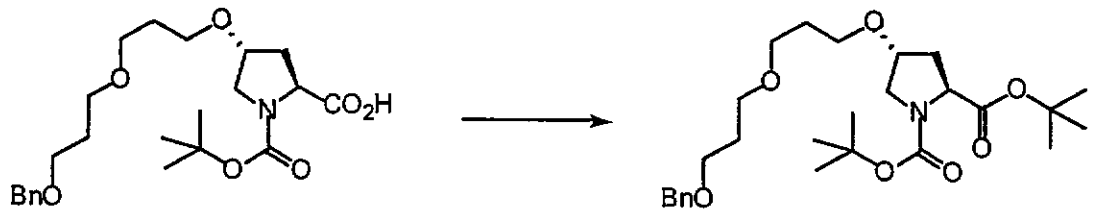
The desired product **45e** was obtained by the procedure described for Example 10 Step A using **45d** as the starting material. The crude product was purified using 90/10 hexanes/EtOAc to provide **45e** in 70 % yield. HRMS (FAB) Calcd for $C_{19}H_{24}O_5SBr$: 443.0528 $(M+H)^+$. Found: 443.0552.

Step D



The desired product **45f** was obtained by the procedure described for Example 1 Step A using **45e** as the starting material. The crude product was carried further without purification.

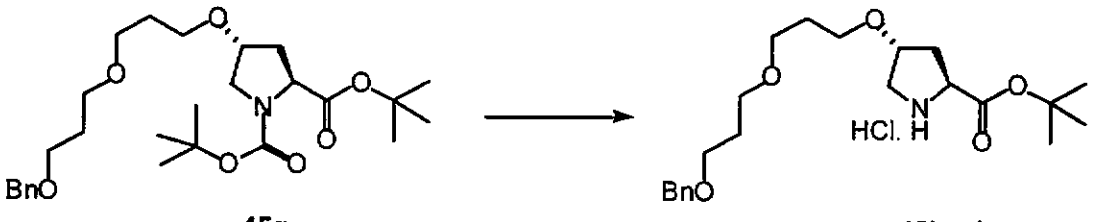
Step E



45f 45g

The desired product **45g** was obtained by the procedure described for Example 18 Step B using **45f** as the starting material. The residue was purified by flash chromatography using 90/10 dichloromethane/EtOAc to provide **45g** in 61% yield (for 2 steps). HRMS (FAB) Calcd for $C_{27}H_{44}NO_7$: 494.3118 $(M+H)^+$. Found: 494.3107.

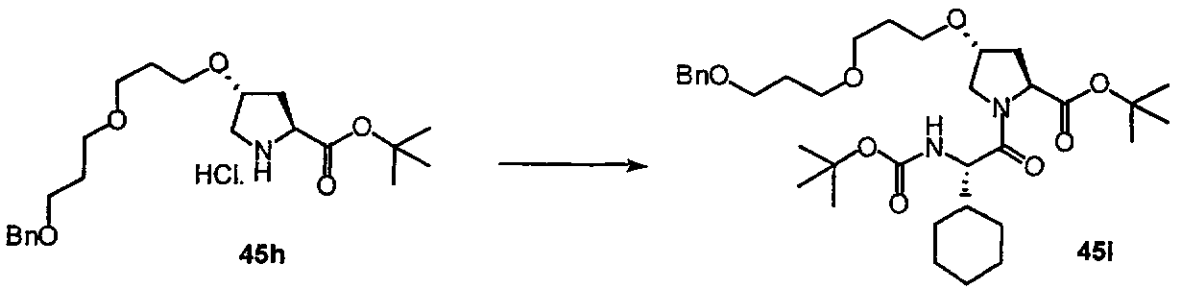
Step F



45g 45h

The desired compound **45h** was prepared by the protocol described for Example 1 Step C. The material was carried forward.

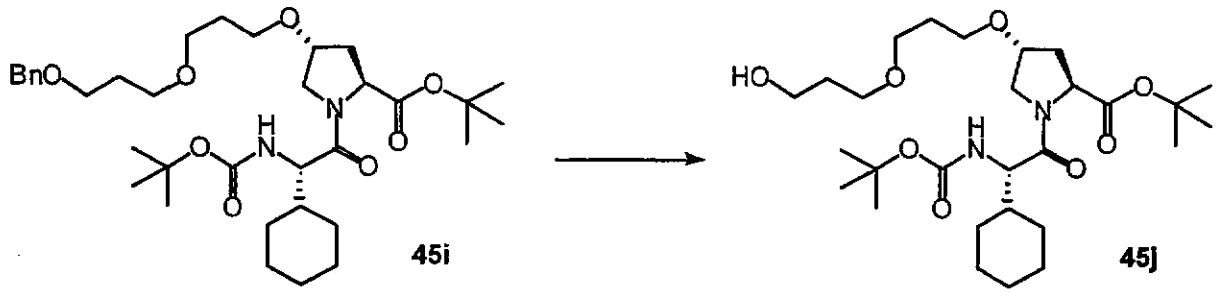
Step G



45h 45l

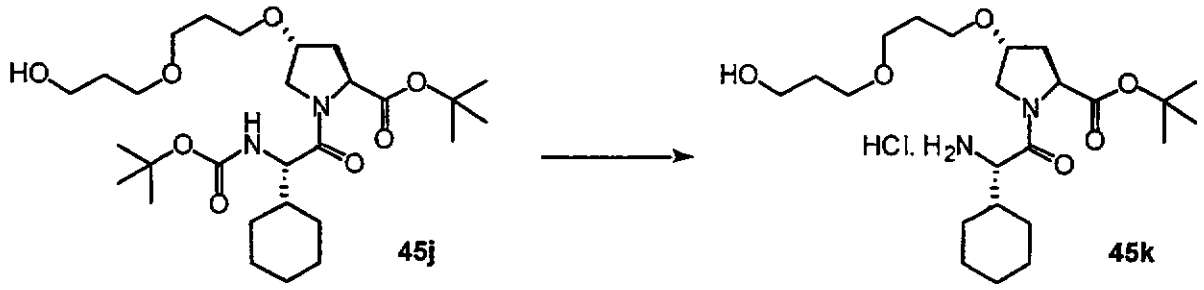
The desired product **45i** was obtained by the procedure described for Example 1 Step D. The residue was purified by flash chromatography using 90/10 to 85/15 dichloromethane/EtOAc to provide **45i** in 41% yield.

Step H



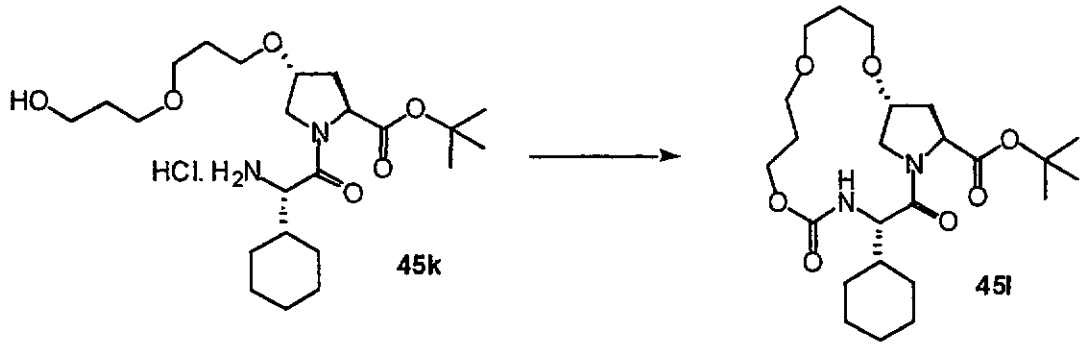
The desired product **45j** is obtained by the hydrogenation protocol described previously for Example 1 Step G.

Step I



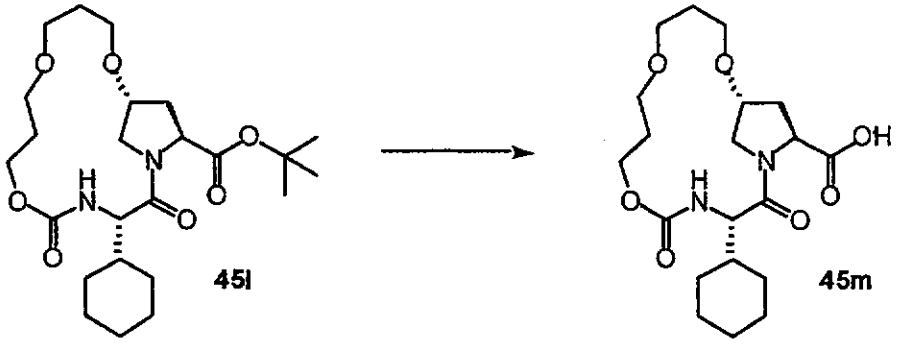
The desired product **45k** is obtained by the procedure described previously for Example 1 Step C.

Step J



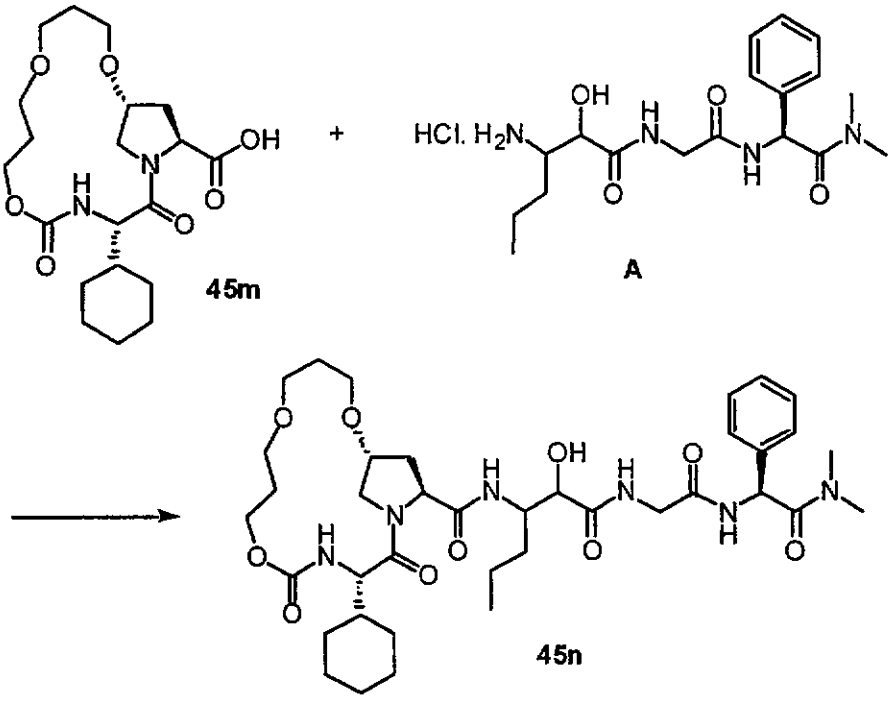
To a cold (0°C) solution of **45k** in dichloromethane is added triethylamine followed by carbonyldiimidazole. Slow warming to ambient temperature overnight is expected to provide the required product **45l**. This product can be purified using conventional flash column chromatography to afford pure **45l**.

Step K



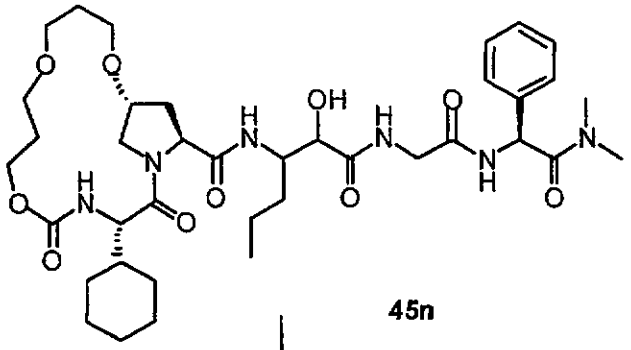
The desired product **45m** is obtained by the producer described previously for Example 3 Step A.

Step L

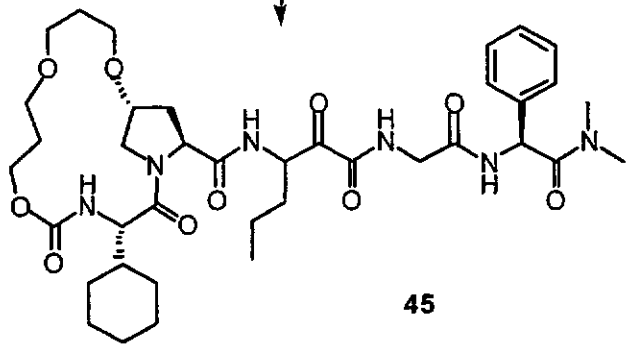


The expected product **45n** is synthesized as described earlier for Example 1 Step J.

Step M



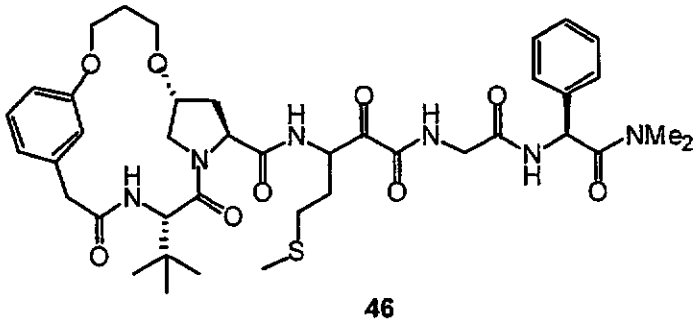
45n



45

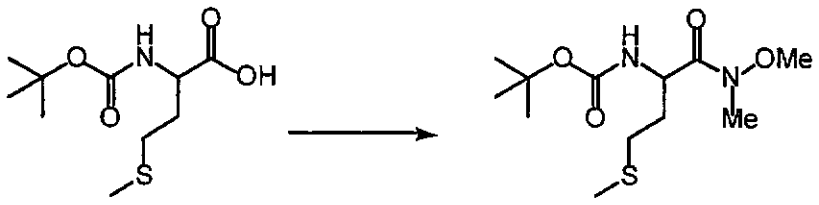
The desired product **45** is obtained by the oxidation protocol described previously for Example 1 Step K. Purification by flash column chromatography will afford pure **45**.

Example 46: Preparation of Compound 46:



46

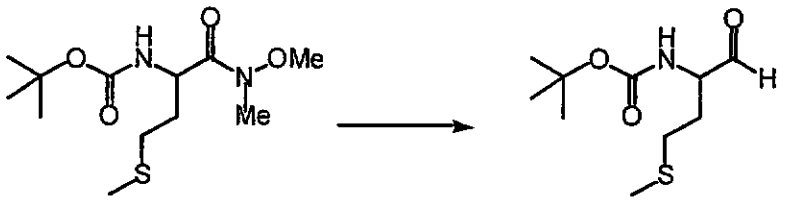
Step A



46a 46b

To a solution of **46a** (10.0 g, 42.9 mmol) in dichloromethane (100 mL) was added BOP (22.75 g, 51.5 mmol) and stirred at room temperature for 10 minutes. N,O-dimethylhydroxylamine hydrochloride (4.18 g, 42.9 mmol) was then added followed by triethylamine (18.1 mL, 128.7 mmol). The reaction mixture was stirred at ambient temperature for 3 hours and then washed with 3N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude material, **46b**, was used in the following step without purification.

Step B

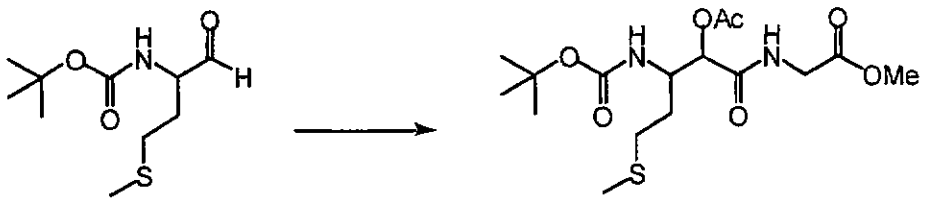


46b 46c

To a cold (0°C) solution of **46b** in THF (60 mL) was added a solution of LAH (1M in THF, 50 mL, 50 mmol) under nitrogen atmosphere. Reaction was kept at that temperature for 30 min. The reaction mixture was quenched (slow addition) with aqueous 10% potassium hydrogen phosphate solution (30 mL). The mixture was extracted with EtOAc twice. The combined organic layer was washed with 3N HCl, saturated $NaHCO_3$, and brine. Dried the EtOAc layer over sodium sulfate and concentrated. The residue was purified

by flash column chromatography using 10/90 to 30/70 EtOAc/dichloromethane to provide 4.2 g of **46c** (45% yield - for 2 steps). HRMS (FAB) Calcd for $C_{10}H_{20}NO_3S$: 234.1164 $(M+H)^+$. Found: 234.1168.

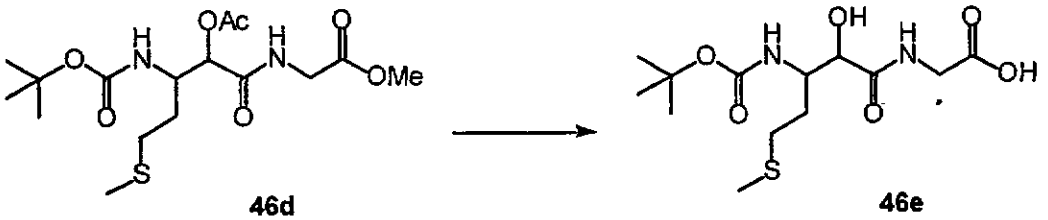
Step C



46c **46d**

To a cold (-15°C) solution of **46c** (4.2 g, 19.4 mmol) in dichloromethane was added acetic acid (2.14 mL, 38.8 mmol) followed by methyl isocyanoacetate (1.76 mL, 19.4 mmol). The reaction mixture was warmed to room temperature and let stand for 16 hrs. Diluted the reaction with EtOAc and washed with saturated $NaHCO_3$, brine and water. The organic layer was dried ($Na2SO_4$) and concentrated. Purification by flash column chromatography using 30/70 EtOAc/dichloromethane afforded pure **46d** (6.5 g) as a white solid in 92% yield. HRMS (FAB) Calcd for $C_{16}H_{29}N_2O_7S$: 393.1695 $(M+H)^+$. Found: 393.1692.

Step D

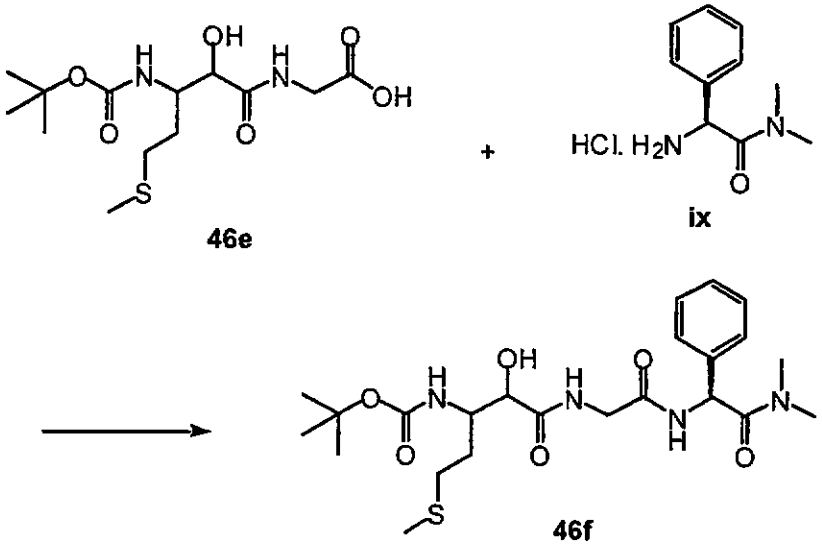


46d **46e**

To a solution of **46d** (6.5 g, 16.6 mmol) in MeOH (30 mL) was added a solution of lithium hydroxide (1.19 g, 50 mmol) in water (30 mL). After 45 minutes the reaction mixture was concentrated. Aqueous citric acid solution was added till acidic pH (3) and the product was extracted into EtOAc.

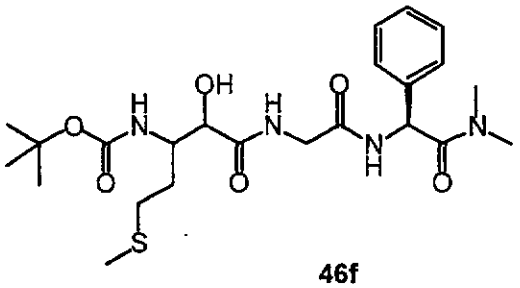
Concentration of the organic layer resulted in the acid **46e** (5.6 g, 90% yield). HRMS (FAB) Calcd for $C_{13}H_{25}N_2O_6S$: 337.1433 $(M+H)^+$. Found: 337.1430.

Step E

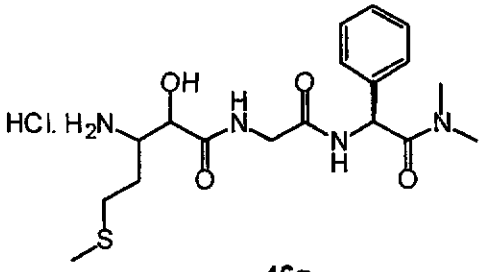


The desired product **46f** was obtained by the method described for Intermediate A, Step 3. Purification of the residue by column chromatography using 20/0/80 to 50/5/45 of EtOAc/NH_3 in MeOH/dichloromethane afforded 3.0 g of **46f** (51%). HRMS (FAB) Calcd for $C_{23}H_{37}N_4O_6S$: 497.2434 $(M+H)^+$. Found: 497.2439.

Step F



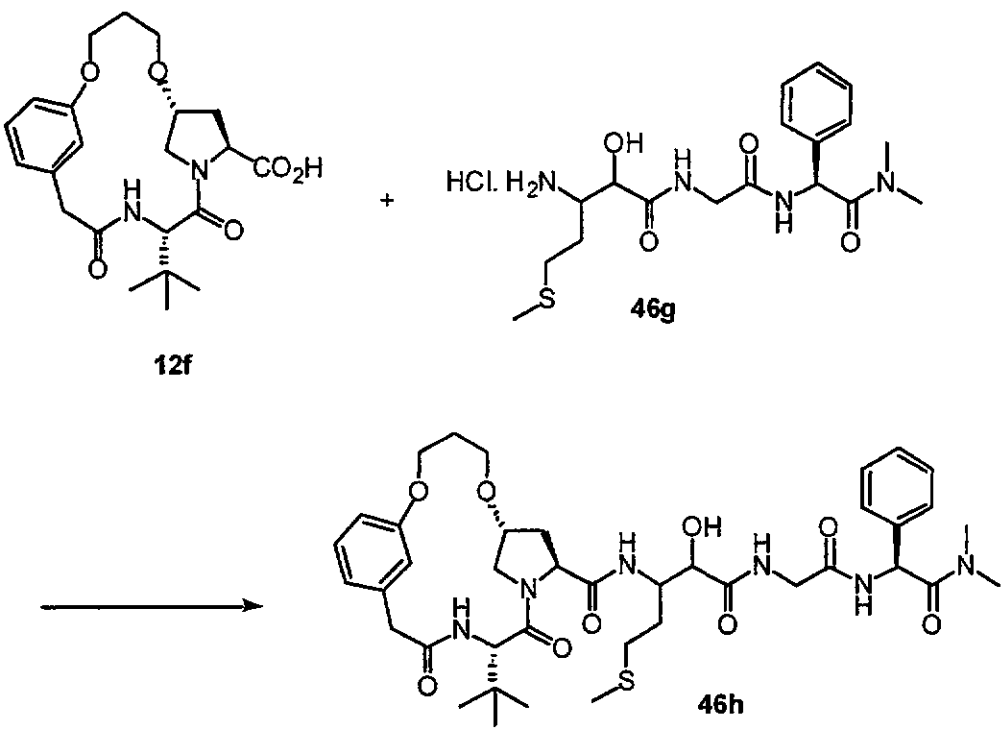
46f



46g

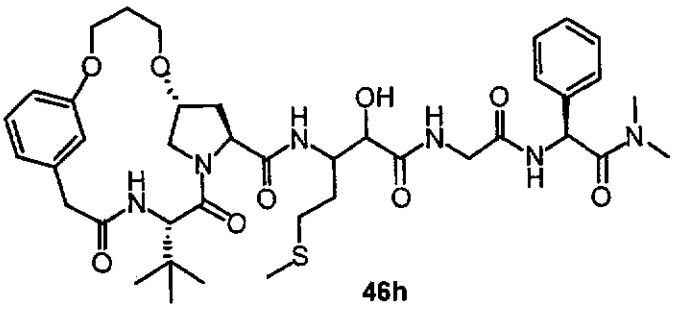
The desired compound **46g** was prepared by the protocol described for Intermediate A, Step 4. The material was carried forward for further studies.

Step G

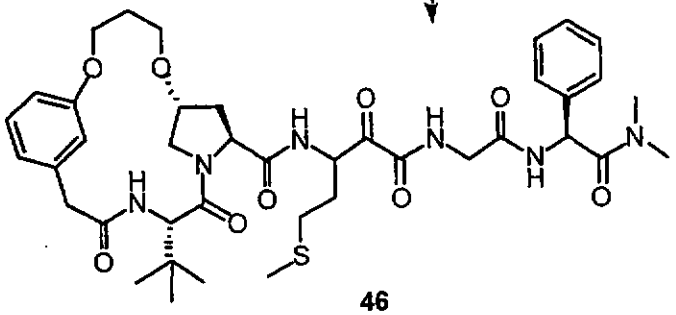


The desired product **46h** was obtained by the procedure described for Example 1, Step J. The crude material was sufficiently pure for further manipulations. HRMS (FAB) Calcd for $C_{40}H_{57}N_6O_9S$: 797.3908 $(M+H)^+$. Found: 797.3896.

Step H



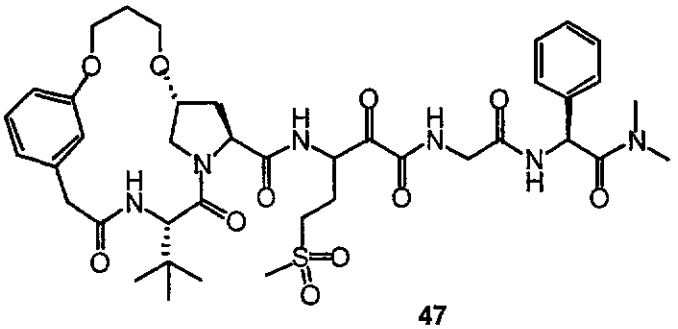
46h



46

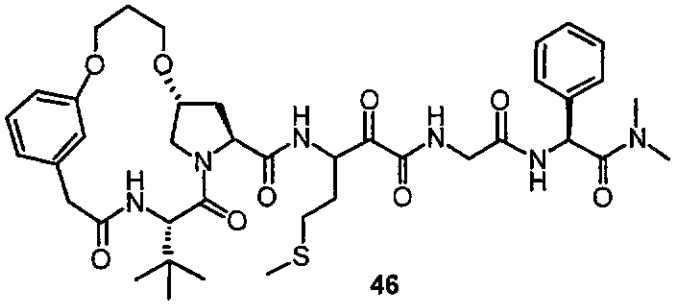
The desired product **46** was obtained by the oxidation protocol described previously for Example 10, Step J. The reaction took 4 days to go to completion. Purification of the residue by flash column chromatography (twice) and preparative TLC using 98/2 dichloromethane/MeOH afforded **46** as a mixture of diastereomers in 12% yield (for 2 steps). HRMS (FAB) Calcd for $C_{40}H_{55}N_6O_9S$: 795.3751 $(M+H)^+$. Found: 795.3761.

Example 47: Preparation of Compound 47:

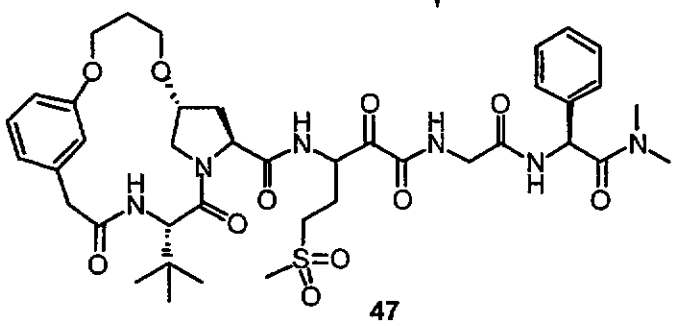


47

Step A



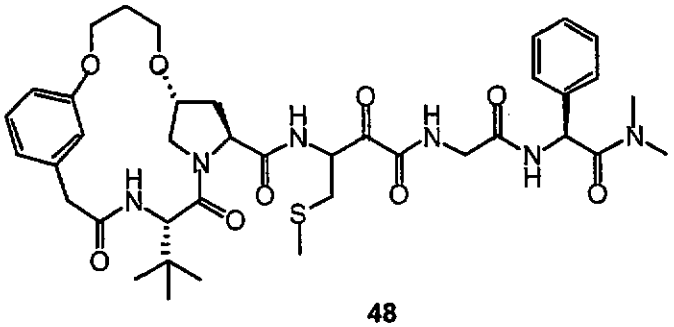
46



47

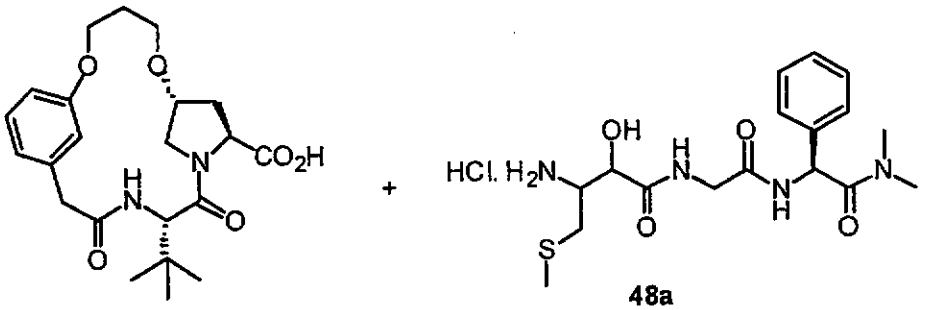
The desired product **47** is obtained by the oxidation protocol described previously for Example 11 Step A.

Example 48: Preparation of Compound 48:

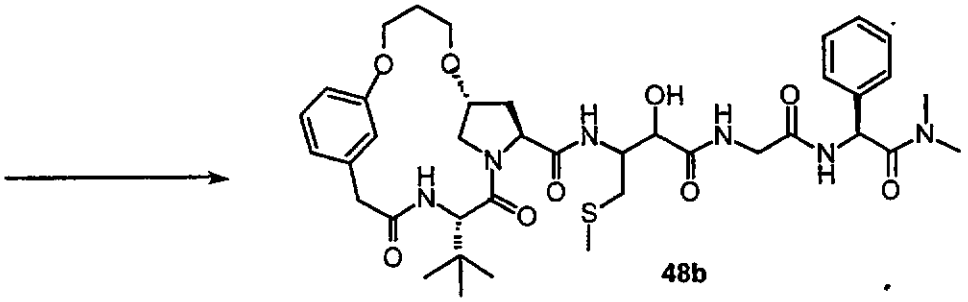


48

Step A



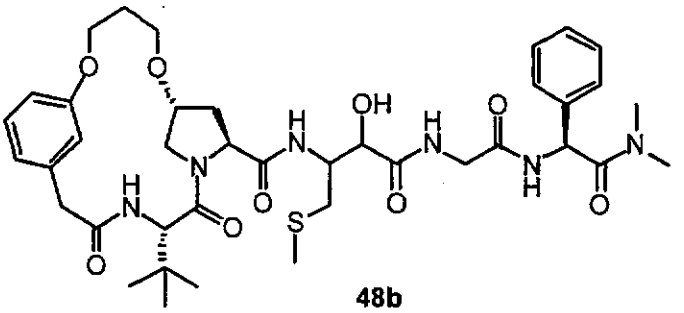
12f **48a**



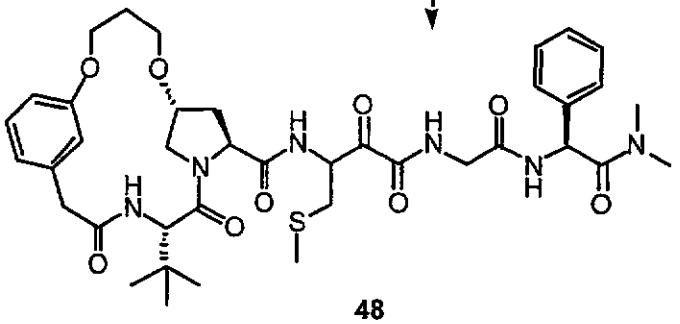
48b

The desired product **48b** was obtained by the procedure described for Example 1 Step J. The crude material was sufficiently pure for further manipulations. (Note: The precursor **48a** was obtained from commercially available *Nboc-S*-methylcysteine by similar procedures described for **46g**)

Step B



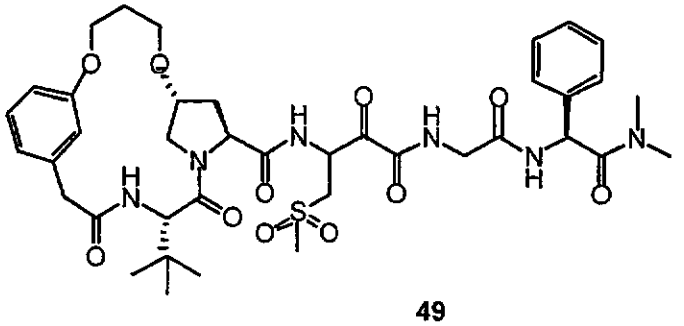
48b



48

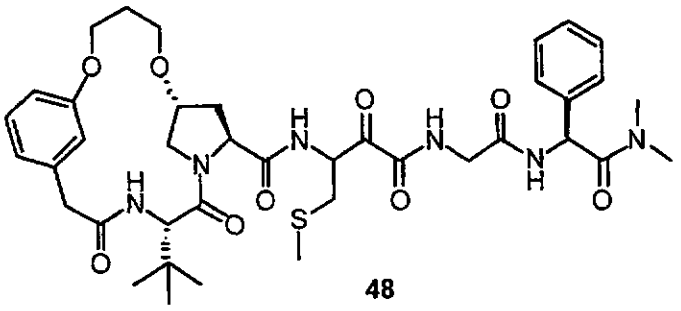
The desired product **48** was obtained by the oxidation protocol described previously for Example 10 Step J. Purification by flash column chromatography using 98/2 dichloromethane/MeOH afforded **48** as a mixture of diastereomers in 21% yield (for 2 steps).

Example 49: Preparation of Compound 49:

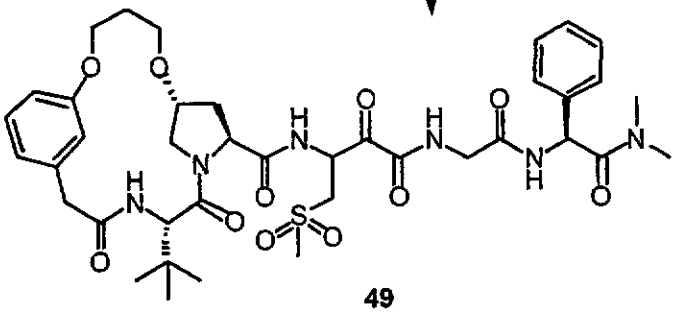


49

Step A



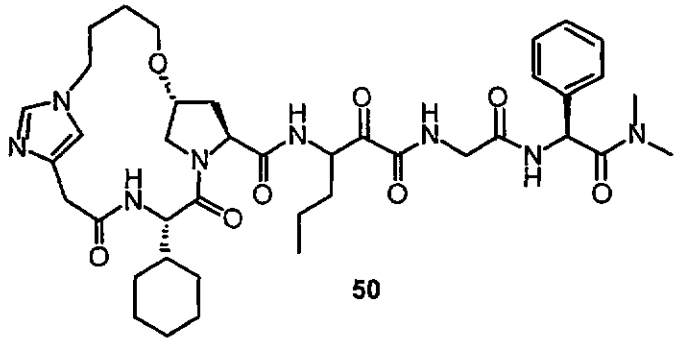
48



49

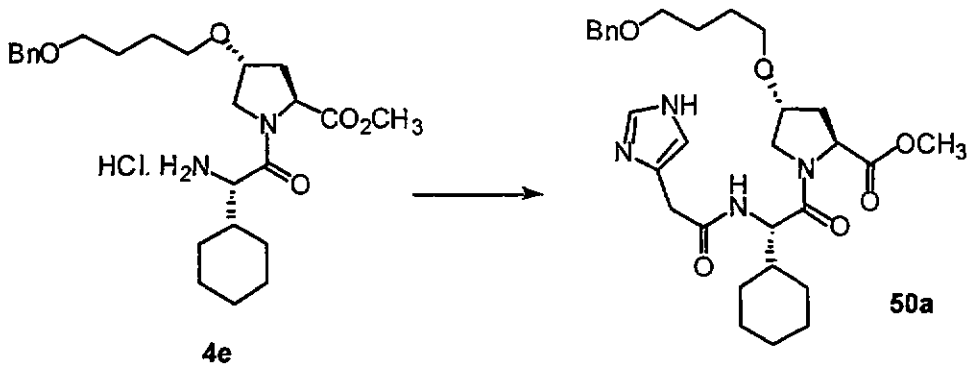
The desired product **49** is obtained by the oxidation protocol described previously for Example 11 Step A.

Example 50: Preparation of Compound 50:



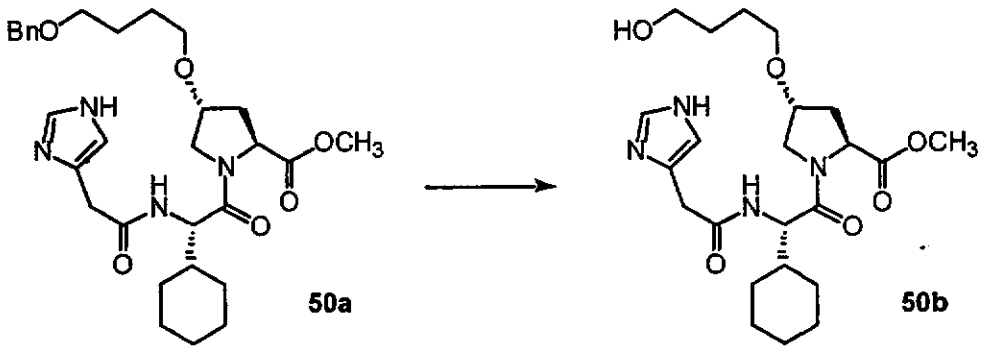
50

Step A



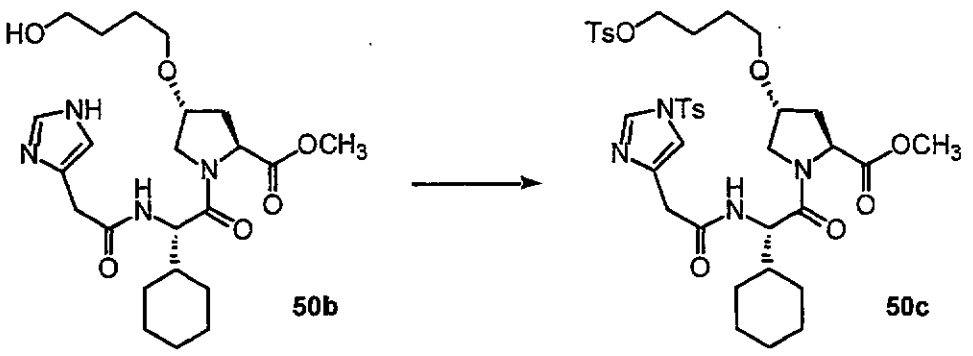
The desired product **50a** is obtained by the method described for Example 1 Step F, using imidazole-4-acetic acid as the coupling partner.

Step B



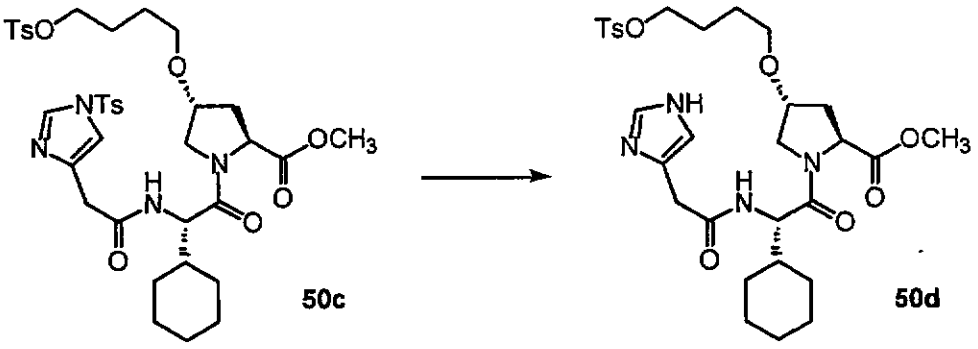
The desired product **50b** is obtained by the method described for Example 1 Step G.

Step C



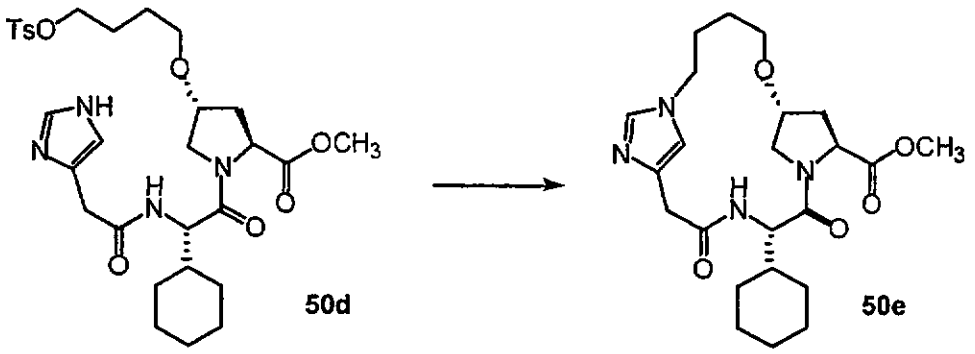
The desired product **50c** is obtained by the method described for Example 10 Step A using *p*-toluenesulfonyl chloride as the starting material.

Step D



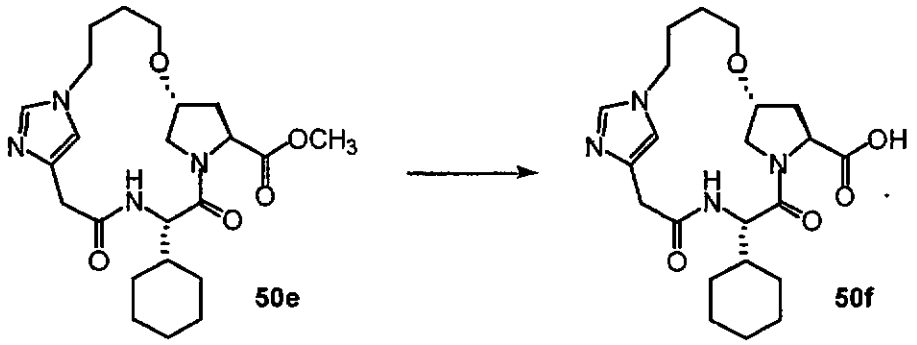
The desired product **50d** is obtained by the treating **50c** with HOBt in THF at ambient temperature over several hrs.

Step E



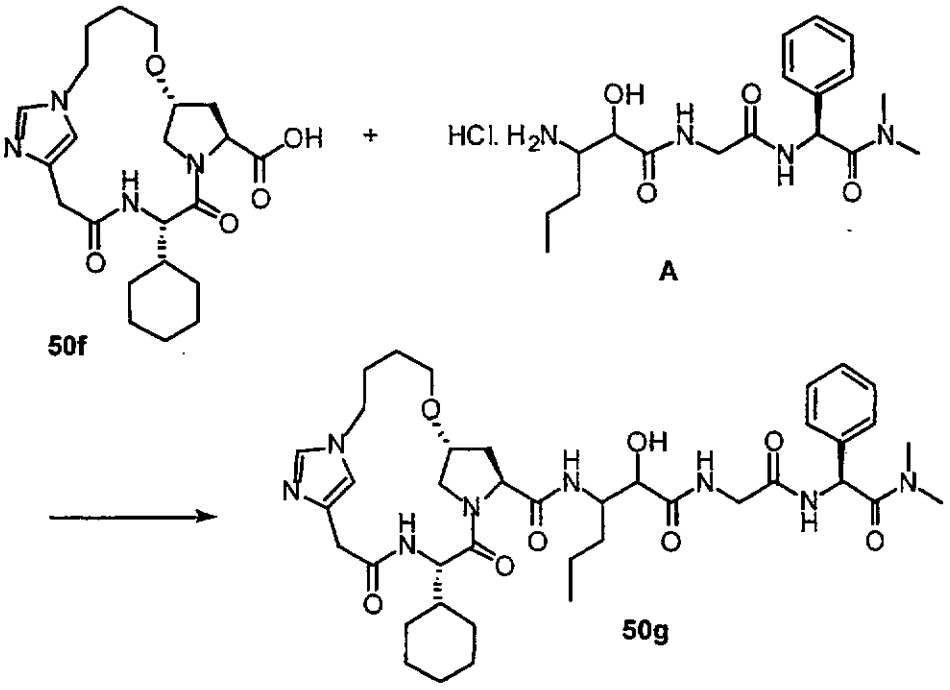
The expected product **50e** is synthesized by heating of **50d** with sodium carbonate, and sodium iodide in acetone at 50°C over several hrs. The product can be purified by conventional flash chromatography.

Step F



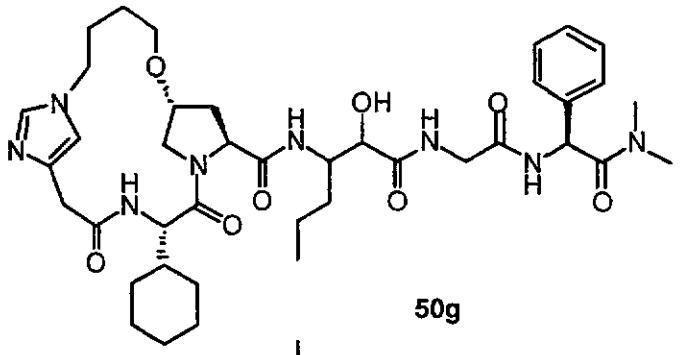
The desired products **50f** is obtained by the hydrolysis protocol described previously for Example 1 Step I.

Step G

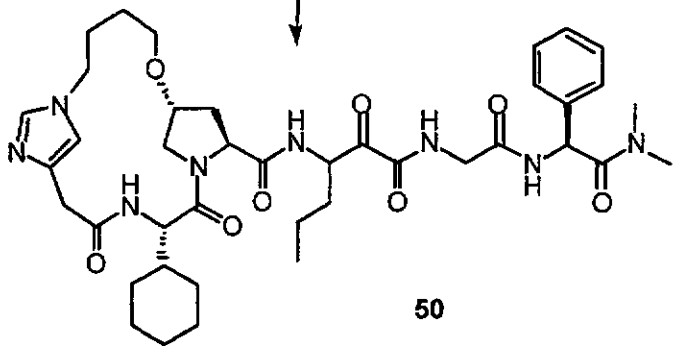


The expected product **50g** is synthesized as described earlier for Example 1 Step J.

Step M



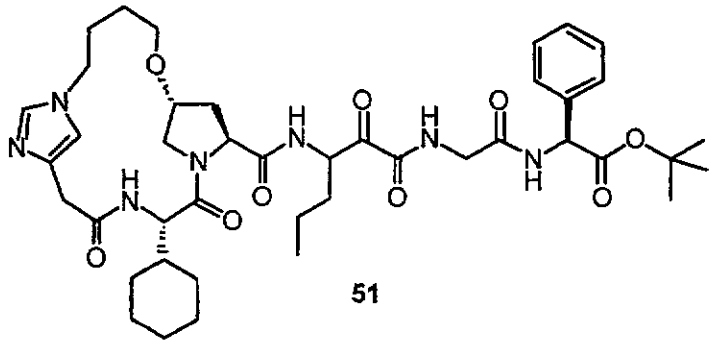
50g



50

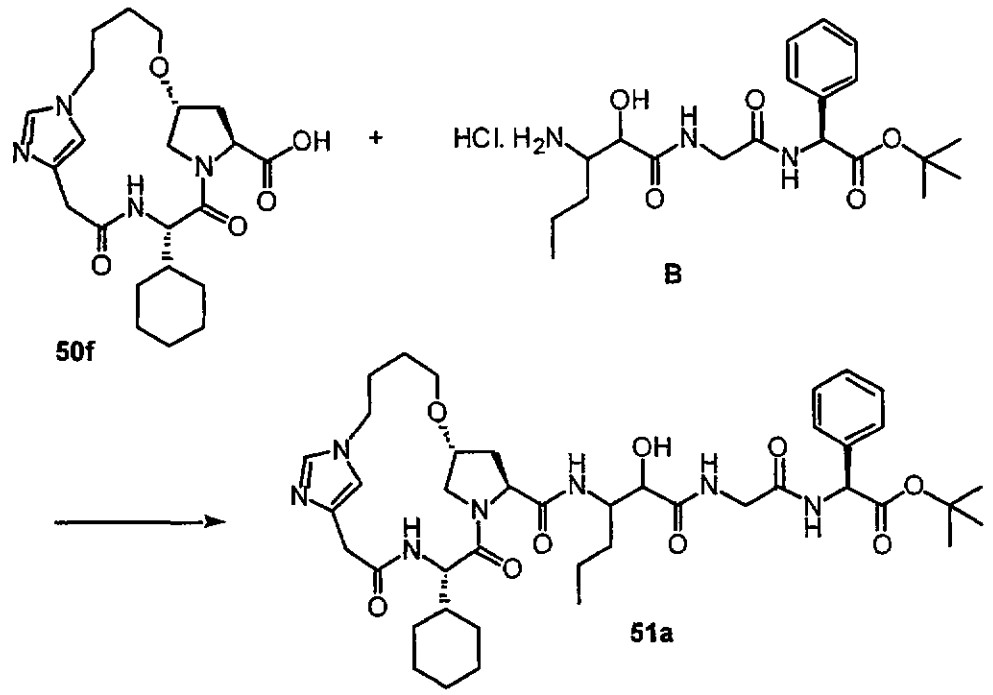
The desired product **50** is obtained by the oxidation protocol described previously for Example 1 Step K. Purification by flash column chromatography will afford pure **50**.

Example 51: Preparation of Compound 51:



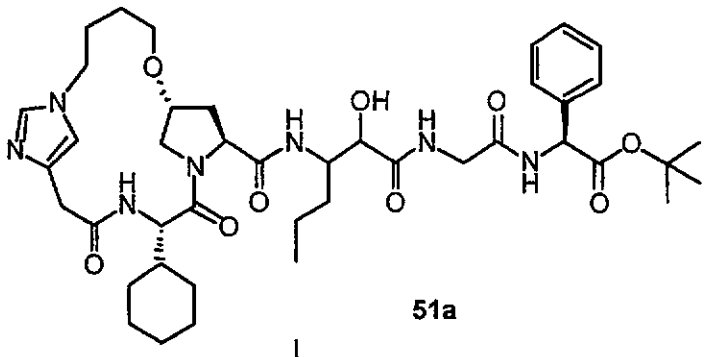
51

Step A

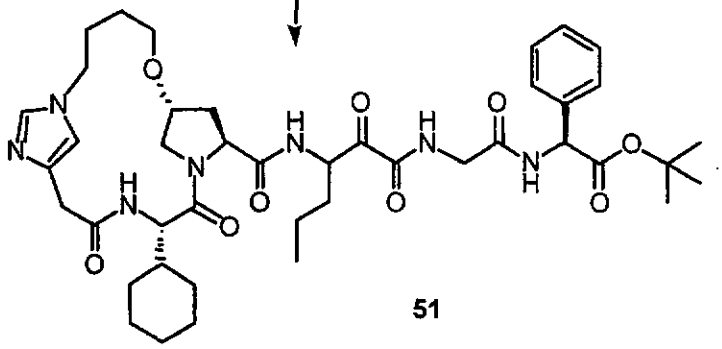


The expected product **51a** is synthesized as described earlier for Example 2 Step A.

Step B



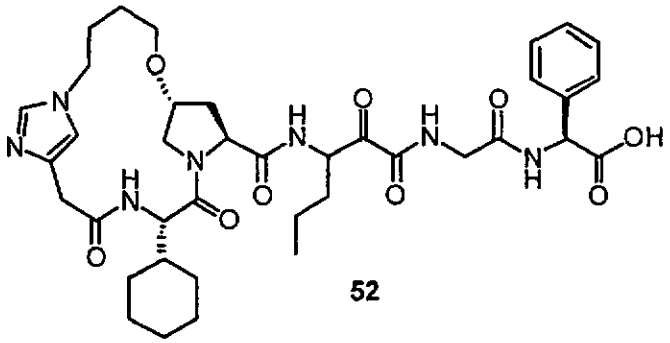
51a



51

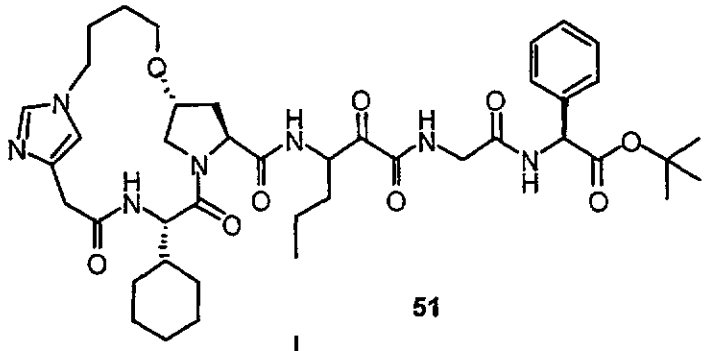
The desired product **51** is obtained by the oxidation protocol described previously for Example 2 Step B. Purification by flash column chromatography will afford pure **51**.

Example 52: Preparation of Compound 52:

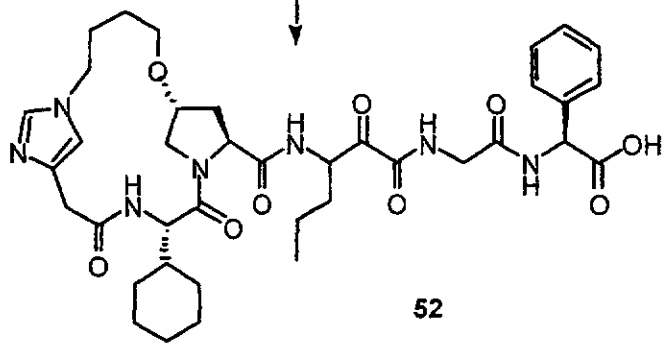


52

Step A



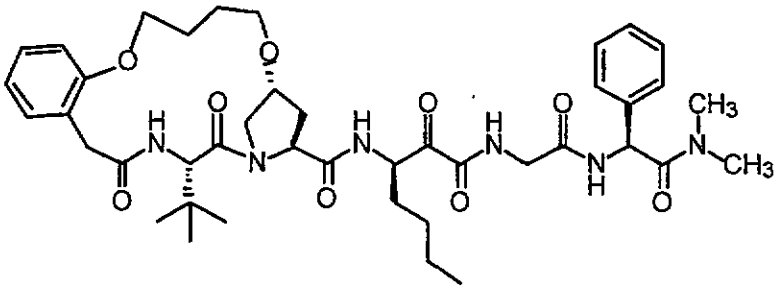
51



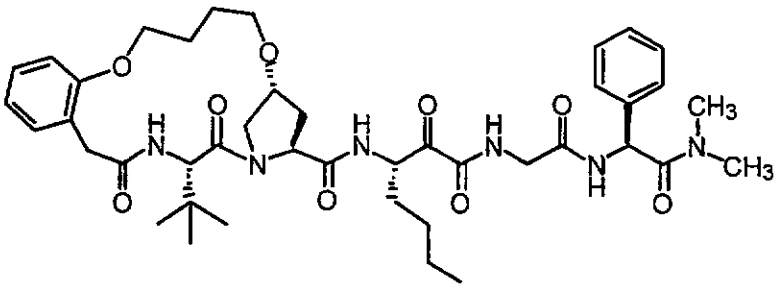
52

The desired product **52** is obtained by the procedure described previously for Example 3, Step A.

Example 53: Preparation of Compounds of Formulas 53A and 53B:

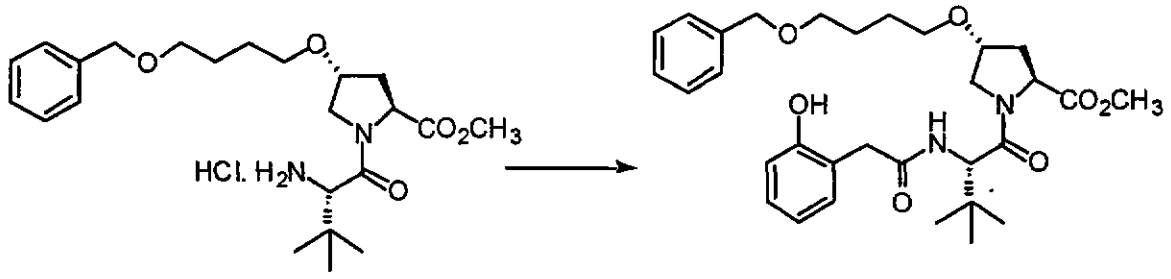


53A



53B

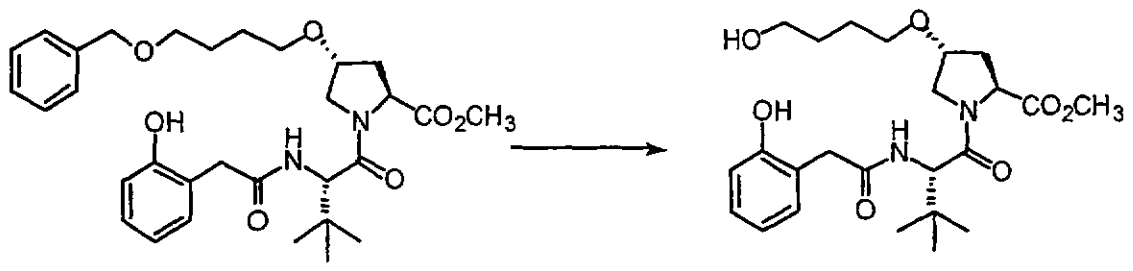
Step A:



44b **53a**

The desired product **53a** was obtained by the method described in Example 1, Step F. The material was purified by flash column chromatography using 80/20 to 60/40 dichloromethane/ethyl acetate to provide **53a**.

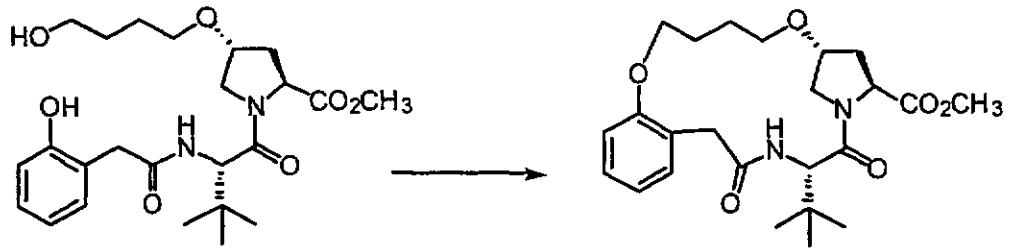
Step B:



53a 53b

The desired product **53b** was obtained by the method described in Example 1, Step G. The crude material was carried to the next step as is.

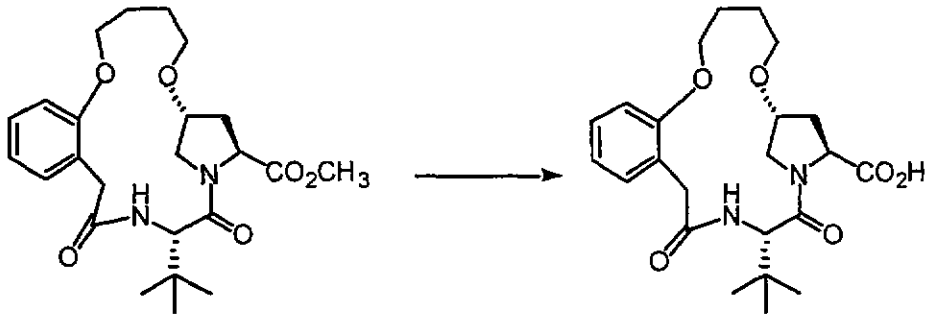
Step C:



53b 53c

The desired product **53c** was obtained by the method described in Example 1, Step H. Purification by column chromatography using 99/1 dichloromethane/methanol afforded **53c** along with triphenylphosphine oxide. This mixture was taken to the next step.

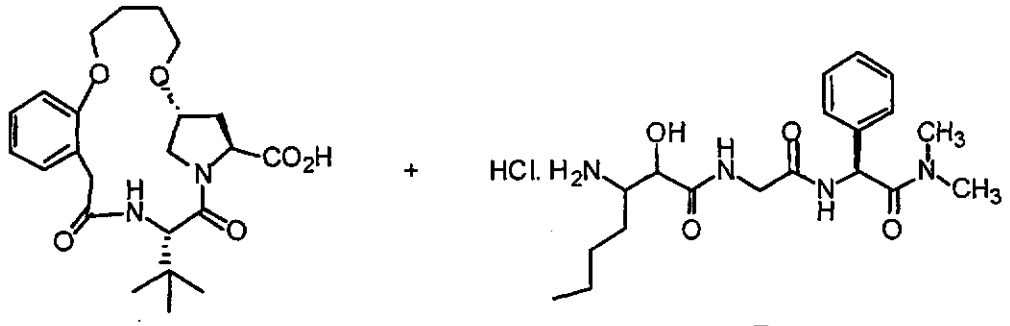
Step D:



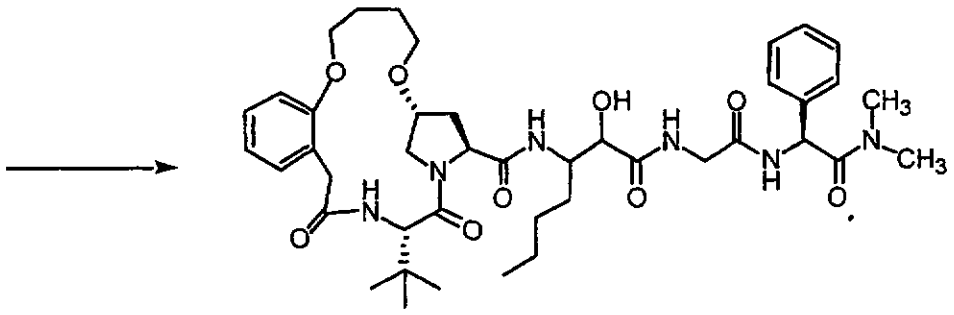
53c 53d

The desired product was obtained by the method described in Example 1, Step I.

Step E:



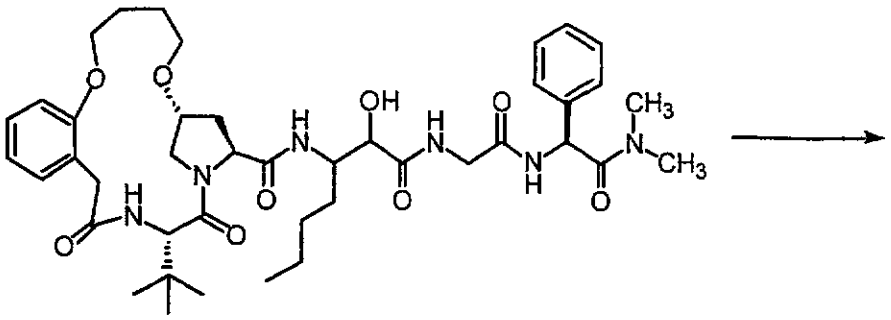
53d E



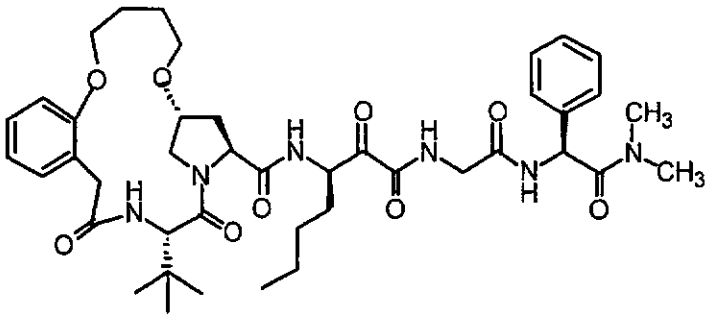
53e

The expected product **53e** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step.

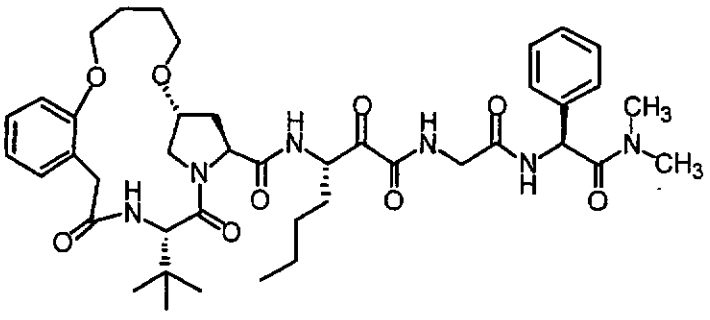
Step F:



53e



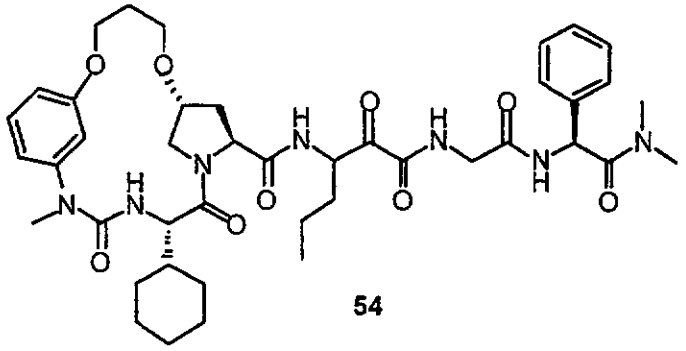
53A



53B

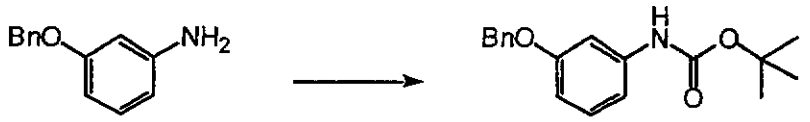
The desired products **53A** and **53B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 100/0 to 99/1 dichloromethane/methanol afforded separate isomers **53A** and **53B**, and some mixture.

Example 54: Preparation of Compound 54:



54

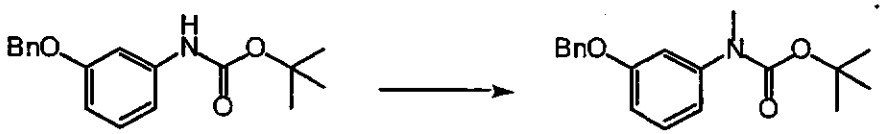
Step A



54a 54b

Commercially available **54a** was converted to the desired product **54b** using the procedure described for Intermediate A Step 3 in quantitative yield.

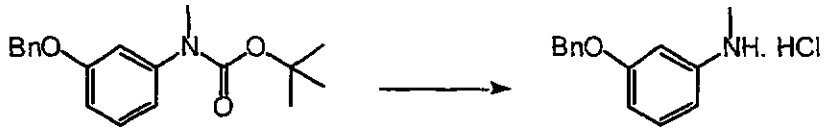
Step B



54b 54c

To a cold (0°C) solution of **54b** (8 g, 26.8 mmol) in DMF (100 mL) was added sodium hydride (60% dispersion in oil, 1.3 g, 32.16 mmol). After 10 minutes iodomethane (2.8 mL, 42.8 mmol) was added and the reaction was warmed to ambient temperature over 2 hrs. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated to afford **54c** which was sufficiently pure for further studies.

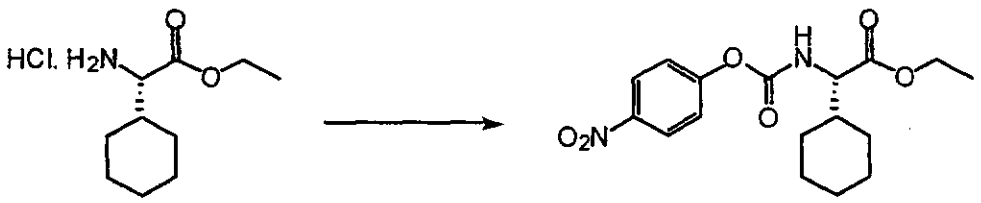
Step C



54c 54d

The desired product **54d** was obtained by the procedure described for Example 1 Step C. The crude product was used without further purification.

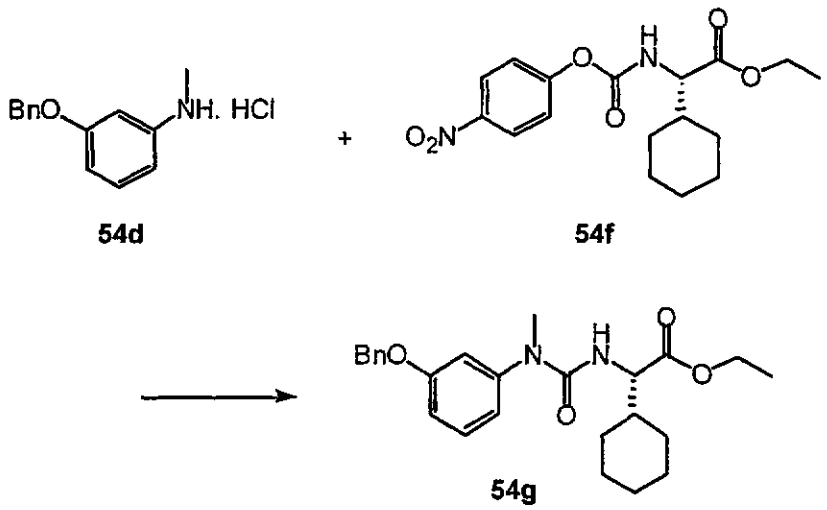
Step D



54e 54f

The desired product **54f** was obtained by the procedure described for Example 26 Step A using **54e** as the starting material. The crude product was purified by flash chromatography using 80/20 to 100/0 dichloromethane/hexanes to afford **54f**.

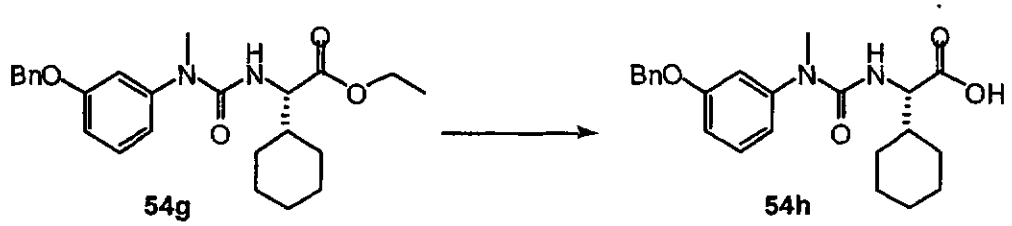
Step E



54d 54f 54g

The desired product **54g** was obtained by the procedure described for Example 26 Step B using **54d** and **54f** as the starting materials. The reaction was carried out in chloroform at 50°C. The residue was purified by flash chromatography using 85/15 hexanes/EtOAc to provide **54g** in 56% yield. HRMS (FAB) Calcd for $C_{25}H_{33}N_2O_4$: 425.2440 $(M+H)^+$. Found: 425.2424.

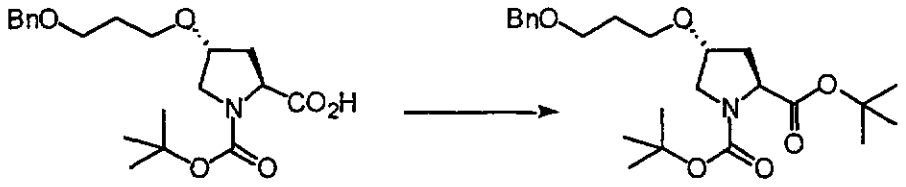
Step F



54g 54h

The desired compound **54h** was obtained by the procedure described earlier for Example 1 Step I using EtOH as the solvent.

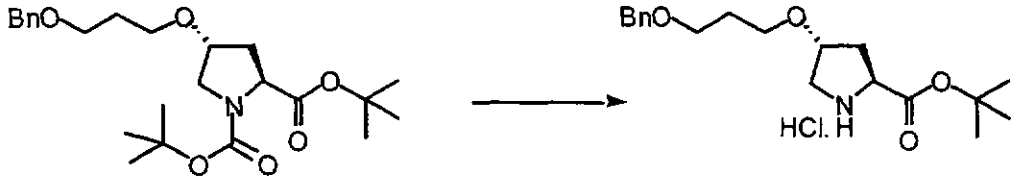
Step G



1b 54i

The desired compound **54i** was prepared by the protocol described for Example 18 Step B.

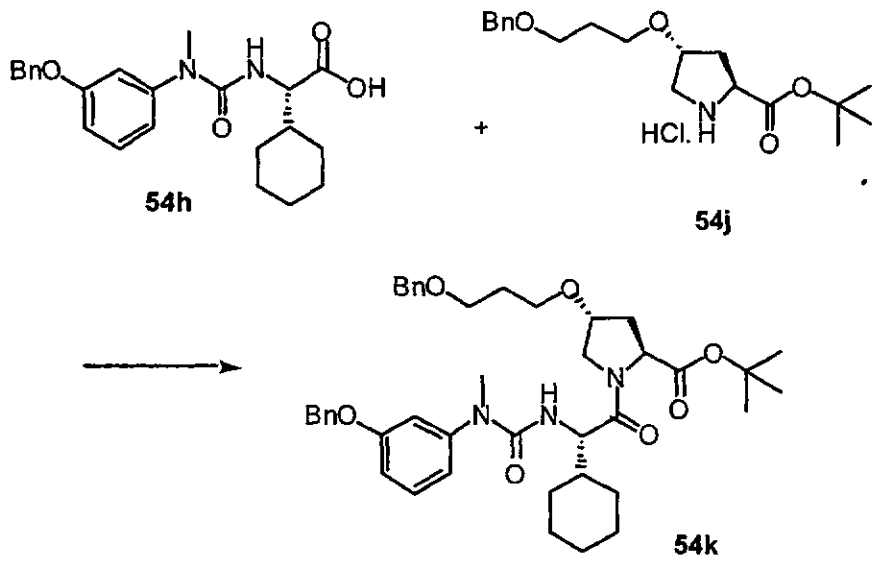
Step H



54i 54j

The desired product **54j** was obtained by the procedure described for Example 1 Step C. The crude material was used without purification.

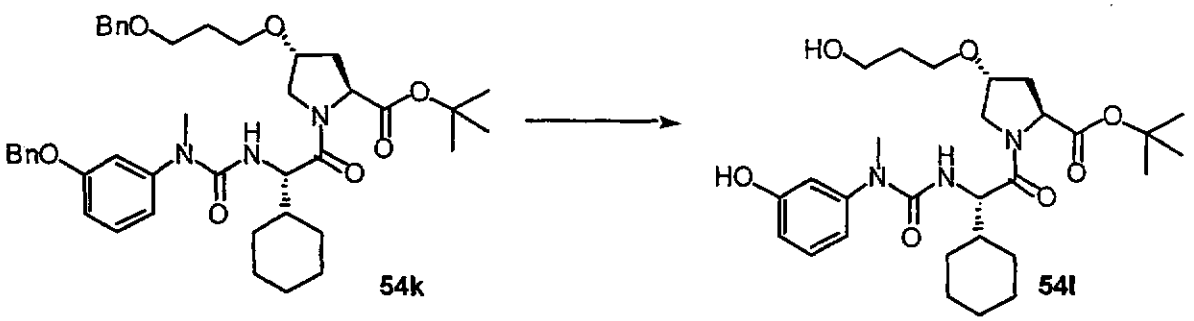
Step I



54h 54j 54k

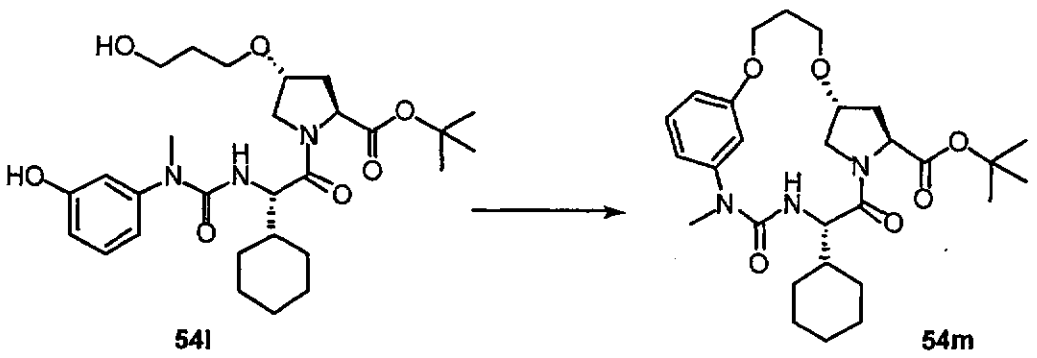
The desired product **54k** was obtained by the coupling protocol described previously for Example 1 Step D.

Step J



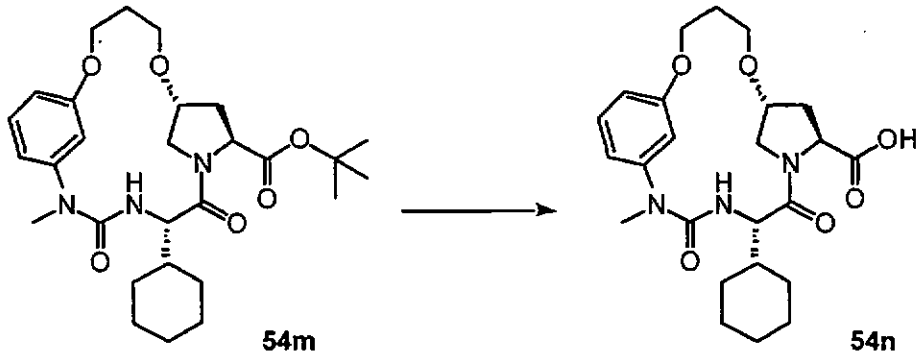
The desired product **54l** is obtained by the hydrogenation procedure described previously for Example 1 Step G.

Step K



The desired product **54m** is obtained by the cyclization protocol described for Example 1 Step H.

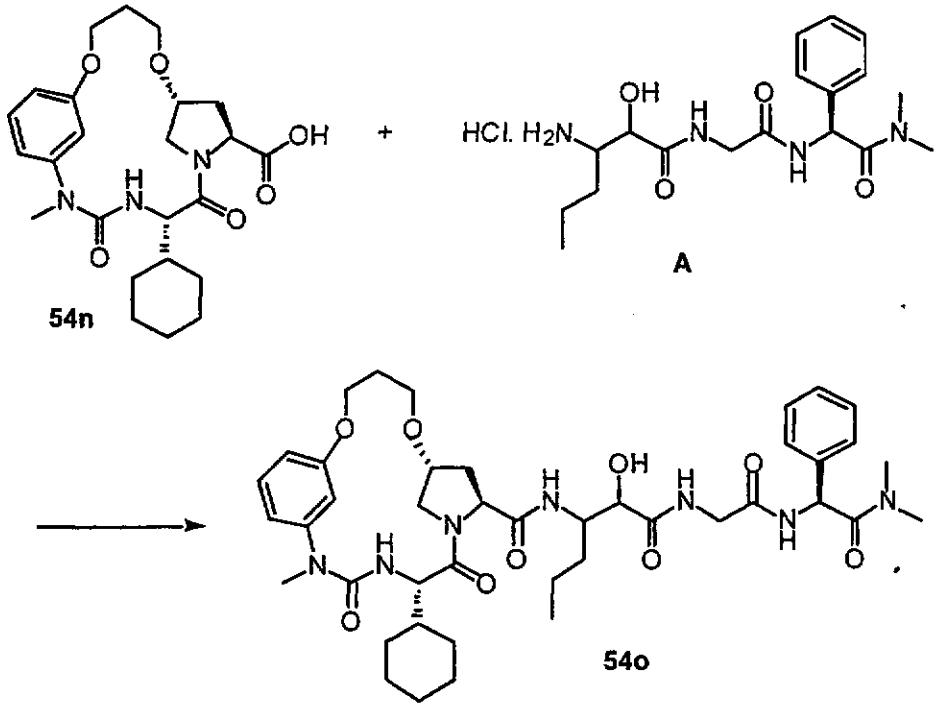
Step L



54m 54n

The desired product **54n** is obtained by the producer described previously for Example 3 Step A.

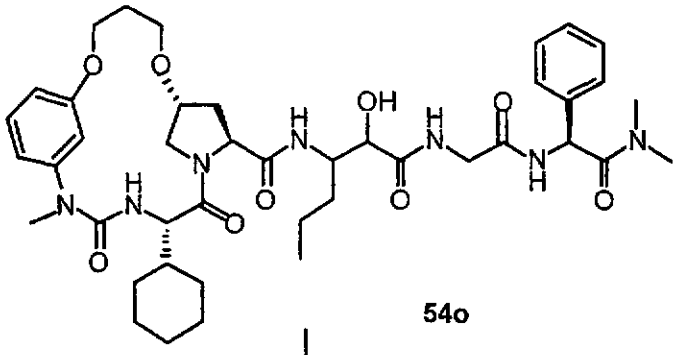
Step M



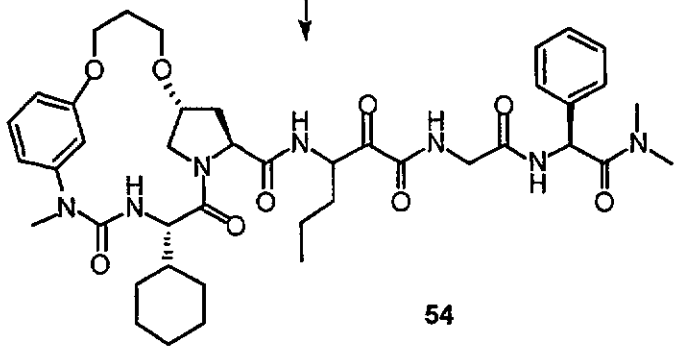
54n A 54o

The expected product **54o** is synthesized as described earlier for Example 1 Step J.

Step N



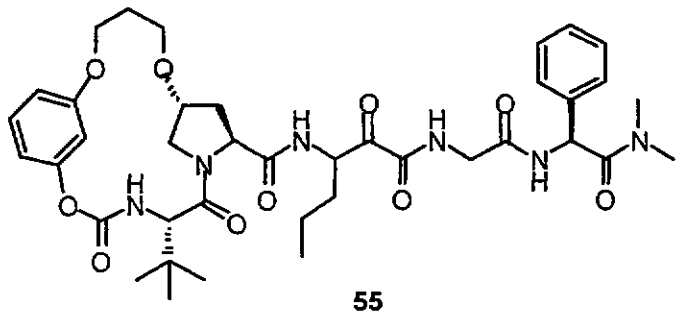
54o



54

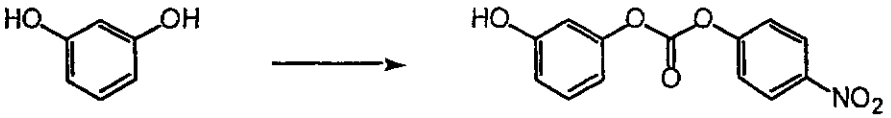
The desired product **54** is obtained by the oxidation protocol described previously for Example 1 Step K. Purification by flash column chromatography will afford pure **54**.

Example 55: Preparation of Compound 55:



55

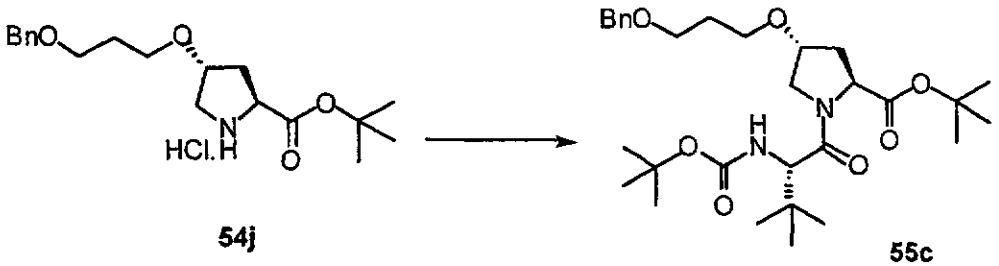
Step A



55a 55b

Commercially available **55a** was converted to the desired product **55b** using the procedure described for Example 26 Step A in 41% yield.

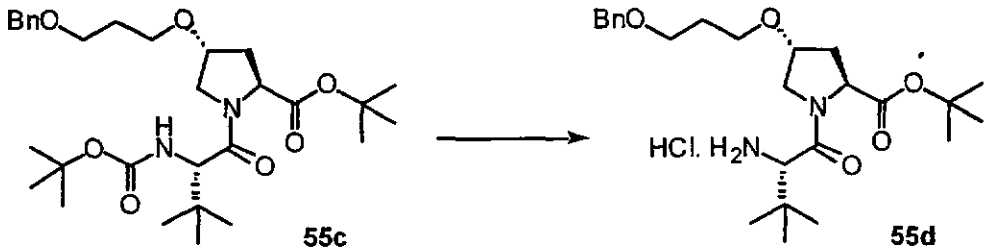
Step B



54j 55c

The desired product **55c** was obtained by the coupling protocol described previously for Example 1 Step D using N-boc-t-butylglycine as the coupling partner. Purification using 95/5 dichloromethane/EtOAc afforded **55c** in 57% yield.

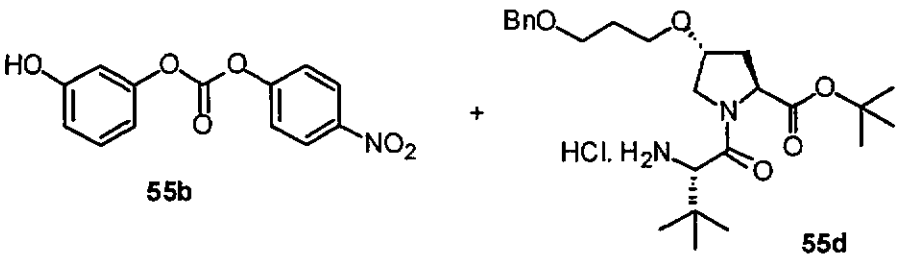
Step C



55c 55d

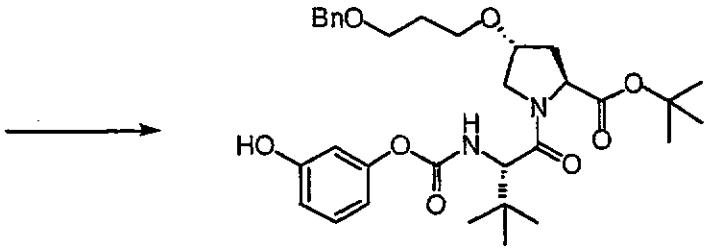
The desired product **55d** was obtained by the procedure described previously for Example 1 Step C. The crude material was carried further.

Step D



55b

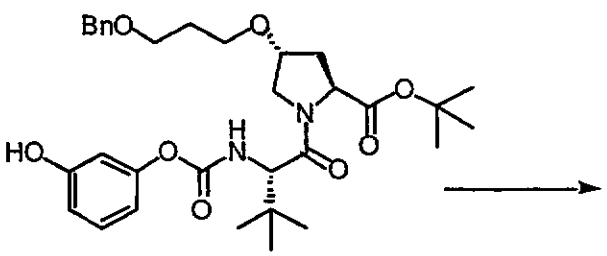
55d



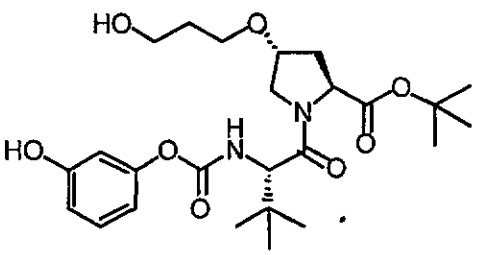
55e

The desired product **55e** was obtained by the protocol described for Example 26 Step B. Purification using 80/20 dichloromethane/EtOAc afforded **55e** in 20% yield. HRMS (FAB) Calcd for $C_{32}H_{45}N_2O_8$: 585.3176 $(M+H)^+$. Found: 585.3177.

Step E



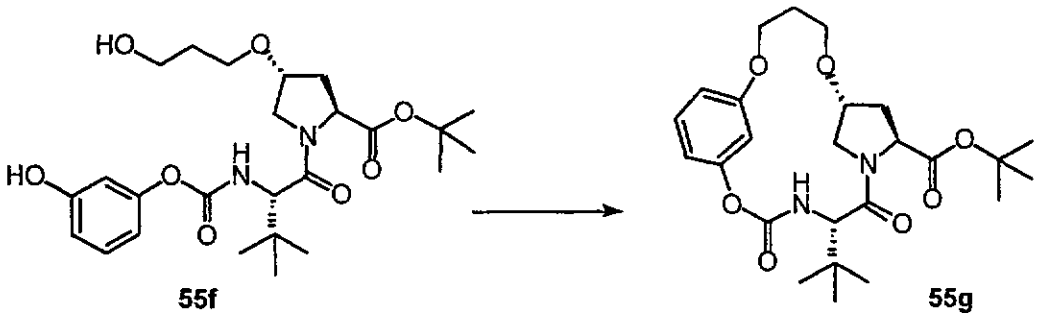
55e



55f

The desired product **55f** was obtained by the producer described previously for Example 1 Step G. HRMS (FAB) Calcd for $C_{25}H_{39}N_2O_8$: 495.2706 $(M+H)^+$. Found: 495.2704.

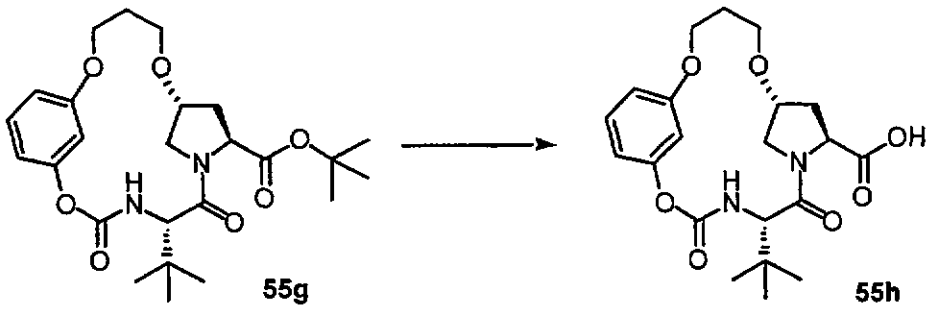
Step F



55f 55g

The expected product **55g** was synthesized as described earlier for Example 1 Step H. Purification by flash chromatography using 85/15 dichloromethane/EtOAc provided **55g** in 10% yield.

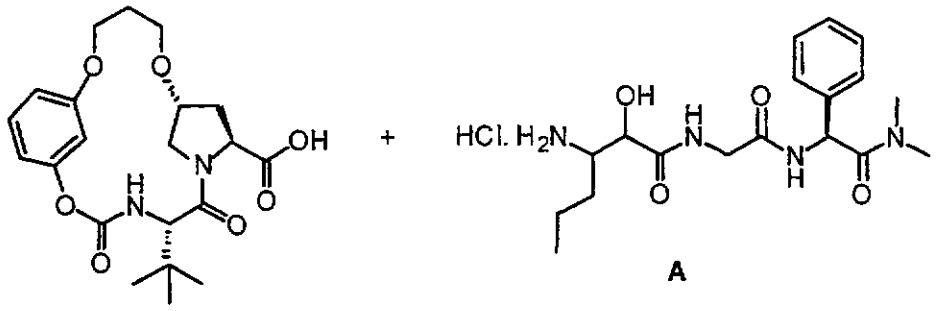
Step G



55g 55h

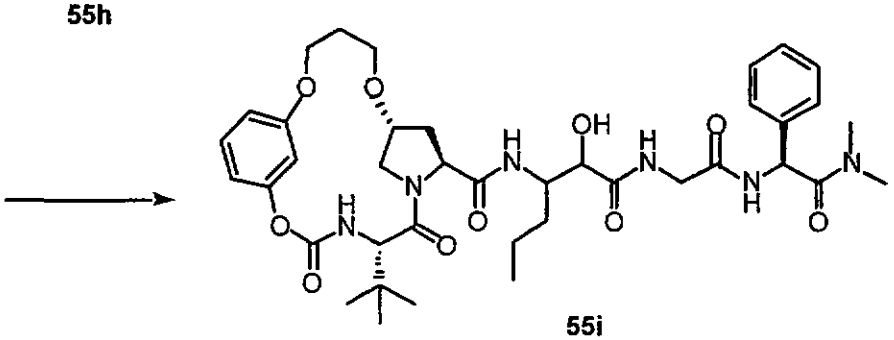
The desired product **55h** was obtained by the method described previously for Example 3 Step A. The crude material was carried further without purification.

Step H



55h

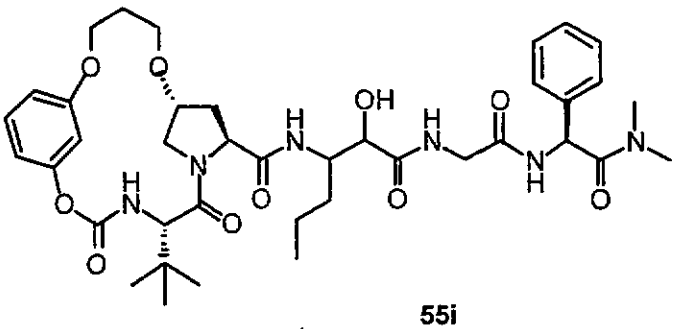
A



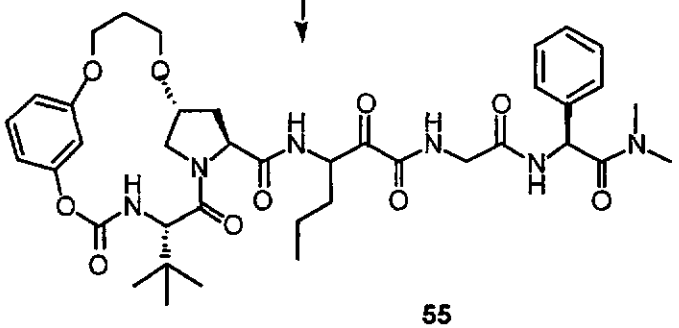
55i

The expected product **55i** was synthesized as described earlier for Example 1 Step J. The crude material was carried further without purification.

Step I



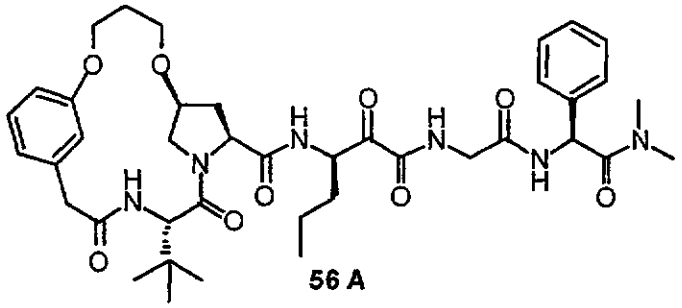
55i



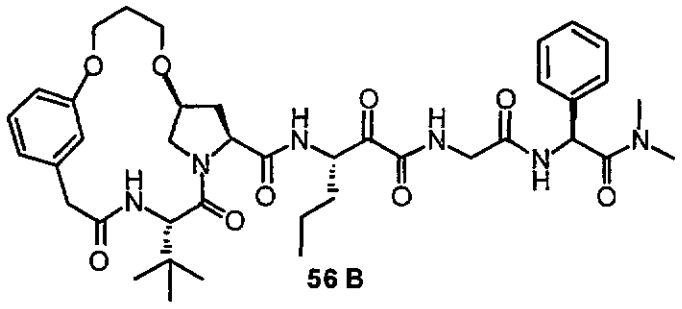
55

The desired product **55** was obtained by the oxidation protocol described previously for Example 1 Step K. Purification by flash column chromatography using 98/2 dichloromethane/MeOH afforded **55**.

Example 56: Preparation of Compound 56:

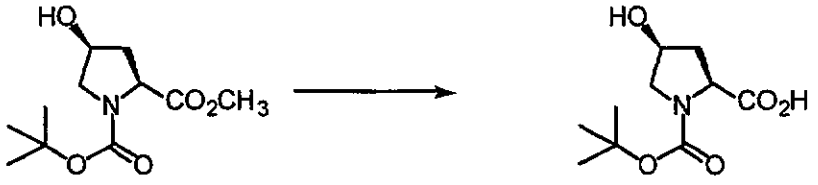


56 A



56 B

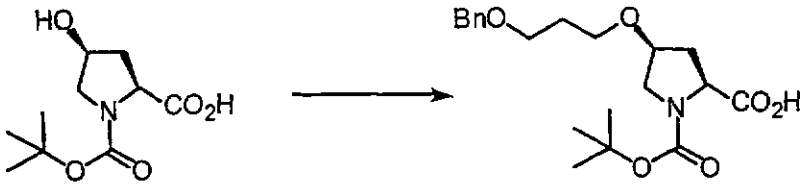
Step A



10a 56a

To a solution of commercially available methyl ester **10a** (5.0 g, 20.4 mmol) in MeOH (20 mL) was added a solution of LiOH (730 mg, 30.6 mmol) in water (20 mL). The reaction mixture was stirred at ambient temperature for 2 hrs. TLC indicated consumption of starting material. The reaction mixture was concentrated and acidified with 10% citric acid solution. Solid NaCl was added and the aqueous layer was extracted with EtOAc several times. The combined EtOAc layer was dried (Na_2SO_4) and concentrated to provide **56a** in quantitative yield. HRMS (FAB) Calcd for $C_{10}H_{18}N_1O_5$: 232.1185 $(M+H)^+$. Found: 232.1189.]

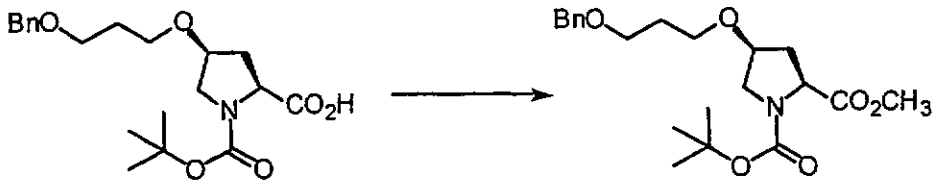
Step B



56a 56b

The desired product **56b** was obtained by the method described for Example 1, Step A. The crude material was converted to the methyl ester without purification.

Step C



56b 56c

The desired product **56c** was obtained by the method described for Example 1, Step B. Purification of the residue by column chromatography using 80/20 to 50/50 hexanes/EtOAc and then 70/30 to 40/60 dichloromethane/EtOAc afforded 13% of **56c**. HRMS (FAB) Calcd for $C_{21}H_{31}NO_6$: 394.2230 $(M+H)^+$. Found: 394.2224.

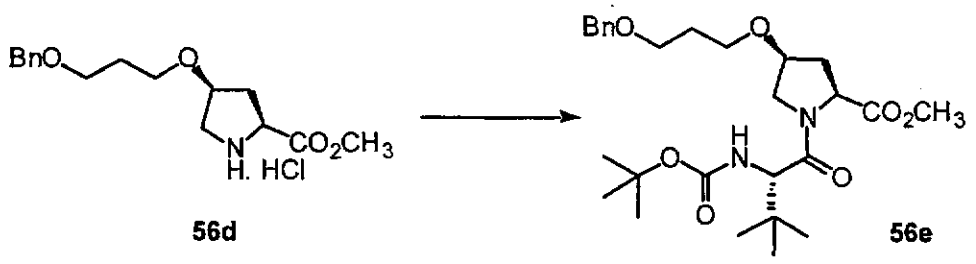
Step D



56c 56d

The desired product **56d** was obtained by the method described for Example 1, Step C. The crude material was used without purification.

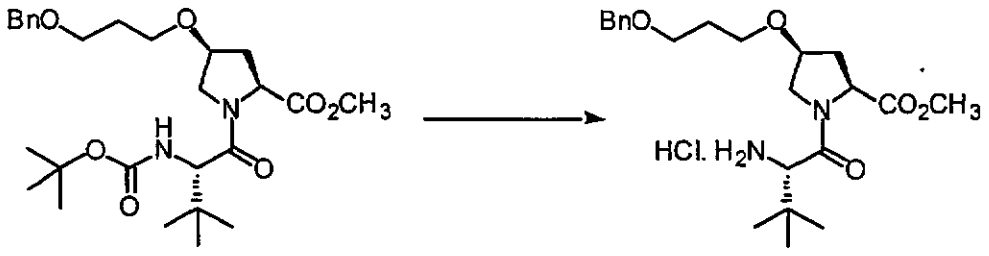
Step E



56d **56e**

The desired product **56e** was obtained by the method described for Example 1, Step D, using N-boc-tert-butyl glycine as the coupling partner. Purification of the residue by column chromatography using 90/10 dichloromethane/EtOAc afforded 86% of **56e**. HRMS (FAB) Calcd for $C_{27}H_{43}N_2O_7$: 507.3070 $(M+H)^+$. Found: 507.3072.

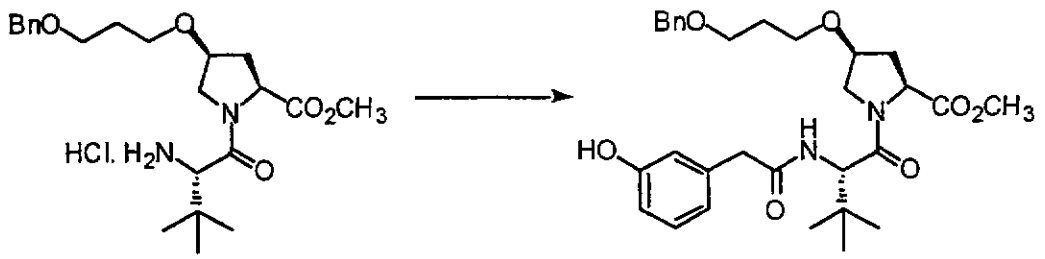
Step F



56e **56f**

The desired compound **56f** was prepared by the protocol described for Example 1, Step E. The material was carried forward as it was.

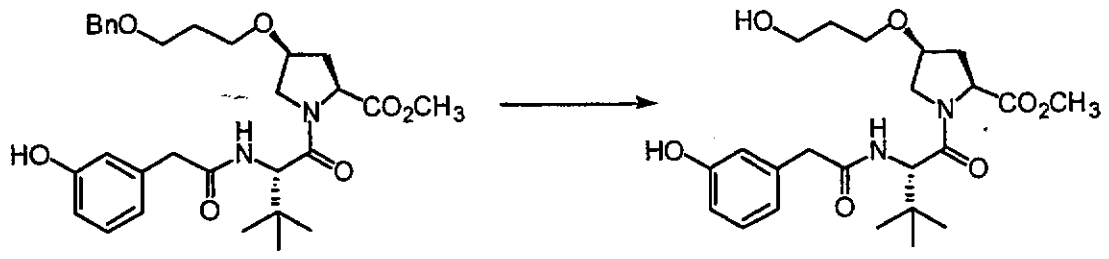
Step G



56f 56g

The desired product **56g** was obtained by the procedure described for Example 1, Step F. The material was purified by flash column chromatography using 98/2 dichloromethane/MeOH to yield **56g** in 78% as a white foam. HRMS (FAB) Calcd for $C_{30}H_{41}N_2O_7$: 541.2914 $(M+H)^+$. Found: 541.2916.

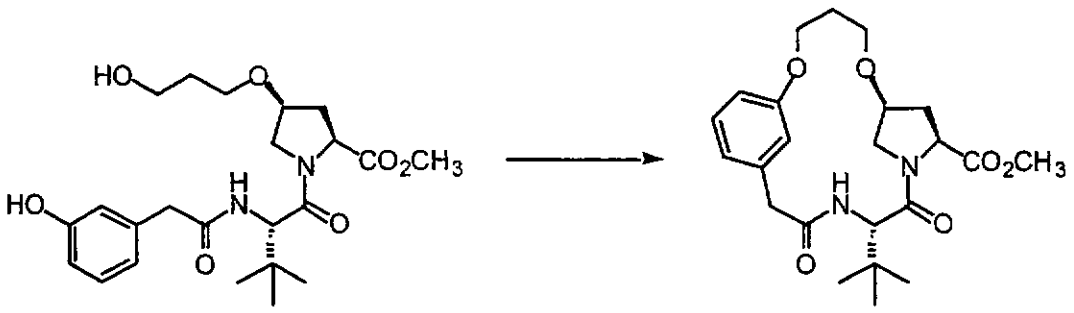
Step H



56g 56h

The desired product **56h** was obtained by the procedure described for Example 1, Step G. The product obtained after filtering off the catalyst was pure enough for subsequent manipulations. HRMS (FAB) Calcd for $C_{23}H_{35}N_2O_7$: 451.2444 $(M+H)^+$. Found: 451.2449.

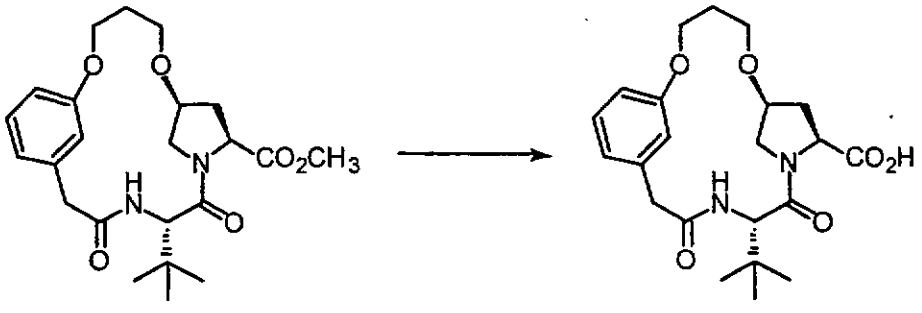
Step I



56h 56i

The desired product **56i** was obtained by the procedure described for Example 1, Step H. Purification of the crude residue using 75/25 hexanes/acetone provided a mixture of the product **56i** along with triphenylphosphine oxide. HRMS (FAB) Calcd for $C_{23}H_{33}N_2O_6$: 433.2339 $(M+H)^+$. Found: 433.2343.

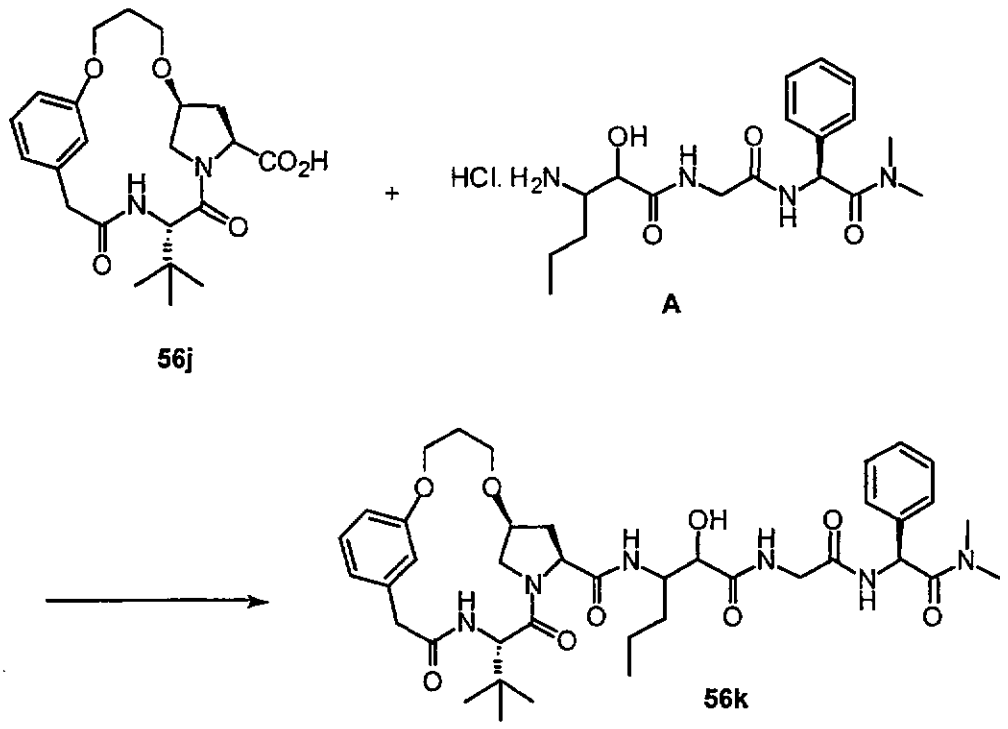
Step J



56i 56j

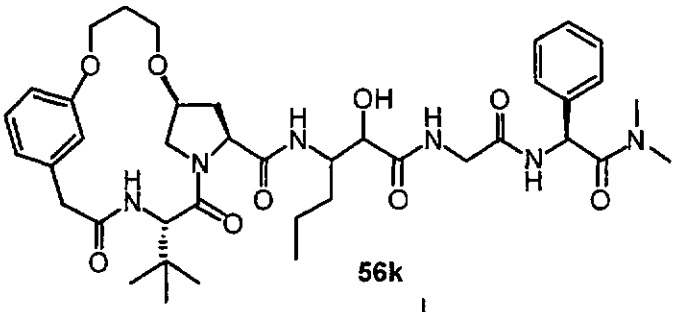
The expected product **56j** was synthesized as described for Example 1, Step I. Yield for two steps = 16%. HRMS (FAB) Calcd for $C_{22}H_{31}N_2O_6$: 419.2182 $(M+H)^+$. Found: 419.2176.

Step K

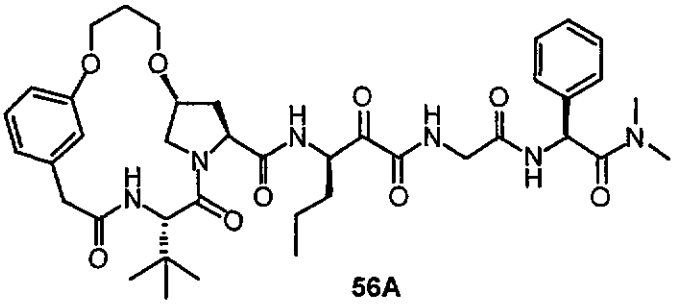


The expected product **56k** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step. HRMS (FAB) Calcd for $C_{40}H_{57}N_6O_9$: 765.4187 $(M+H)^+$. Found: 765.4198.

Step L

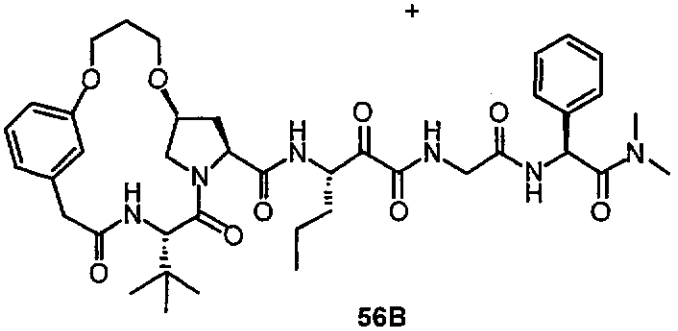


56k



56A

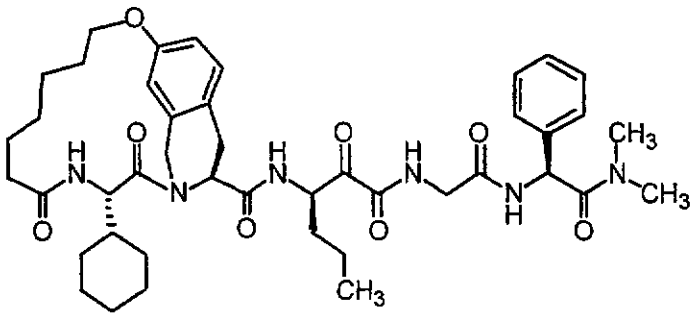
+



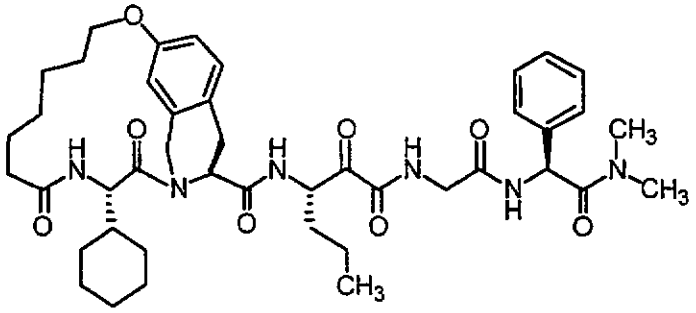
56B

The desired products **56A** and **56B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 98/2 to 96/4 dichloromethane/MeOH afforded separate isomers **56A** and **56B**, and some mixture. Combined yield = 35% (for 2 steps). HRMS (FAB) Calcd for $C_{40}H_{55}N_6O_9$: 763.4031 $(M+H)^+$. Found: 763.4025 (**56A**), 763.4040 (**56B**).

Example 57: Preparation of Compounds of Formulas 57A and 57B:

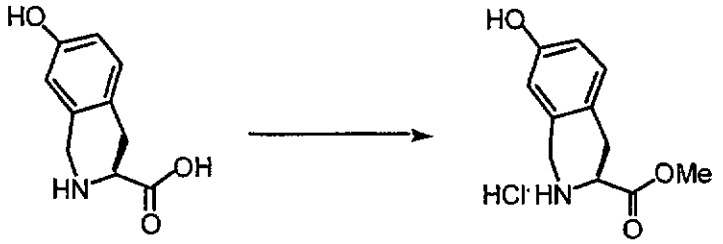


57A



57B

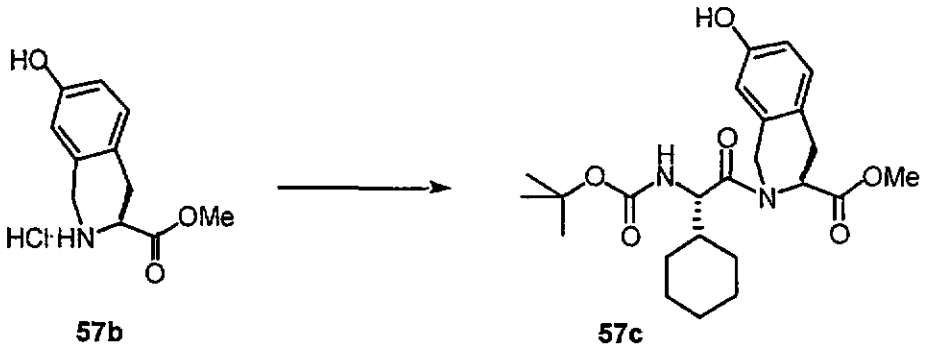
Step A:



57a **57b**

To the solution of the commercial dihydrate of the amino acid (3*S*)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **57a** (5.0 g, 21.8 mmol) in methanol (180 mL) was added concentrated hydrochloric acid (5.0 mL, 60 mmol). The resulting clear solution was then heated to reflux in an oil bath for 18h. Solvents were removed in vacuo to give methyl ester **57b** as a white solid, which was used in the next reaction without further purification.

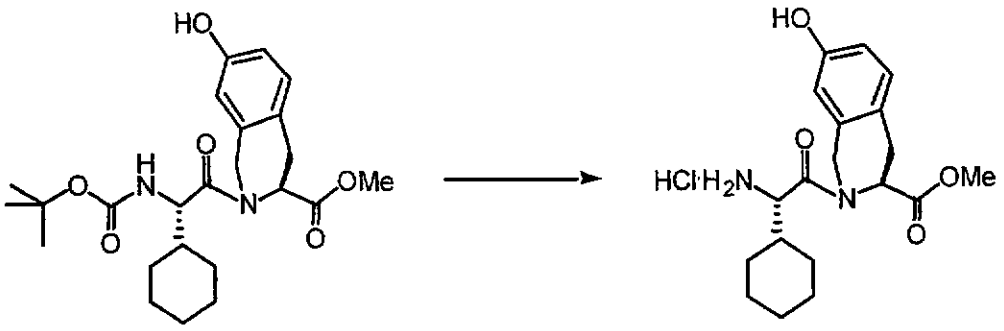
Step B:



57b **57c**

To a solution of amine hydrochloride **57b**, *N*-Boc-cyclohexylglycine (5.95 g, 21.8 mmol), HOOBt (3.73 g, 22.9 mmol) and EDCI (5.00 g, 26.1 mmol) in anhydrous DMF (200 mL) and CH_2Cl_2 (200 mL) at -20°C was added NMM (7.20 mL, 65.5 mmol). After stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h), after which EtOAc (600 mL), brine (150 mL) and 5% H_3PO_4 (150 mL) were added. The separated organic solution was washed with 5% H_3PO_4 (200 mL), saturated aqueous sodium bicarbonate solution (2 X 200 mL), water (200 mL), and brine (200 mL), dried with magnesium sulfate, filtered and concentrated in vacuo to afford **57c** (10.3 g, quant. 2 steps) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.32 (s, 1 H), 8.35- 8.32 (m, 1 H), 6.99 (d, *J* =8.3 Hz, 1 H), 6.65-6.54 (m, 1 H), 4.92 (d, *J* =15.5 Hz, 1 H), 4.50 (d, *J* = 15.5 Hz, 1 H), 4.43-4.36 (m, 1 H), 4.29-4.19 (m, 1 H), 3.53 (s, 3 H), 3.02-2.81 (m, 2 H), 1.98-1.62 (m, 8 H), 1.42-1.11 (m, 14 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 171.6, 171.2, 162.3, 156.0, 133.7, 128.8, 125.3, 114.1, 112.6, 78.0, 54.8, 52.4, 51.9, 45.0, 29.5, 28.1, 28.0, 25.9, 25.6, 25.5 ; HRMS *m/z* 447.2492 [calcd for $C_{24}H_{34}N_2O_6$, 447.2495].

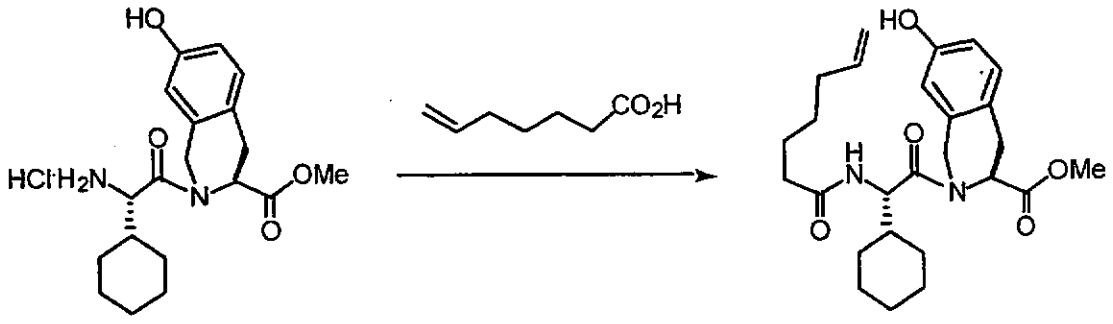
Step C:



57c 57d

The Boc-amino methyl ester **57c** (7.20 g, 16.1 mmol) was dissolved in 4 N HCl (100 mL, 400 mmol) and the resulting solution was stirred at rt. The progress of the reaction was monitored by TLC. After 4 h, the solution was concentrated in vacuo and the residue was under vacuum overnight to give **57d** as a white solid which was used in the next coupling reaction without further purification.

Step D:

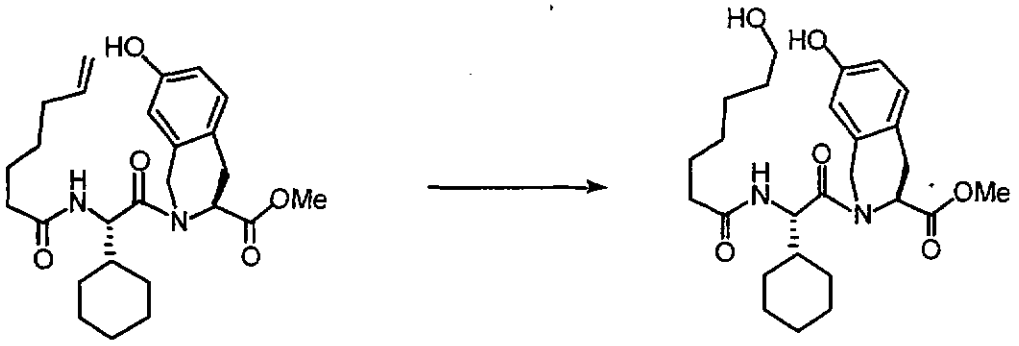


57d 57e

To a solution of amine hydrochloride **57d** (from Step D), 6-heptenoic acid (2.90 g, 22.6 mmol), HOOBt (3.70 g, 22.7 mmol) and EDCI (4.80 g, 25.0 mmol) in anhydrous DMF (250 mL) and CH_2Cl_2 (150 mL) at -20°C was added NMM (7.50 mL, 68.2 mmol). After stirred at this temperature for 30 min, the reaction mixture was kept in a freezer for 2 days. It was then stirred in air and

allowed to warm to rt. in 1h. EtOAc (500 mL), brine (100 mL) and 5% H_3PO_4 (100 mL) were added. The separated organic solution was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (5 to 30 % EtOAc-CH_2Cl_2) afforded **57e** (2.30 g, 5.04 mmol, 31 % (2 steps)) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 9.32 (s, 1 H), 8.06-8.01 (m, 1 H), 7.00-6.6.96 (m, 1 H), 6.63-6.54 (m, 2 H), 5.78-5.70 (m, 1 H), 5.04-4.89 (m, 4 H), 4.73-4.69 (m, 1 H), 4.53 (d, *J* = 15.5 Hz, 1 H), 3.54 (s, 3 H), 3.01-2.91 (m, 2 H), 2.15-1.93 (m, 4 H), 1.76-0.97 (m, 15 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.0, 171.5, 171.1, 156.0, 138.6, 134.0, 128.7, 122.5, 114.6, 114.1, 112.5, 52.9, 52.2, 51.9, 45.0, 34.5, 32.8, 32.7, 29.4, 28.7, 28.1, 27.7, 25.9, 25.5, 25.5, 24.8; HRMS *m/z* 457.1 [calcd for $C_{26}H_{36}N_2O_5$, 456.6].

Step E:

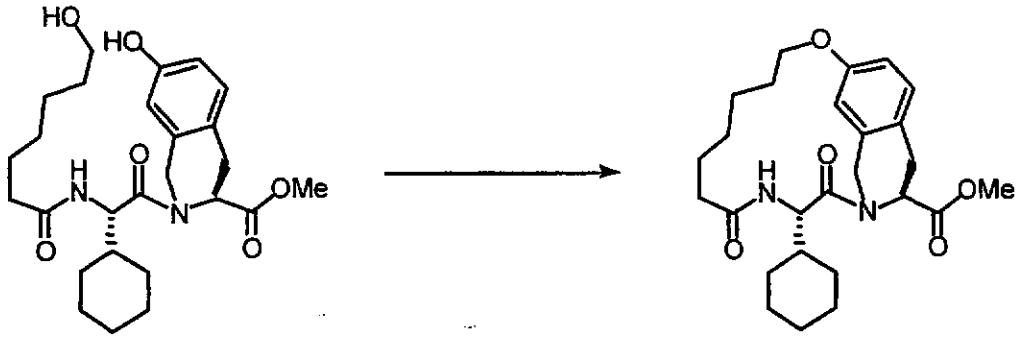


57e **57f**

To the solution of **57e** (2.20 g, 4.82 mmol) in anhydrous THF (100 mL) under nitrogen at 0°C was added borane-THF solution (20 mL, 1.0 M, 20 mmol) cautiously. The resulting solution was stirred at 0°C under hydrogen for 1 h 40 min. Then ethanol (10 mL) and pH 7 buffer (15 mL) were added, followed by 30 % H_2O_2 solution (15 mL). After stirred at 0°C for 20 min, it was warmed to rt. and stirred for 2 h. EtOAc (400 mL) and brine (200 mL) were added and layers were separated. Aqueous solution was extracted with EtOAc (2 X 150 mL). Combined organic solution was dried with magnesium

sulfate, filtrated, concentrated in vacuo. Flash chromatography (3 to 5 % MeOH-CH_2Cl_2) afforded **57f** (2.18 g, 4.47 mmol, 93 %) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 9.32 (s, 1 H), 8.04-8.00 (m, 1 H), 6.99-6.96 (m, 1 H), 6.63-6.51 (m, 2 H), 5.05-5.00 (m, 1 H), 4.73-4.21 (m, 3 H), 4.51 (d, *J* = 15.5 Hz, 1 H), 3.54 (s, 3 H), 3.03-2.90 (m, 2 H), 2.15-2.00 (m, 2 H), 1.75-1.56 (m, 6 H), 1.49-0.97 (m, 13 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.2, 171.6, 171.2, 156.0, 134.1, 128.7, 122.6, 114.2, 112.5, 60.7, 52.9, 52.3, 51.9, 45.1, 34.8, 32.4, 29.5, 28.7, 28.53, 28.47, 28.10, 25.9, 25.6, 25.5, 25.4, 25.2; HRMS *m/z* 475.2812 [calcd for $C_{26}H_{38}N_2O_6$, 475.2808].

Step F:

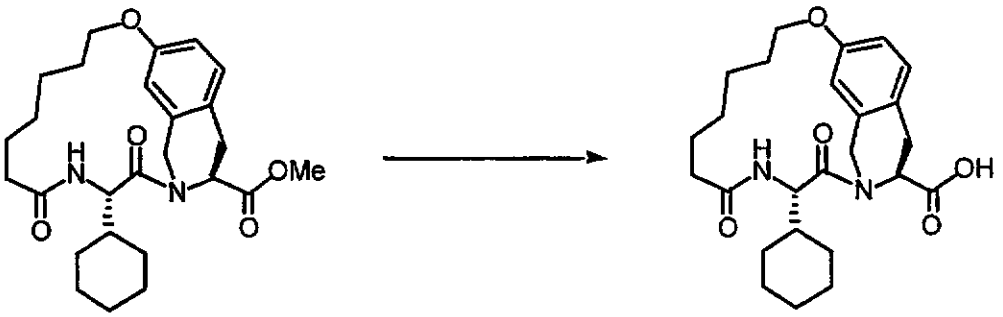


57f **57g**

A solution of phenol alcohol **57f** (2.08 g, 4.38 mmol) and ADDP (3.00 g, 11.9 mmol) in anhydrous CH_2Cl_2 was bubbled with Argon through a frit glass bubbler for 20 min. To this solution at 0°C was added triphenylphosphine (3.45 g, 13.2 mmol). After stirring at 0°C for 20 min, the solution was warmed to rt. and stirred overnight (18 h) under nitrogen. TLC indicated the presence of substantial amount of starting material. A second batch of ADDP (3.00 g, 11.9 mmol) and triphenylphospine (3.45 g, 13.2 mmol) were added, and the mixture was stirred under nitrogen for 2 days and 16 h. TLC showed the complete consumption of the starting material. After removal of solvent in vacuo, the residue was partially purified by flash chromatography (1 to 2 % MeOH in CH_2Cl_2) to afford a mixture of the macrocycle **57g** and triphenylphosphine oxide. The macrocyclic **57g** was hydrolyzed to the

corresponding acid without further purification. ^{1}H NMR (400 MHz, d6-DMSO) δ 8.00 (d, *J* = 10.0 Hz, 1 H), 7.17 (d, *J* = 8.2 Hz, 1 H), 6.82-6.76 (m, 2 H), 5.14 (d, *J* = 14.5 Hz, 1 H), 4.79-4.74 (m, 1 H), 4.39 (dd, *J* = 11.5, 6.4 Hz, 1 H), 4.25 (d, *J* = 14.7 Hz, 1 H), 4.22-4.18 (m, 1 H), 4.08-4.02 (m, 1 H), 3.68 (s, 3 H), 3.18 (dd, *J* = 15.1, 6.4 Hz, 1 H), 2.85 (dd, *J* = 14.7, 11.5 Hz, 1 H), 2.07-2.04 (m, 2 H), 1.81-1.40 (m, 10 H), 1.32-0.85 (m, 9 H); ^{13}C NMR (100 MHz, d6-DMSO) δ 171.9, 171.5, 170.2, 157.1, 137.0, 131.5, 126.4, 115.9, 112.6, 66.5, 54.4, 52.2, 51.9, 46.8, 44.9, 44.4, 33.6, 29.4, 29.1, 28.0, 27.3, 27.0, 26.0, 25.3, 25.2, 24.3, 24.2, 23.9; HRMS *m/z* 457.2707 [calcd for $C_{26}H_{36}N_2O_5$, 457.2702].

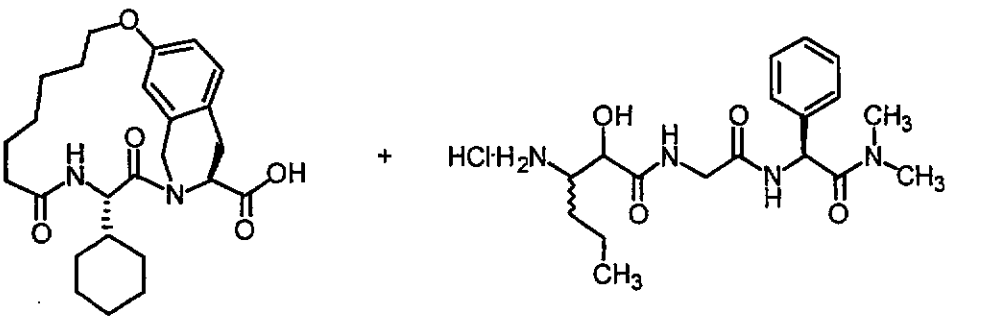
Step G:



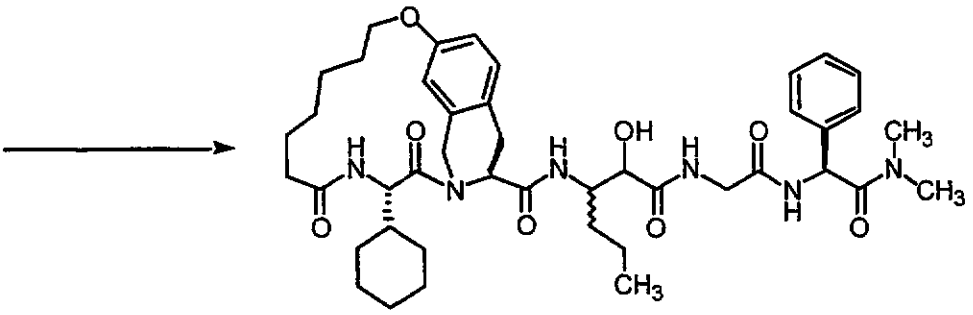
57g **57h**

An aqueous lithium hydroxide solution (0.21 g, 30 mL H_2O, 8.75 mmol) was added to a 0°C solution of methyl ester **57g** (from step 1F) in THF (30 mL) and methanol (30 mL). The mixture was stirred in an ice bath and warmed to rt. along with it in 4 h. The progress of the reaction was monitored by TLC. After the volatiles were removed in vacuo, EtOAc (100 mL) and water (30 mL) were added and the two layers separated. The aqueous solution was extracted again with CH_2Cl_2 (100 mL), after which it was acidified to pH = 1. EtOAc was then added (150 mL) and the aqueous solution was saturated with solid sodium chloride. After separation of the layers, the aqueous layer was extracted with EtOAc (2 X 100 mL). Organic solutions were combined, dried with magnesium sulfate, filtered and concentrated in vacuo to afford **57h** (1.23 g, 2.78 mmol, 63 % (2 steps)) as a white solid.

Step H:



57h A

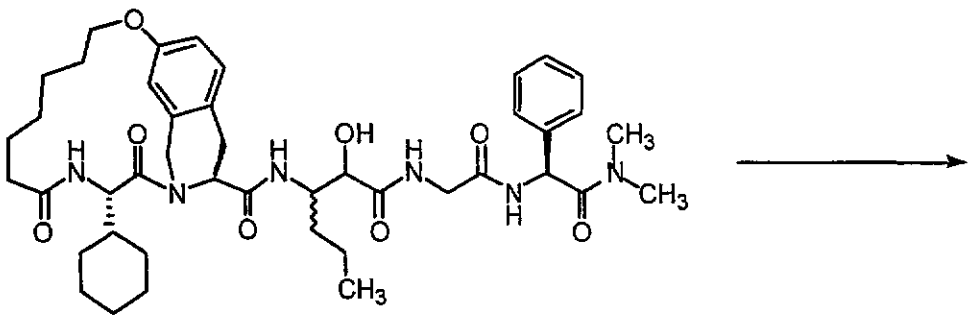


57i

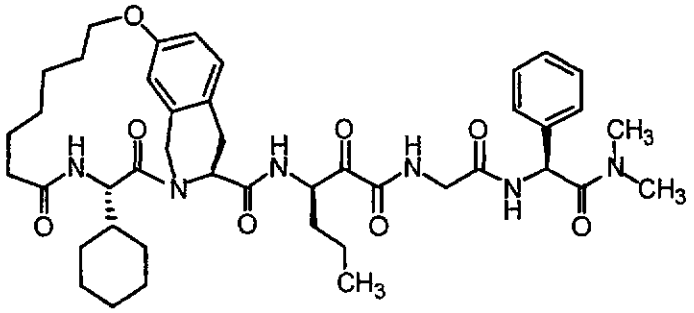
To a solution of acid **57h** (0.390 g, 0.881 mmol), amine **A** (0.360 g, 0.898 mmol), HOOBt (160 mg, 0.981 mmol) and EDCI (210 mg, 1.10 mmol) in anhydrous DMF (50 mL) and CH_2Cl_2 (30 mL) at -20°C was added NMM (0.40 mL, 3.64 mmol). After stirred at this temperature for 30 min, the reaction mixture was kept in a freezer for 66 h. Then EtOAc (200 mL), brine (50 mL) and 5% H_3PO_4 (50 mL) were added. The separated organic solution was washed, successively, with 5% H_3PO_4 (80 mL), saturated aqueous sodium bicarbonate solution (2 X 80 mL), water (80 mL), and brine (80 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (2 to 5 % MeOH-CH_2Cl_2) afforded **57i** as a mixture of four diastereomers (0.340 g, 0.431 mmol, 49%) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.56-8.46 (m, 1 H), 7.96-7.82 (m, 2 H), 7.40-7.25 (m, 6 H), 7.15-6.99 (m, 2 H), 6.81-6.74 (m, 2 H), 6.05-5.71 (m, 2 H), 5.11-5.02 (m, 1 H), 4.85-4.68 (m, 1 H), 4.40-3.70 (m, 8 H), 3.14-3.02 (m, 1 H), 2.95-2.73 (m, 7 H), 2.06-2.05 (m, 2

H), 1.81-1.39 (m, 10 H), 1.30-1.05 (m, 11 H), 0.89-0.75 (m, 5 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.24, 172.21, 171.87, 171.81, 171.78, 171.7, 170.8, 170.77, 170.74, 170.5, 170.4, 170.0, 169.97, 169.24, 169.22, 169.1, 169.0, 168.0, 167.9, 167.82, 167.78, 157.2, 156.9, 137.61, 137.57, 137.54, 137.47, 137.43, 137.38, 133.2, 132.2, 128.9, 128.44, 128.41, 128.37, 128.0, 127.96, 127.6, 127.4, 127.3, 127.19, 127.16, 115.7, 115.6, 115.5, 112.8, 112.77, 112.7, 112.6, 73.6, 73.39, 73.37, 72.4, 71.7, 66.9, 66.7, 55.8, 55.6, 55.09, 55.07, 53.02, 52.95, 52.9, 52.6, 51.0, 50.96, 50.91, 50.86, 50.76, 45.6, 45.5, 45.44, 45.36, 41.7, 41.6, 41.5, 41.4, 36.6, 36.55, 36.49, 35.3, 33.7, 33.6, 33.5, 33.0, 32.4, 30.7, 30.3, 30.1, 30.0, 29.8, 29.48, 29.45, 29.41, 28.3, 28.2, 28.1, 27.3, 27.2, 27.13, 27.09, 27.0, 26.9, 26.85, 26.82, 26.1, 25.4, 25.2, 24.1, 24.08, 24.03, 24.0, 23.9, 23.8, 18.8, 18.7, 18.6, 18.4, 13.9, 13.8, 13.7; HRMS *m/z* 789.4560 [calcd for $C_{43}H_{60}N_6O_8$, 789.4551, error = 1 ppm].

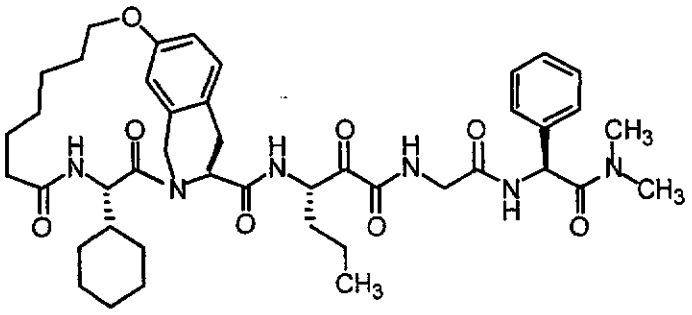
Step I:



57i



57A

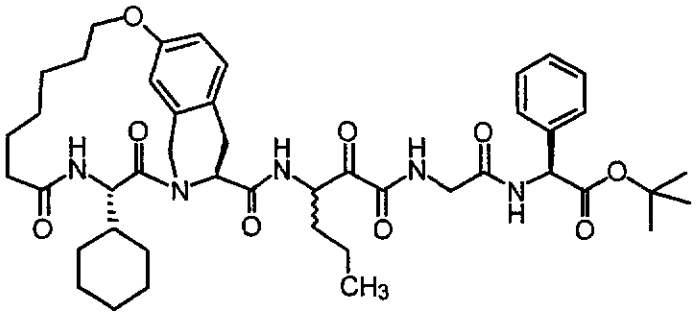


57B

To the mixture of hydoxy amide **57i** (0.320 g, 0.406 mmol) and Des-Martin reagent (0.400 g, 0.943 mmol) at 0°C was added anhydrous CH_2Cl_2 (80 mL). The resulting white suspension was vigorously stirred at 0°C and warmed to rt. along with the ice bath in 4 h. Saturated aqueous sodium bicarbonate and sodium bisulfite solutions (30 mL each) were added and the mixture was vigorously stirred for 10 min before layers were separated. The aqueous solution was extracted with CH_2Cl_2 (2 X 80 mL). Combined organic solution was dried with magnesium sulfate, filtered and concentrated in vacuo.

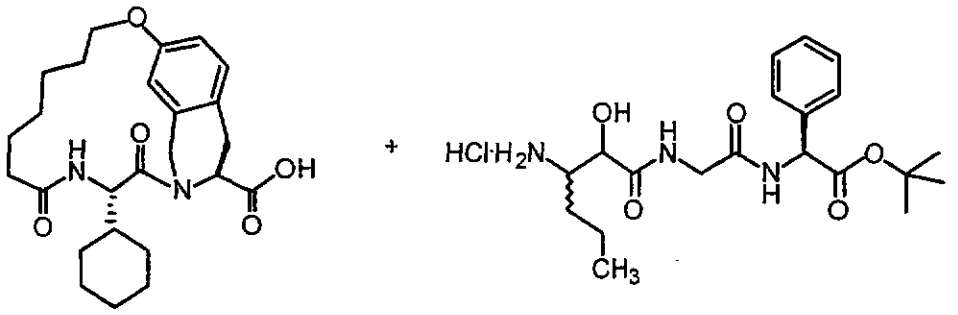
Flash chromatography (2 to 5 % MeOH-CH_2Cl_2) afforded two stereo-isomers **57A** (109 mg, 0.139 mmol) and **57B** (102 mg, 0.130 mmol, 66% combined yield) as white solids.

Example 58: Preparation of Compound of Formula 58:

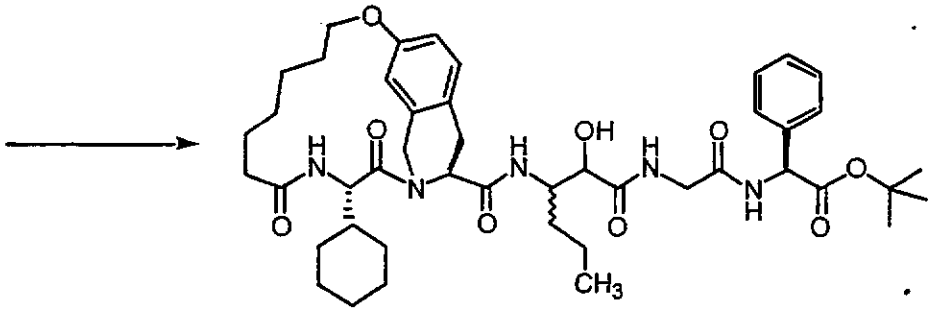


58

Step A:



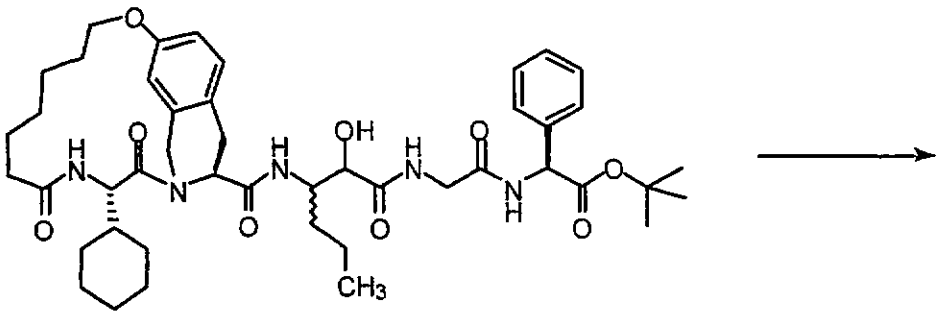
57h **B**



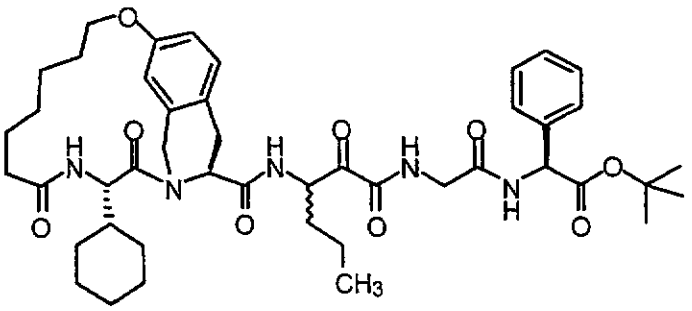
58a

The desired compound **58a** was prepared according to the method of Example 1, Step J, except substituting amine hydrochloride **B** for **A**. The hydroxy amide **58a** was obtained as a mixture of inseparable diastereomers in the form of a white solid in 53 % yield.

Step B:



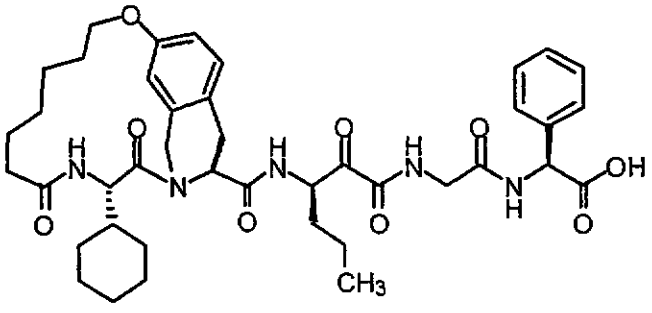
58a



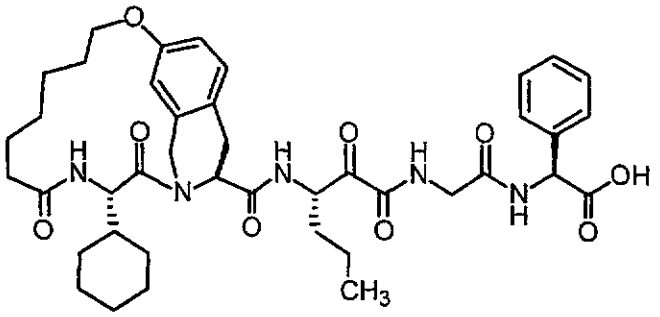
58

The desired compound **58** was prepared from hydroxy amide **58a** according to the method of Example 2, Step B. It was obtained as a mixture of inseparable diastereomers in the form of a white solid in 88 % yield.

Example 59: Preparation of Compounds of Formulas 59A and 59B:

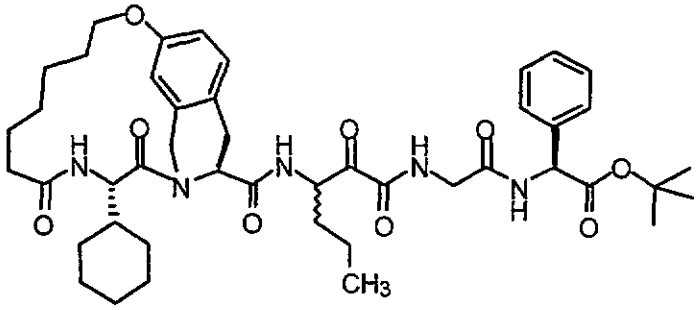


59A

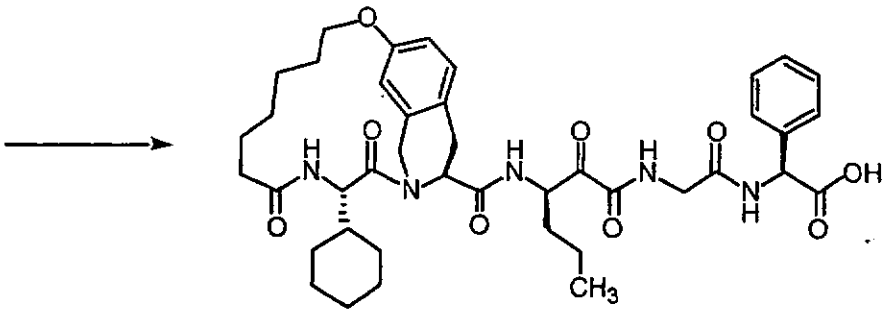


59B

Step A:

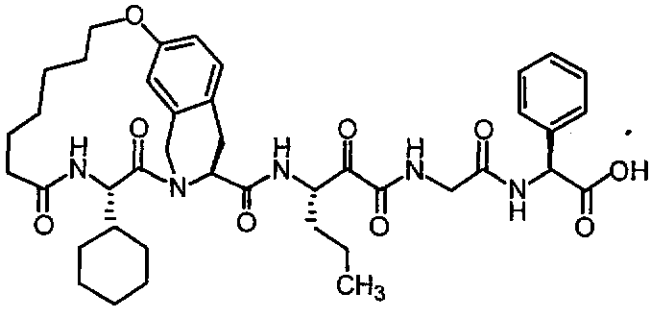


58



59A

+

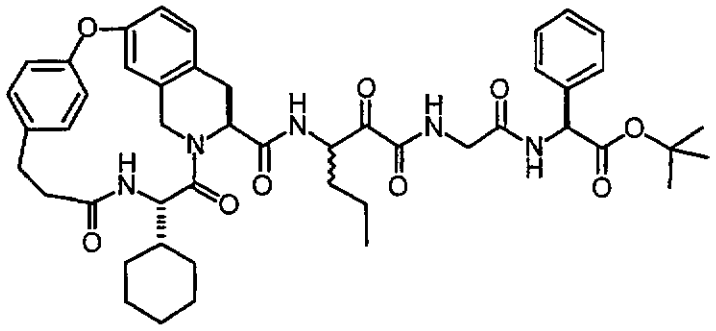


59B

A solution of the t-Butyl ester **58** (18 mg, 0.022 mmol) in trifluoroacetic acid (2 mL) and CH_2Cl_2 (2 mL) was stirred at rt. for 3 h. After the volatiles

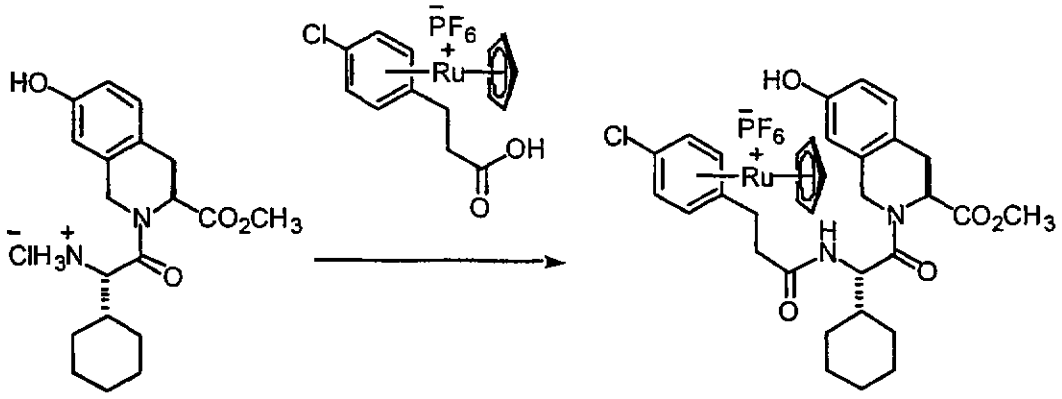
were removed in vacuo, the residue was dissolved in 50% MeOH-CH_2Cl_2 (3 mL), and concentrated to dryness in vacuo to afford an off-white solid. Flash chromatography (8-15 % MeOH, 0.3-0.5% AcOH in CH_2Cl_2) afforded two stereo-isomers **59A** (6.5 mg, 0.0086 mmol) and **59B** (6.1 mg, 0.008 mmol, 75% combined yield) as white solids. Analytical data for **59A**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.75-8.72 (m, 1 H), 8.60-8.57 (m, 1 H), 8.10-8.08 (m, 1 H), 7.91-7.88 (m, 1 H), 7.38-7.27 (m, 5 H), 7.12 (d, *J* = 8.14 Hz, 1 H), 6.81-6.73 (m, 2 H), 5.24-5.22 (m, 1 H), 5.06-5.01 (m, 1 H), 4.77-4.73 (m, 1 H), 4.39 - 4.17 (m, 3 H), 4.07-4.01 (m, 1 H), 3.92-3.79 (m, 3 H), 3.15-3.05 (m, 1 H), 2.78-2.72 (m, 1 H), 2.08-2.05 (m, 1 H), 1.78-1.45 (m, 13 H), 1.41-1.22 (m, 4 H), 1.18-1.03 (m, 4 H), 0.93-0.81 (m, 5 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 196.6, 171.8, 171.5, 171.9, 170.3, 167.2, 161.0, 157.1, 137.4, 128.4, 128.1, 127.7, 127.5, 127.4, 126.9, 115.6, 112.6, 66.8, 56.6, 55.1, 53.4, 52.7, 52.6, 45.4, 41.6, 33.5, 31.7, 30.0, 29.6, 28.2, 27.2, 27.1, 26.1, 25.42, 25.36, 24.0, 23.8, 18.7, 13.5; HRMS *m/z* 760.3915 [calcd for $C_{41}H_{53}N_5O_9$, 760.3922]. Analytical data for **59B**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.76-8.73 (m, 1 H), 8.55 (dd, *J* = 6.9, 3.2 Hz, 1 H), 8.24 (d, *J* = 7.11 Hz, 1 H), 7.93-7.88 (m, 1 H), 7.37-7.25 (m, 1 H), 7.15-7.11 (m, 1 H), 6.82-6.74 (m, 2 H), 5.23-5.20 (m, 1 H), 5.09-5.01 (m, 1 H), 4.75-4.71 (m, 1 H), 4.38 -4.29 (m, 1 H), 4.24-4.17 (m, 2 H), 4.07-4.02 (m, 1 H), 3.92-3.78 (m, 2 H), 3.13-3.08 (m, 1 H), 2.78-2.70 (m, 1 H), 2.08-2.05 (m, 2 H), 1.75-1.13 (m, 21 H), 0.89-0.85 (m, 5 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 196.7, 171.6, 171.2, 169.9, 167.1, 160.8, 157.0, 137.5, 128.3, 128.2, 128.0, 127.97, 127.9, 127.4, 127.3, 127.1, 115.7, 115.6, 112.7, 112.6, 66.7, 56.8, 54.8, 53.3, 45.5, 41.6, 33.6, 31.8, 29.5, 28.1, 27.3, 27.0, 26.1, 25.4, 24.2, 23.9, 18.6, 13.5; HRMS *m/z* 760.3915 [calcd for $C_{41}H_{53}N_5O_9$, 760.3922].

Example 60: Preparation of Compound 60:



60

Step A

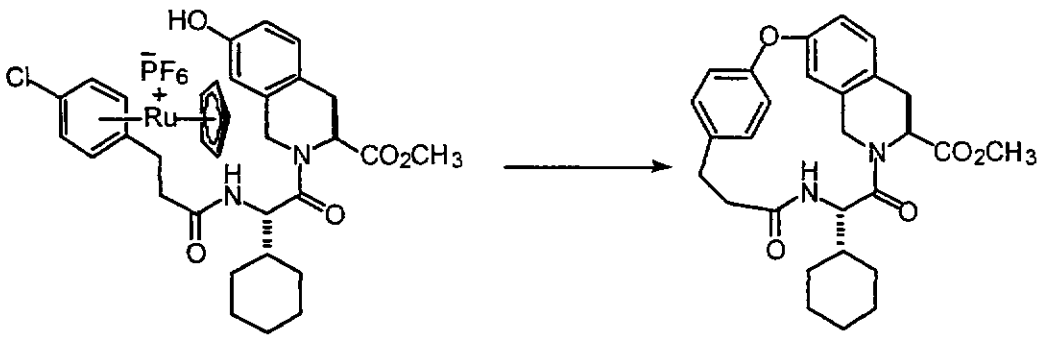


57d 60a

A solution of [CpRu(η^6- 4-chlorophenylpropionic acid)]PF_6 (4.14 g, 8.36 mmol) in dry DMF (20 mL) was treated with HOBt (1.69 g, 12.54 mmol, 1.5 equiv.) and Hünigs base (6.47 g, 9.20 mL, 50.16 mmol, 6.0 equiv.) The reaction mixture was cooled to 0 ° C and treated with EDCI (2.39 g, 12.54 mmol, 1.5 equiv.) The reaction mixture was stirred at 0 °C for 30 min and the Tic-ammonium salt **57d** (2.90 g, 7.6 mmol mmol, 1.0 equiv.) was added. The reaction mixture was stirred at rt. for 12h and the DMF was distilled out in vacuo. The residue was diluted with aq. HCl (1M, 100 mL) and extracted into CH_2Cl_2 (3x100 mL). The combined organic layers were washed with aq. $NaHCO_3$ (1x100 mL) , brine (100 mL), dried (Na_2SO_4), filtered, concentrated in vacuo to yield a brown solid **60a** (5.2 g, 83%) which was used for

cyclization. MS: (Electron spray): 647 $[(M\text{-}CH_3OH\text{-}PF_6)^+$, 100]. HRMS calcd. for $C_{32}H_{34}ClN_2O_4Ru$ $[(M\text{-}CH_3OH\text{-}PF_6)]^+$ 647.1256; Found: 647.1241.

Step B



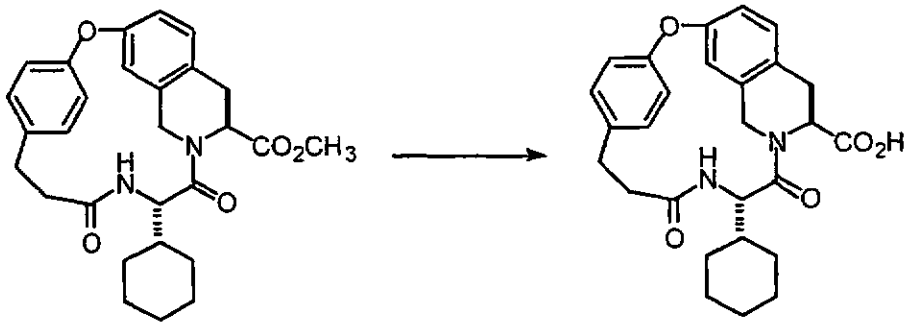
60a **60b**

A solution of Ruthenium complex **60a** (5.0 g 6.01 mmol) in dry DMF (300 mL) was degassed with dry N_2 at rt. and Cs_2CO_3 (10.0 g, 30 mmol, 5.0 equiv.) was added and stirred at rt. for 24 h. The solvent DMF was distilled off and the residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (3x100 mL) and propionitrile (3x100 mL). The combined organic layers were extracted, with brine(100 mL), dried (Na_2SO_4) filtered, concentrated in vacuo and dried in vacuum overnight to yield a brown solid (5.1 g). It was used for photolytic removal of Ru without further purification. MS: (Electron spray) : 643 $[(M\text{-}PF_6)^+$, 100].

The cyclized compound from the previous step was dissolved in CH_3CN (50 mL) and filtered into a quartz tube. The solution was degassed and photolysed in a Raynot instrument (λ=350 nm) for 48 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography (SiO_2, EtOAc/Hexanes 3:2) to yield a tan colored solid **60b** (289 mg, 20%). R_f: 0.73 (acetone/hexanes 3:7) ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, 2 H, *J*=8.1 Hz), 7.20-7.09 (m, 2 H), 6.92 (d, 2 H, *J*=7.8 Hz), 6.86 (dd, 1 H, *J*=2.1, 7.2 Hz), 6.76 (s, 1 H), 5.41 (d, 1 H, *J*=17.4 Hz), 4.23-4.18 (m, 2 H),

4.00 (bs, 1 H), 3.68 (s, 3 H), 3.41 (dd, 1 H *J*=12, 3.9 Hz), 3.01-2.86 (m, 1 H), 1.9-1.62 (m, 4 H), 1.52 (bd, 1 H, *J*=9.3 Hz), 1.36-1.07 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 173.2, 167.2, 163.8, 156.5, 155.1, 135.8, 132.7, 130.2, 129.6, 126.2, 119.1, 117.5, 115.8, 60.2, 55.5, 51.6, 44.2, 42.0, 35.7, 30.2, 29.3, 26.5, 26.2, 25.8, 25.7 MS: (Electron spray): 477 [$(M+1)^+$, 100], 315 (20); HRMS calcd. for $C_{28}H_{33}N_2O_5$ $(M+1)^+$: 477.2389; Found 477.2375; CHN Calcd. for $C_{28}H_{32}N_2O_5$ 0.5H_2O: C 69.26% H 6.85% N 5.77%; Found: C 69.62% H 6.59% N 5.77%

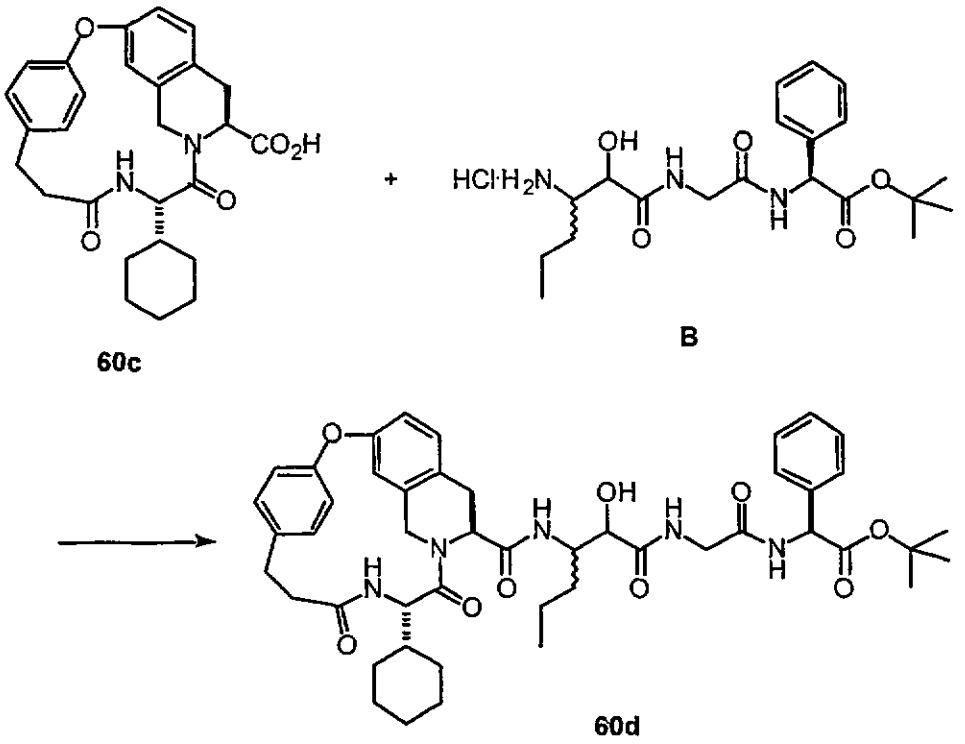
Step C



60b **60c**

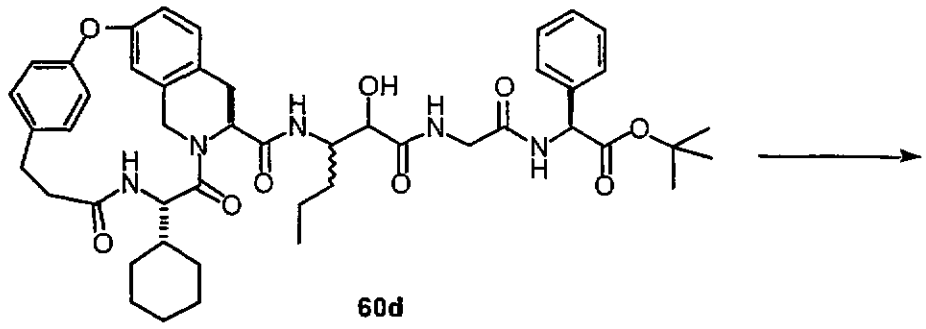
A solution of methyl ester **60b** (235 mg, 0.5 mmol) of Tic-macrocycle in dioxane(10.0 mL), H_2O (10.0 mL), CH_3OH (50.0 mL) was treated with $LiOH•H_2O$ (41 mg, 1.0 mmol, 2.0 equiv.) and stirred at rt. for 3 h. The reaction mixture was acidified and (4M HCl in Dioxane). The reaction mixture was concentrated in vacuo and the remaining water was frozen and lyophilized to obtain a colorless solid **60c** used for coupling.

Step D

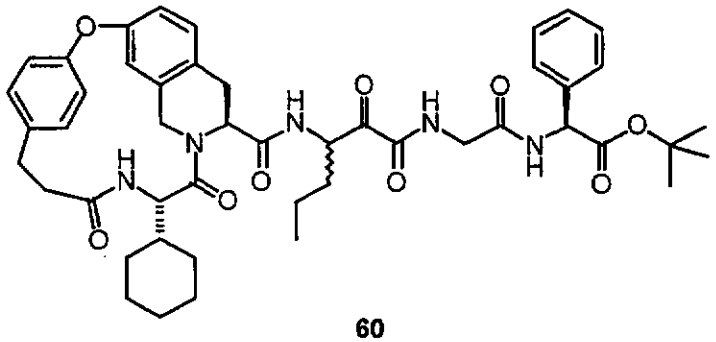


A solution of the hydrolyzed acid **60c** (0.5 mmol) in dry DMF (5.0 mL) and CH_2Cl_2 (5.0 mL) was treated with HOOBt (132 mg, 0.75 mmol, 1.5 equiv.), and cooled to 0 °C and Hünigs base (258 mg, 2.0 mmol, 4.0 equiv., 369 μL) was added. To this mixture was added EDCI (143 mg, 0.75 mmol, 1.5 equiv.) and amine hydrochloride **B** (214 mg, 0.5 mmol, 1.0 equiv.) sequentially. The reaction mixture was stored in freezer for 48 h and concentrated in vacuo to remove DMF and CH_2Cl_2. The residue was diluted with aq. HCl (2M, 50 mL) and extracted with CH_2Cl_2 (3x30 mL) The combined organic layer was extracted with aq. HCl (1M, 2x50 mL), aq. NaOH (2 M 2x30 mL), brine, dried ($MgSO_4$) and concentrated in vacuo. The residue **60d** (172 mg) was oxidized without further purification; MS: (Electron spray): 838 $[(M+1)^+$, 50], 490 (100); HRMS calcd. for $C_{47}H_{60}N_5O_9$ $(M+1)^+$: 838.4391; Found: 838.4398.

Step E



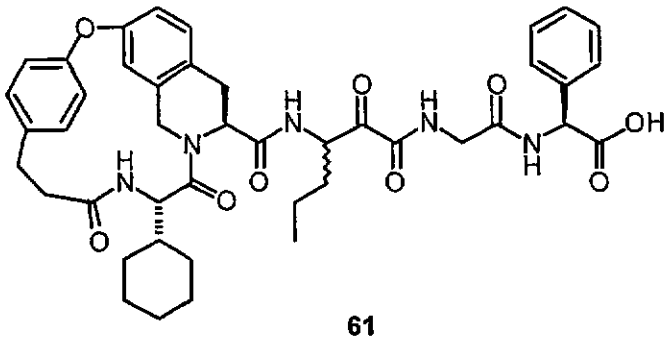
60d



60

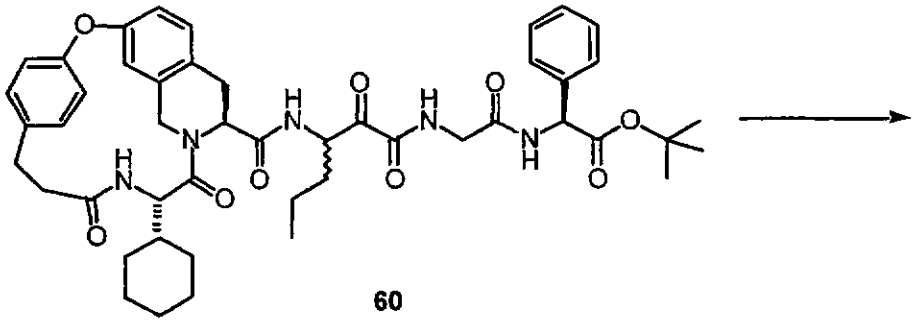
A solution of alcohol **60d** (171 mg, 0.20 mmol) in CH_2Cl_2 (6.0 mL) was treated with Dess-Martin reagent (175 mg, 0.41 mmol, 2.0 equiv.). The reaction mixture was stirred at rt. for 4 h and diluted with aq. $NaHCO_3$ and aq. $Na_2S_2O_3$. The reaction mixture was stirred at rt. for 20 min and the reaction mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were extracted with aq. Na_2CO_3, dried (Na_2SO_4), filtered concentrated in vacuo and the residue was purified by chromatography (SiO_2, CH_3OH (2M NH_3)/CH_2Cl_2 1:20) to yield ketoamide **60** (56 mg, 32%) as a colorless solid. R_f: 0.35 (CH_3OH (2M NH_3)/CH_2Cl_2 1:18) MS: (Electron spray, *m/z relative intensity*): 836 ($[M+1]^+$, 90), 490 (100). HRMS calcd. for $C_{47}H_{58}N_5O_9$ $(M+1)^+$ 836.4235; Found: 836.4269.

Example 61: Preparation of Compound 61:

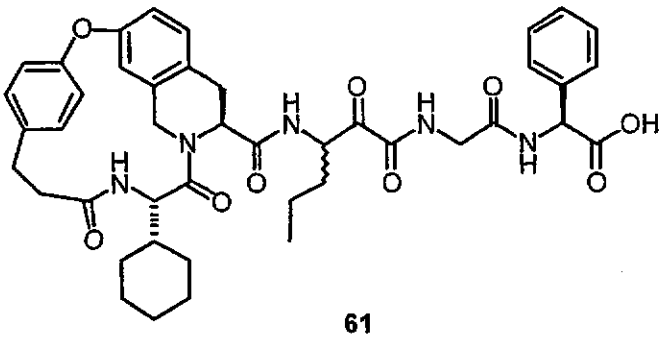


61

Step A



60

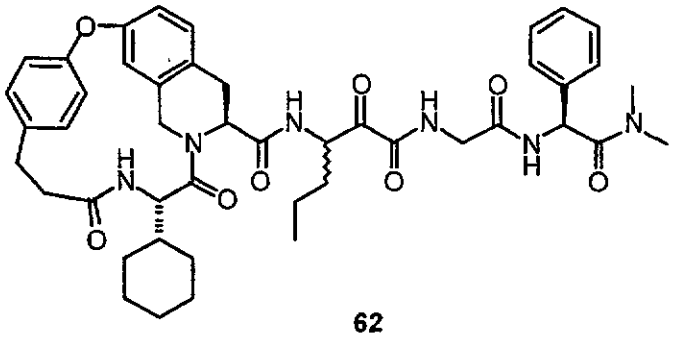


61

A solution of *tert*-butyl ester **60** (50 mg, 0.059 mmol) in dry CH_2Cl_2 (10.0 mL) was treated with TFA (10.0 mL) and stirred at rt. for 4 h. The disappearance of the ester to the base line was followed by TLC (CH_3OH/CH_2Cl_2, 1:19). The reaction mixture was concentrated in vacuo and the residue was repeatedly dissolved in heptanes/CH_2Cl_2 and concentrated

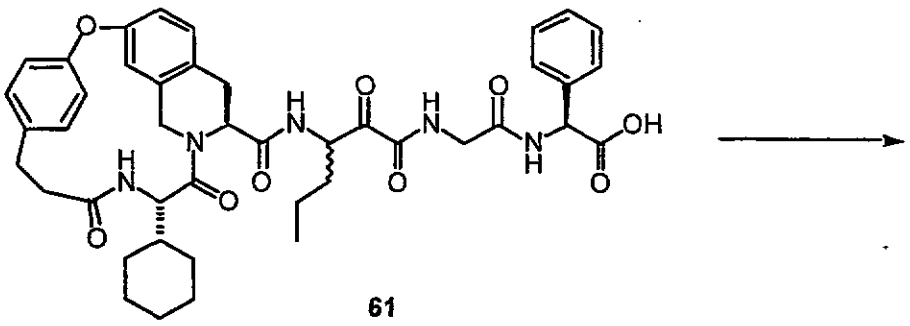
in vacuo several times to yield a fine colorless solid **61** (51 mg) which was dried in vacuo.; MS (FAB) 780 [$(M+1)^+$, 85], 516 (20), 417 (20), 403 (100), 321 (20), 248 (40), 236 (40); HRMS calcd. for $C_{43}H_{50}N_5O_9$ $(M+1)^+$: 780.3609; found 780.3618.

Example 62: Preparation of Compound 62:

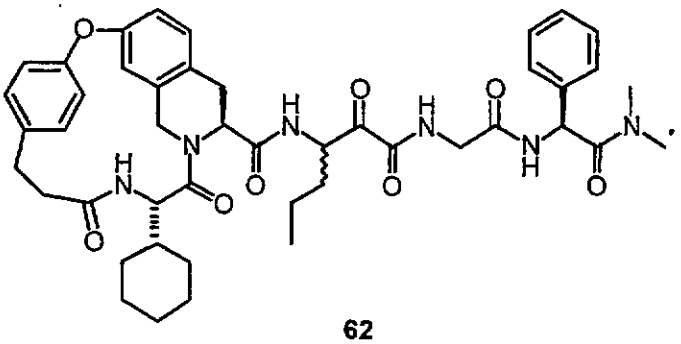


62

Step A



61

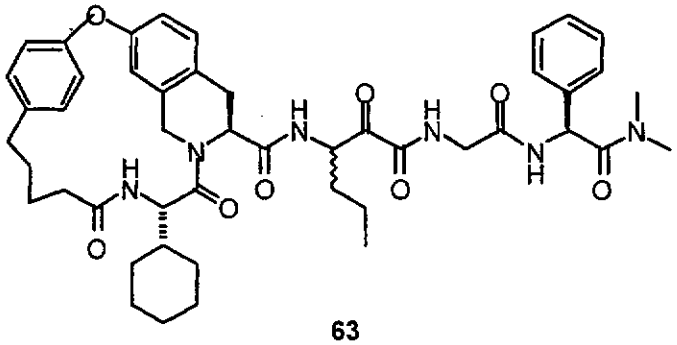


62

A solution of the acid **61** (30 mg, 0.038 mmol), dimethyl amine hydrochloride (6.2 mg, 0.076 mmol, 2.0 equiv.) in CH_2Cl_2 (1.0 mL) was

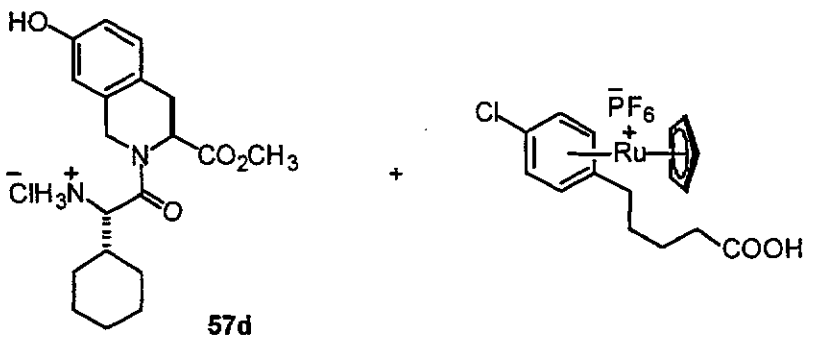
treated with Hünigs base (9.1 mg, 0.076 mmol, 2.0 equiv., 15 µL), PyBrOP (35 mg, 0.076 mmol, 2.0 equiv.) and stirred at rt. for 24 h. The reaction mixture was concentrated in vacuo and purified by chromatography (SiO_2, acetone/Hexanes 1:1) to yield dimethyl amide **62** (14 mg, 46%) as a colorless solid; R_f (0.31 acetone/Hexanes 1:1). MS (FAB) 807 [$(M+1)^+$, 100], 805 (60), 794 (60), 747 (40), 629 (40), 589 (62).

Example 63: Preparation of Compound 63:

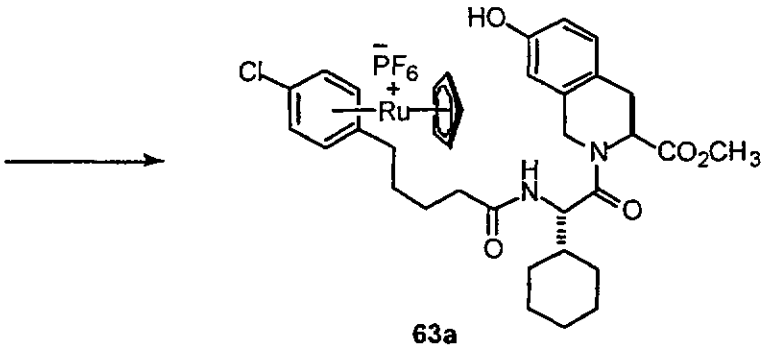


63

Step A



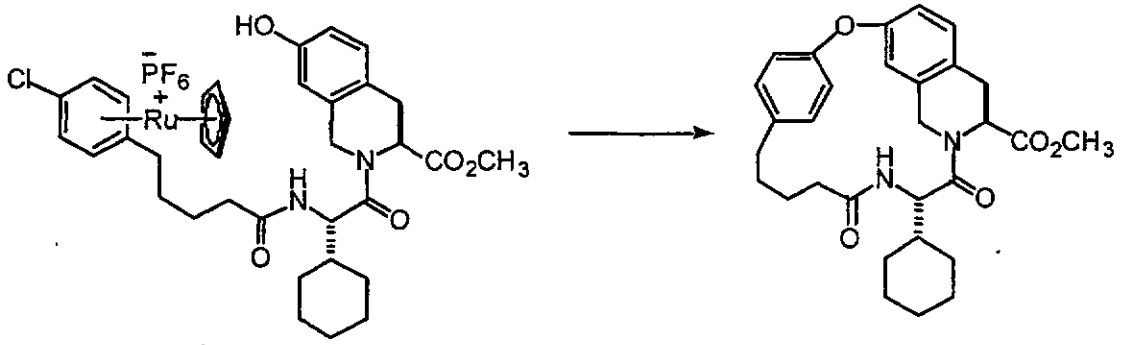
57d



63a

A solution of [CpRu(η^6- 4-chlorophenylpentanoic acid)]PF_6 (2.2 g, 4.0 mmol) in dry DMF (10 mL) was treated with HOBt (810 mg 5.99 mmol, 1.5 equiv.) and Hünigs base (2.58 g, 3.6 mL, 19.9 mmol, 5.0 equiv.) The reaction mixture was cooled to 0 °C and treated with EDCI (1.14 g, 6.0 mmol, 1.5 equiv.) The reaction mixture was stirred at 0 °C for 30 min. and the Tic-ammonium salt **57d** (1.60 g, 4.0 mmol, 1.0 equiv.) was added. The reaction mixture was stirred at rt. for 12 and the DMF was distilled out in vacuo. The residue was diluted with aq. HCl (1M, 100 mL) and extracted into CH_2Cl_2 (3x100 mL). The combined organic layers were extracted with aq. $NaHCO_3$ (1x40 mL), brine (100 mL), dried (Na_2SO_4), filtered, concentrated in vacuo to yield a brown solid **63a** (2.41 g, 75%) which was used for cyclization.

Step B



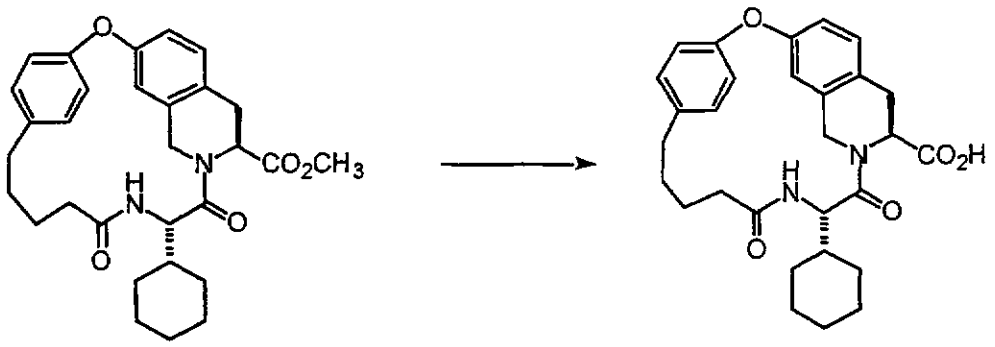
63a **63b**

A solution of Ruthenium complex **63a** (2.40 g, 2.8 mmol) in dry DMF (250 mL) was degassed with dry N_2 at rt. and Cs_2CO_3 (4.6 g, 14.0 mmol, 5.0 equiv.) was added and stirred at rt. for 14 h. The solvent DMF was distilled off and the residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were extracted, with aq. HCl (1M, 100 mL), $NaHCO_3$ (100 mL), brine(100 mL) dried (Na_2SO_4) filtered, concentrated in vacuo and dried in vacuum overnight to yield a brown solid

(1.9 g, 79%). It was used for photolytic removal of Ru without further purification. MS: (Electron spray): 671 $[(M-PF_6)^+, 40]$.

The cyclized compound from the previous step was dissolved in CH_3CN (60 mL) and filtered into a quartz tube. The solution was degassed and photolyzed in a Raynot (λ=350 nm) for 48 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography (SiO_2, acetone/Hexanes 3:7) to yield a tan colored solid **63b** (140 mg, 13%).; R_f: 0.73 (acetone/hexanes 3:7); MS: (FAB): 505 $[(M+1)^+, 80]$, 232 (40); HRMS calcd. for $C_{30}H_{37}N_2O_5$ $(M+1)^+$: 505.2702; Found: 505.2698.

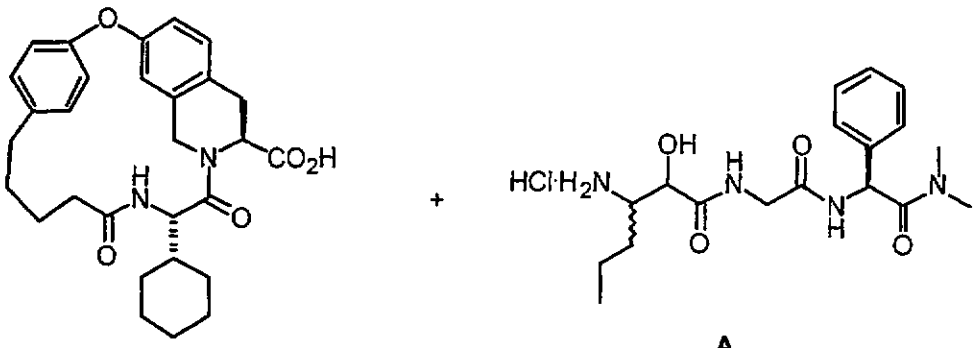
Step C



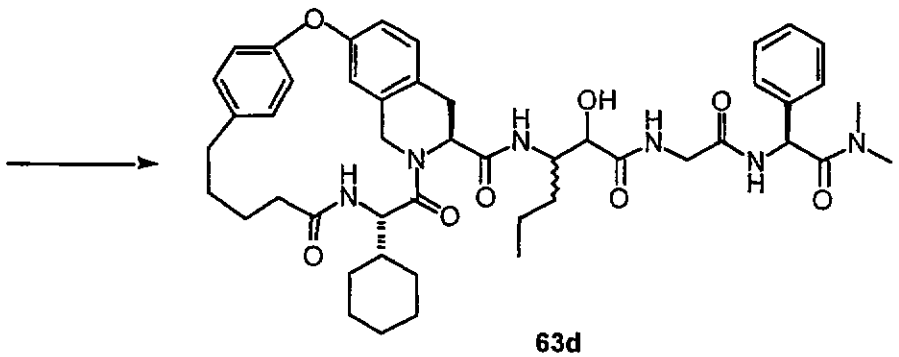
63b **63c**

A solution of methyl ester **63b** (235 mg, 0.5 mmol) of Tic-macrocycle in dioxane(10.0 mL), H_2O (10.0 mL), CH_3OH (50.0 mL) was treated with LiOH H_2O (41 mg, 1.0 mmol, 2.0 equiv.) and stirred at rt. for 3 h. The reaction mixture was acidified and (4M HCl in Dioxane). The reaction mixture was concentrated in vacuo and the remaining water was frozen and lyophilized to obtain a colorless solid **63c** used for coupling.

Step D



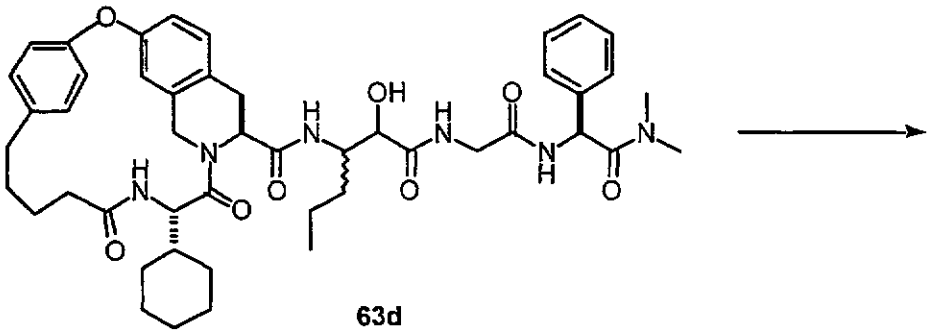
63c A



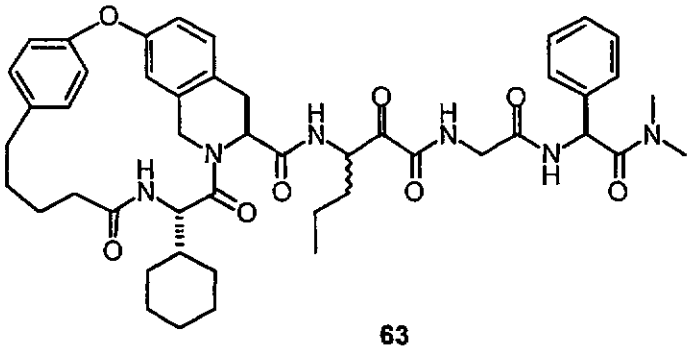
63d

A solution of the hydrolyzed acid **63c** (100 mg, 0.21. mmol) in dry DMF (4.0 mL) and CH_2Cl_2 (2.0 mL) was cooled to 0 °C and treated with HOOBt (53 mg, 0.32 mmol, 1.5 equiv.), Hünigs base (122 mg, 0.95 mmol, 4.5 equiv., 175 μL), EDCI (61.0 mg, 0.32 mmol, 1.5 equiv.) and stirred for 0.5 h and treated with the amine hydrochloride **A** (100 mg, 0.25 mmol, 1 equiv.). The reaction mixture was stirred at rt. for 16 h and concentrated in vacuo to remove DMF and CH_2Cl_2. The residue was diluted with aq. HCl (2M, 50 mL) and extracted with CH_2Cl_2 (3x50 mL) The combined organic layer was extracted with aq. HCl (1M, 100 mL), aq. NaOH (2M 100) brine, dried (Na_2SO_4) and concentrated in *vacuo*. The residue **63d** (72 mg) was oxidized without further purification.

Step E:



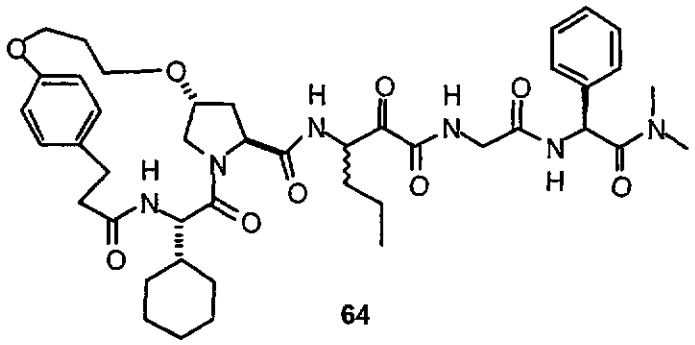
63d



63

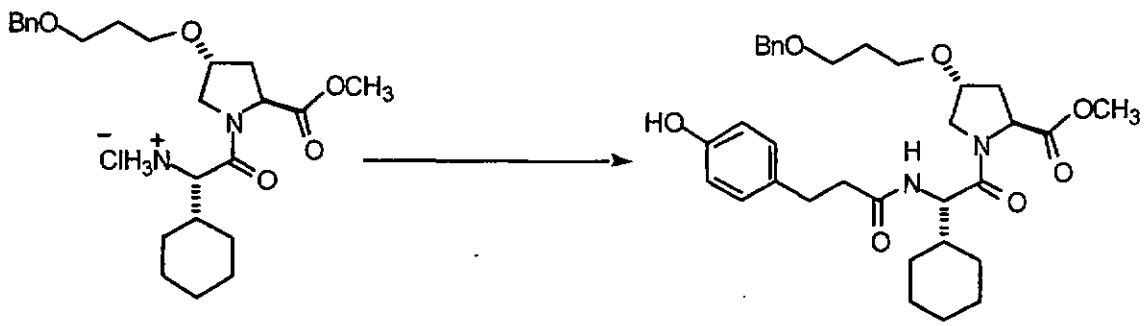
A solution of alcohol **63d** (72 mg, 0.86 μmol) in CH_2Cl_2 (5.0 mL) was treated with Dess-Martin reagent (125 mg, 0.28 mmol, 3.2 equiv.). The reaction mixture was stirred at rt. for 3 h and concentrated in vacuo and the residue was purified by chromatography (SiO_2, CH_3OH/CH_2Cl_2 1:19) to yield ketoamide **63** (11 mg, 15%) of a colorless solid; MS (FAB): 835 ($[M+1]^+$, 90), 490 (100).

Example 64: Preparation of Compound 64:



64

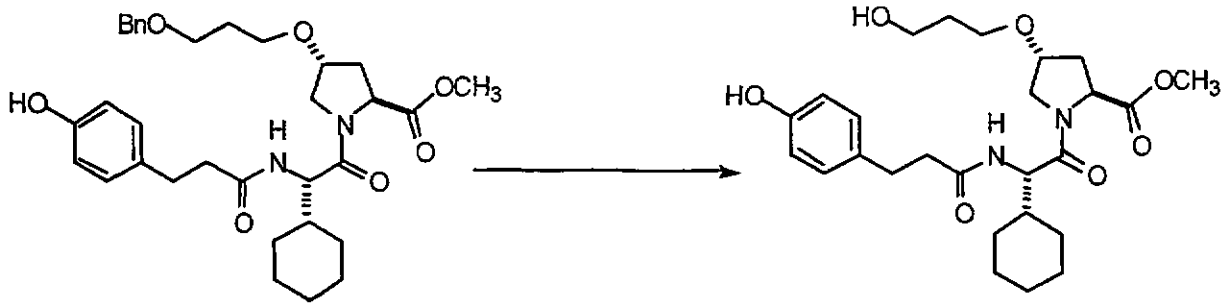
Step A



1f 64a

The desired product **64a** was obtained by the procedure described for Example 1, Step F. The material was purified by flash column chromatography using EtOAc/Hex (7:3) to yield **64a** in 80%.; ^{1}H NMR ($CDCl_3$, δ): 7.35-7.29 (m, 5 H), 7.02 (d, 2 H, *J*=8.4 Hz), 6.72 (d, 2 H, *J*= 6.9Hz) 6.01 (d, 1 H), 4.60 (t, 1 H), 4.52 (s, 1 H), 3.8-3.61(m, 2 H), 3.72 (s, 3 H), 3.54-3.51(m, 4 H), 2.83 (t, 2 H, *J*=7.5 Hz), 2.39 (t, 2 H, *J*= 8.1 Hz) 2.41-2.20 (m, 1 H), 2.05-1.83 (m, 1 H), 1.85-1.58 (m, 8 H), 1.26-1.24 (m, 5 H); ^{13}C NMR ($CDCl_3$, δ): 172.2, 171.9, 171.0, 154.4, 138.3, 132.2, 129.4, 128.4, 127.7, 127.6, 115.4, 73.0, 66.9, 66.2, 57.9, 54.9, 52.5, 52.3, 41.0, 38.5, 34.7, 30.8, 30.0, 29.4, 27.9, 26.1, 26.0, 25.9.

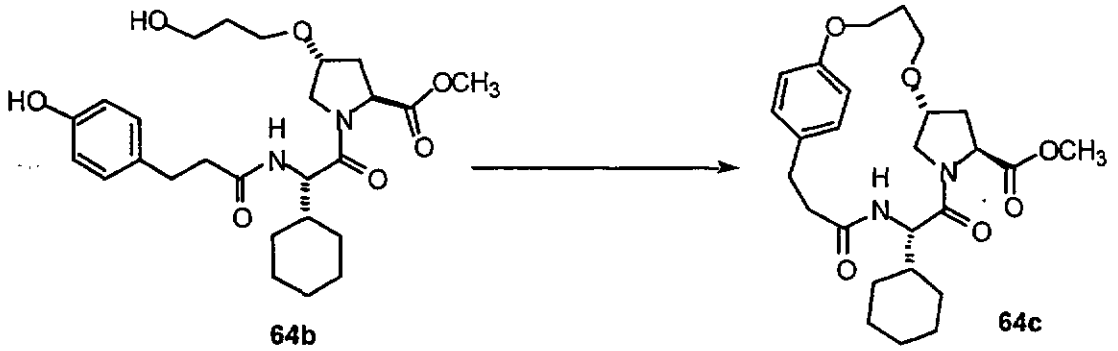
Step B



64a 64b

The desired product **64b** was obtained by the procedure described for Example 1, Step G. The product obtained after filtering off the catalyst was pure enough for next step.

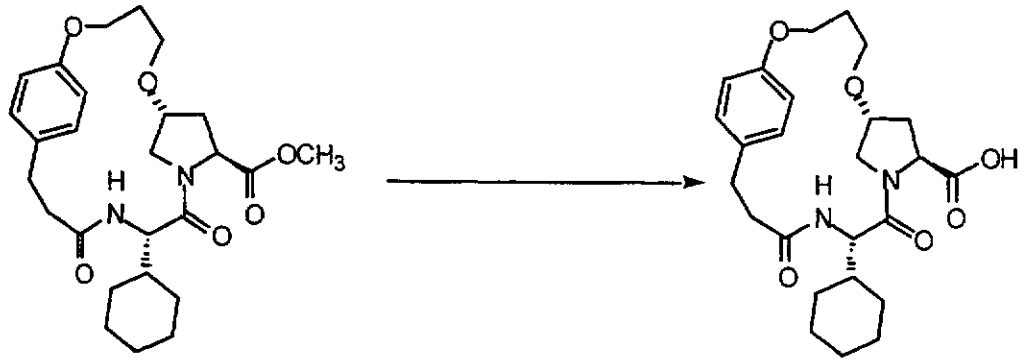
Step C



64b 64c

The desired product **64c** was obtained by the procedure described for Example 1, Step H. The crude reaction mixture was purified by SiO_2 gel chromatography (acetone/Hexanes 3:7) to yield **64c** (64 mg, 16%) as a colorless solid.; ^{13}C NMR ($CDCl_3$) 172.1, 171.1, 171.0, 157.7, 131.0 129.9, 114.3, 78.1, 64.7, 63.3, 58.7, 55.3, 52.2, 52.0, 42.1, 37.9, 36.1, 30.8, 30.7, 29.7, 28.7, 28.5, 26.2, 26.0; MS (FAB) 473 $(M+1)^+$, (100), 327 (20).

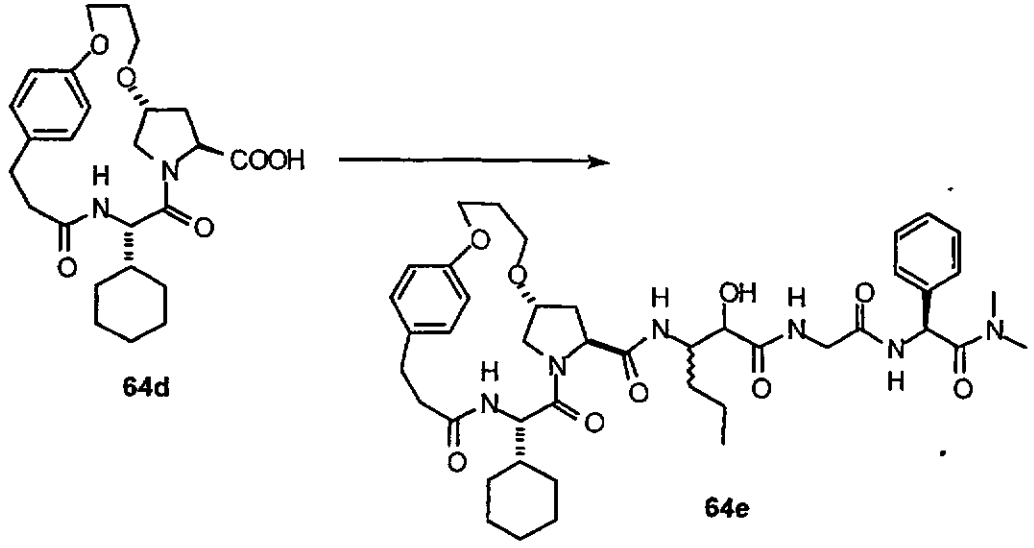
Step D



64c 64d

The acid was synthesized as described for Example 1, Step I in quantitative yield. The crude mixture after evaporation was directly used for the next step.

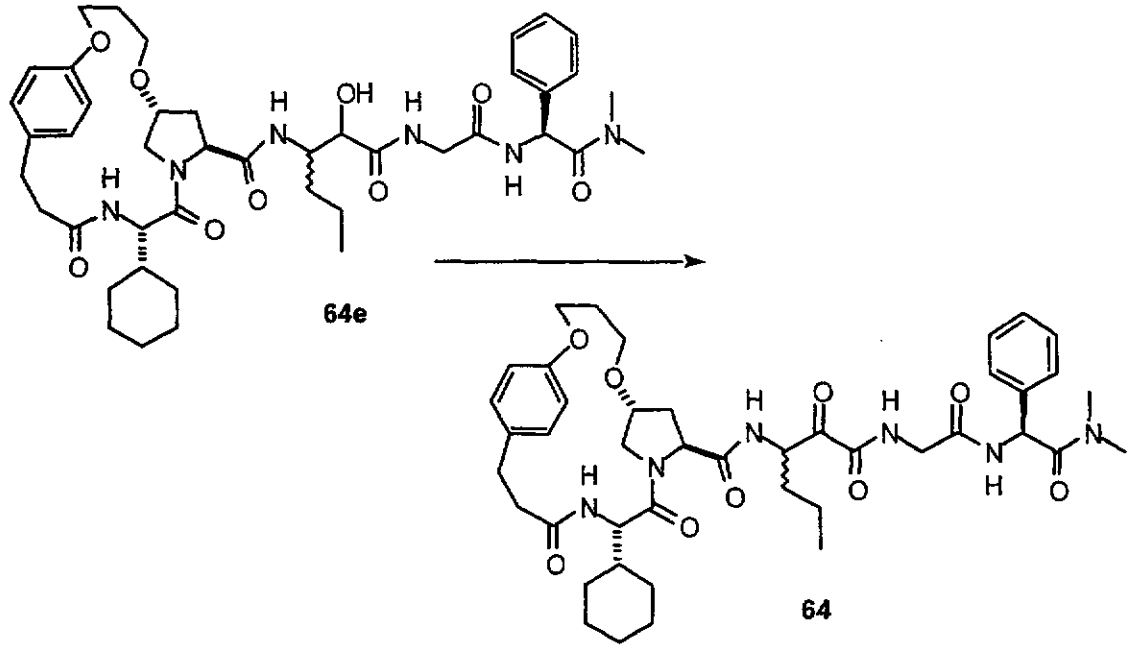
Step E



64d 64e

The expected product **64e** was synthesized as described earlier for the Example 1, Step J. The coupled material was used directly for the next step to synthesize **64**.

Step F

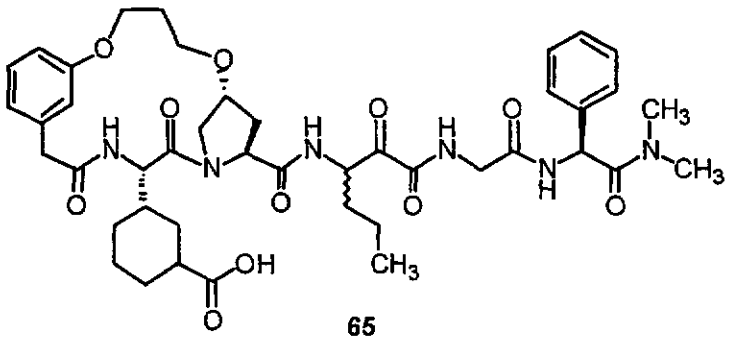


64e

64

The desired product is obtained by the oxidation protocol described previously for Example 1, Step K.

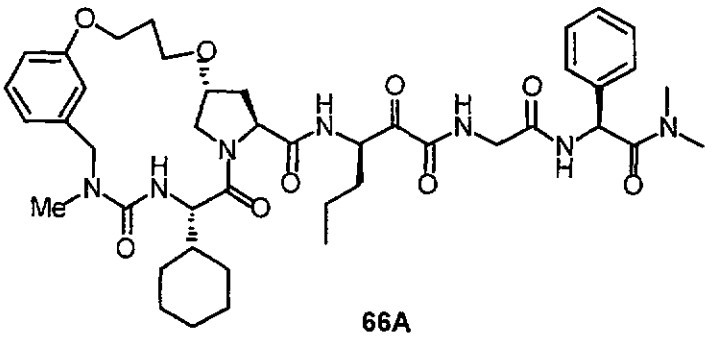
Example 65: Preparation of Compound 65:



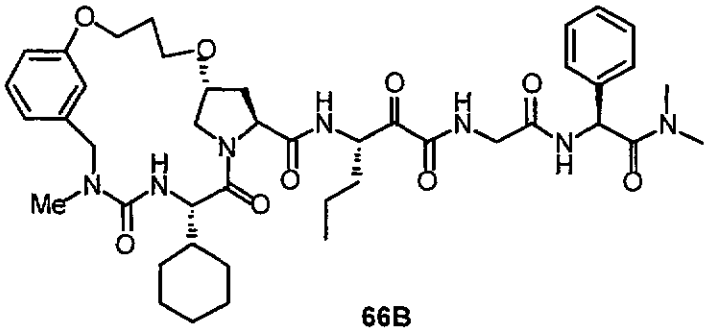
65

The synthesis of Example **65** was identical to the synthesis of Example **14** except the synthesis was initiated with 3-vinylbenzoic acid. The reduction of phenyl moiety was similar to Example 14, Step C. However, a mixture of diastereomers was obtained.

Example 66: Preparation of Compounds of Formulas 66A and 66B:



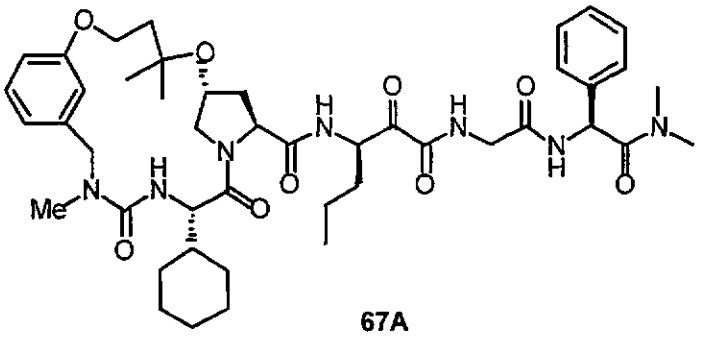
66A



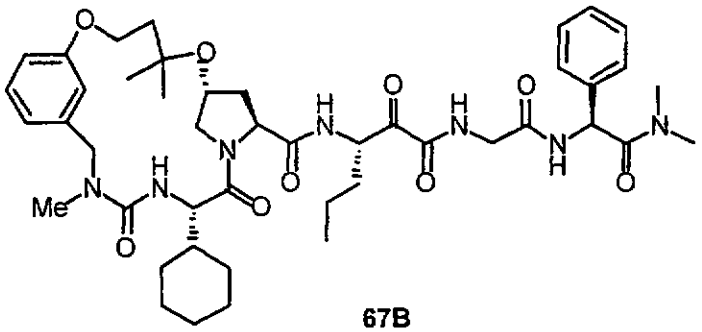
66B

The synthetic sequences for Example **66** followed that described for Example **54** using suitable starting materials with appropriate modifications. The isomers **66A** and **66B** were separated after oxidation using column chromatography. LCMS data: 818.2 $(M+H)^+$ (for **66A** and **66B**).

Example 67: Preparation of Compounds of Formulas 67A and 67B:



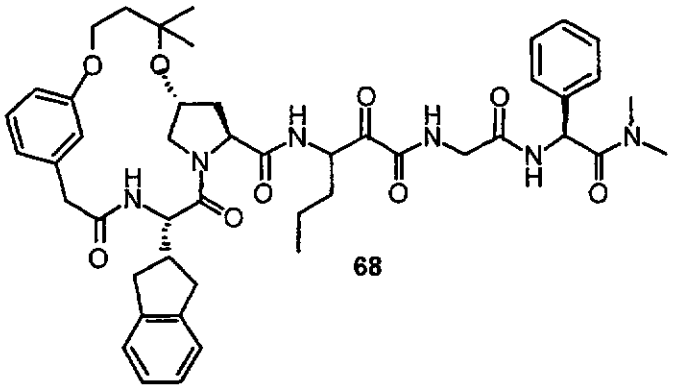
67A



67B

The synthetic sequences for Example **67** followed that described for Example **54** using suitable starting materials with appropriate modifications. The isomers **67A** and **67B** were separated after oxidation using column chromatography. HRMS (FAB) Calcd for $C_{45}H_{64}N_7O_9$: 846.4766 $(M+H)^+$. Found: 846.4782 (for **67A**) and 846.4774 (for **67B**).

Example 68: Preparation of Compound of Formula 68:

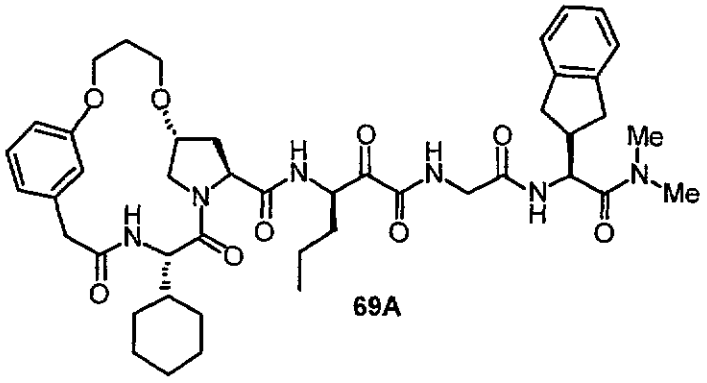


68

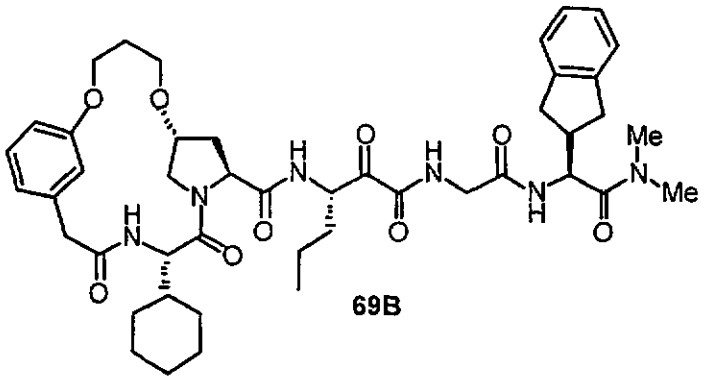
The synthetic sequences for Example **68** followed that described for Example **30** using suitable starting materials and appropriate modifications.

After oxidation the desired product **68** was obtained as a mixture of isomers using column chromatography. HRMS (FAB) Calcd for $C_{47}H_{59}N_6O_9$: 851.4344 $(M+H)^+$. Found: 851.4149.

Example 69: Preparation of Compounds of Formula 69A and 69B:



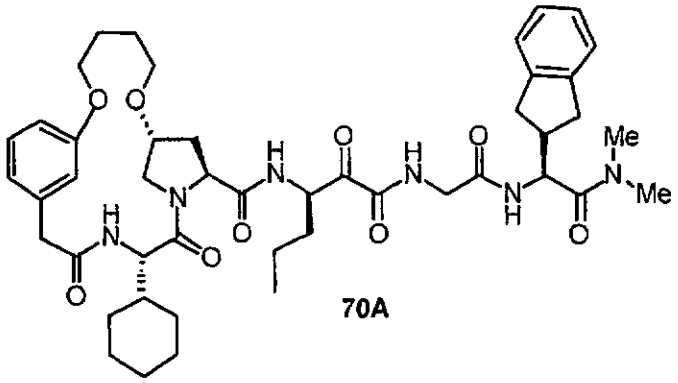
69A



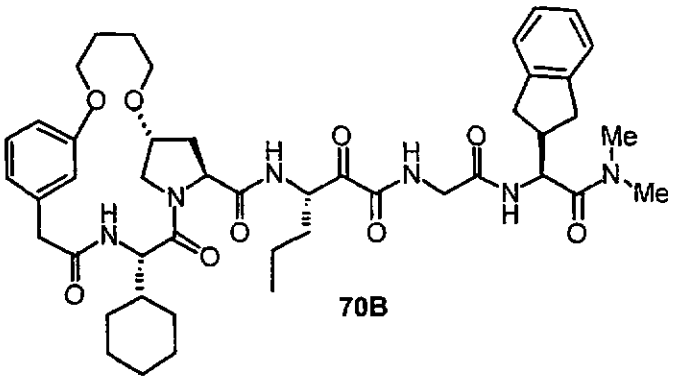
69B

The synthetic sequences for Example **69** followed that described for Example **1** using suitable starting materials and appropriate modifications. After oxidation the isomers **69A** and **69B** were separated using column chromatography. LCMS data: 829.2 $(M+H)^+$ (for **69A** and **69B**).

Example 70: Preparation of Compounds of Formula 70A and 70B:



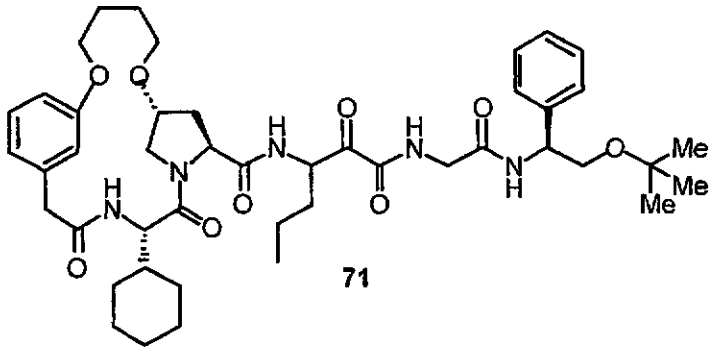
70A



70B

The synthetic sequences for Example **70** followed that described for Example **4** using suitable starting materials and appropriate modifications. After oxidation the isomers **70A** and **70B** were separated using column chromatography. LCMS data: 843.2 $(M+H)^+$ (for **70A** and **70B**).

Example 71: Preparation of Compound of Formula 71:

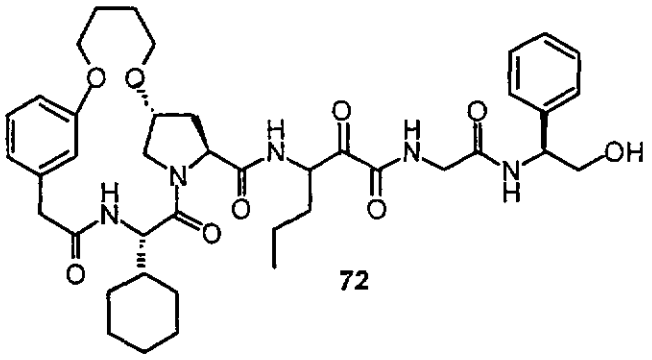


71

The synthetic sequences for Example **71** followed that described for Example **5** using suitable starting materials and appropriate modifications.

After oxidation the desired product **71** was obtained as a mixture of isomers using column chromatography. LCMS data: 818.2 $(M+H)^+$.

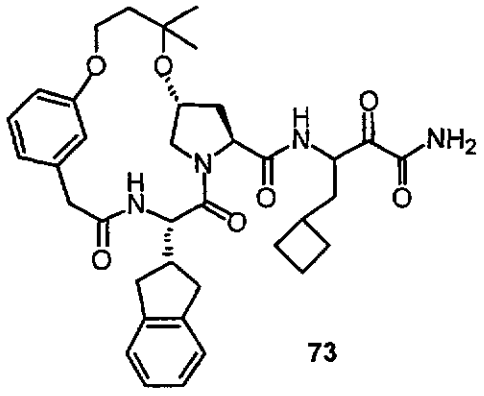
Example 72: Preparation of Compound of Formula 72:



72

The synthetic sequences for Example **72** followed that described for Example **6** using suitable starting materials and appropriate modifications. After oxidation the desired product **72** was obtained as a mixture of isomers using column chromatography. LCMS data: 762.2 $(M+H)^+$.

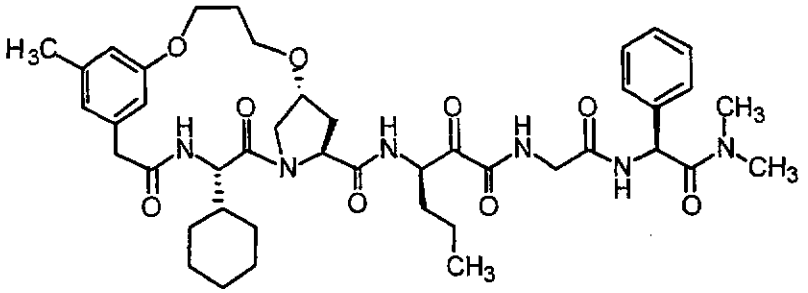
Example 73: Preparation of Compound of Formula 73:



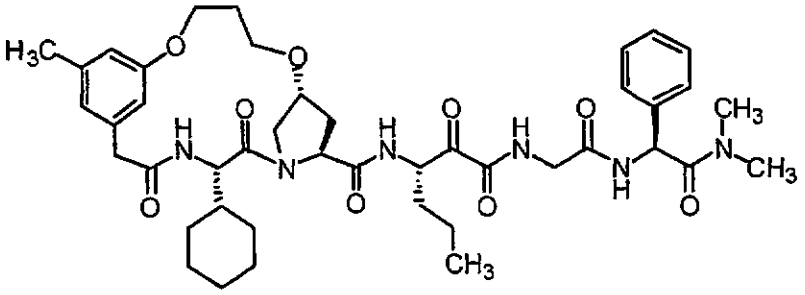
73

The synthetic sequences for Example **73** followed that described for Example **10** using suitable starting materials and appropriate modifications. After oxidation the desired product **73** was obtained as a mixture of isomers using column chromatography. LCMS data: 659.2 $(M+H)^+$.

Example 74: Preparation of compound 74A and 74B:



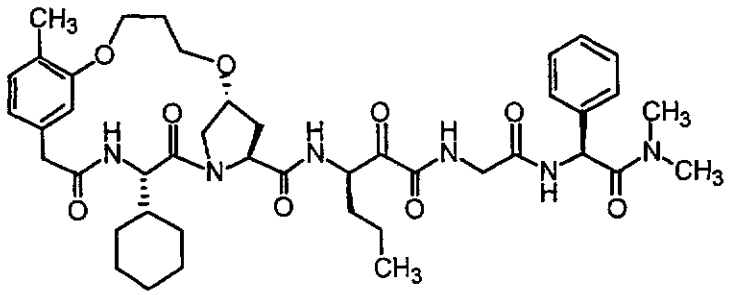
74A



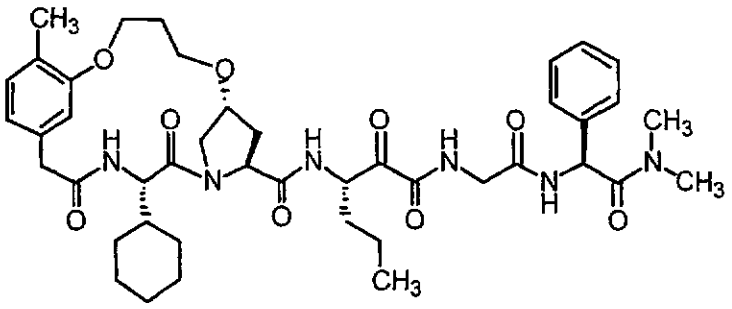
74B

The desired compounds **74A** and **74B** were prepared by the same method as described in the preparation of compounds **1A** and **1B** in Example 1, except that 5-methyl-3-hydoxy phenylacetic acid was used to substitute 3-hydroxy phenylacetic acid in Step F. LRMS $(M+H)^+$ *m/z* 803.1 [calcd for $C_{43}H_{58}N_6O_9$, 802.4].

Example 75: Preparation of compounds 75A and 75B:



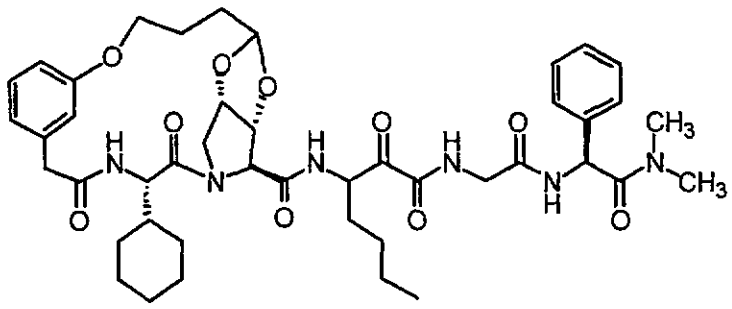
75A



75B

The desired compounds **75A** and **75B** were prepared by the same method as described in the preparation of compounds **1A** and **1B** in Example 1, except that 4-methyl-3-hydoxy phenylacetic acid was used to substitute 3-hydroxy phenylacetic acid in Step F. LRMS $(M+H)^+$ *m/z* 803.1 [calcd for $C_{43}H_{58}N_6O_9$, 802.4].

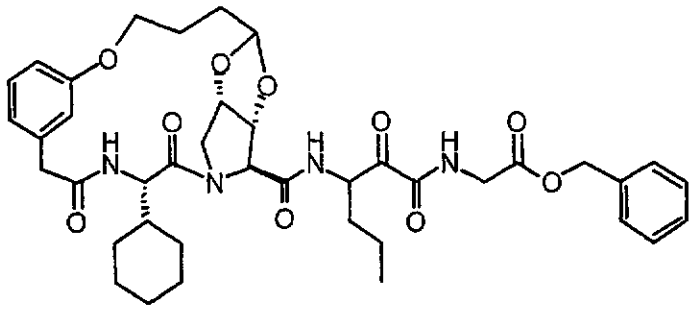
Example 76: Preparation of compound 76:



76

The desired compound **76** was prepared by the same method as described in the preparation of compounds **27A** and **27B** in Example 27, except that amine **E** was used to substitute amine **A** in Step J. LRMS $(M+H)^+$ *m/z* 831.1 [calcd for $C_{44}H_{58}N_6O_{10}$, 830.4].

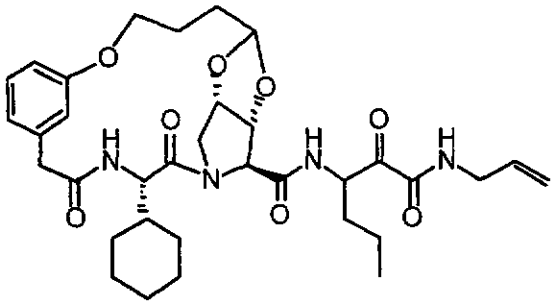
Example 77: Preparation of compound 77:



77

The desired compound **77** was prepared by the same method as described in the preparation of compounds **27A** and **27B** in Example 27, except that a different amine intermediate was used to substitute amine **A** in Step J. LRMS $(M+H)^+$ *m/z* 761.1 [calcd for $C_{41}H_{52}N_4O_{10}$, 760.4].

Example 78: Preparation of compound 78:

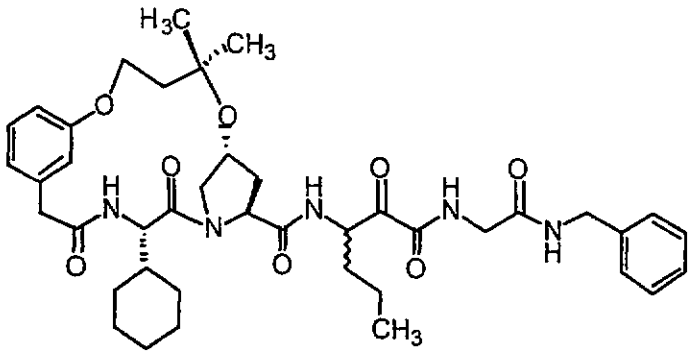


78

78

The desired compound **78** was prepared by the same method as described in the preparation of compounds **27A** and **27B** in Example 27, except that a different amine intermediate was used to substitute amine **A** in Step J. LRMS $(M+H)^+$ *m/z* 653.1 [calcd for $C_{35}H_{48}N_4O_8$, 652.4].

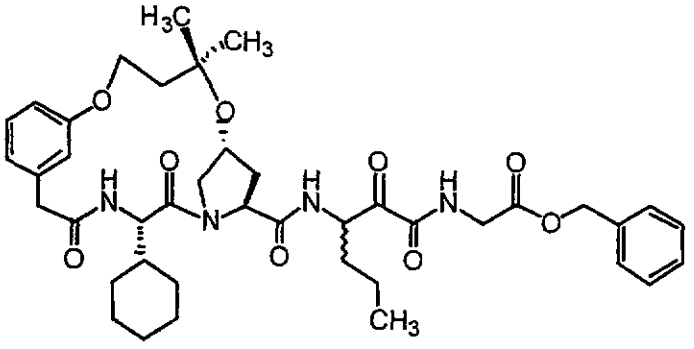
Example 79: Preparation of compound 79:



79

The desired compound **79** was prepared by the same method as described in the preparation of compound **30** in Example 30, except that a different amine intermediate was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 746.1 [calcd for $C_{41}H_{55}N_5O_8$, 745.4].

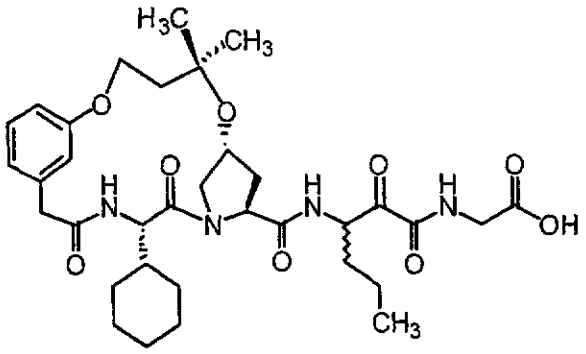
Example 80: Preparation of compound 80:



80

The desired compound **80** was prepared by the same method as described in the preparation of compound **30** in Example 30, except that a amine **D** was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 746.1 [calcd for $C_{41}H_{55}N_5O_8$, 745.4].

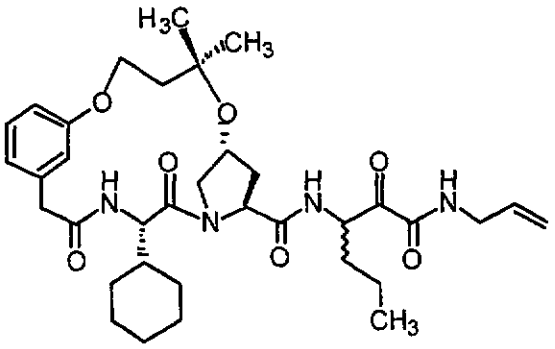
Example 81: Preparation of compound 81:



81

The desired compound **81** was prepared by the same method as described in the preparation of intermedaite **A**, Step 5. LRMS $(M+H)^+$ *m/z* 657.1 [calcd for $C_{34}H_{48}N_4O_9$, 656.3].

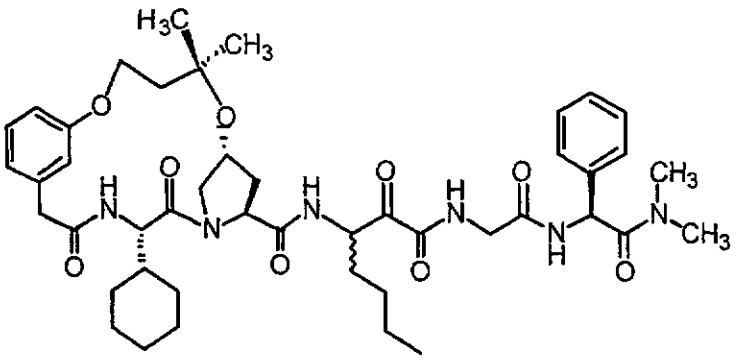
Example 82: Preparation of compound 82:



82

The desired compound **82** was prepared by the same method as described in the preparation of compound **30** in Example 30, except that a different amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 639.1 [calcd for $C_{35}H_{50}N_4O_7$, 638.4].

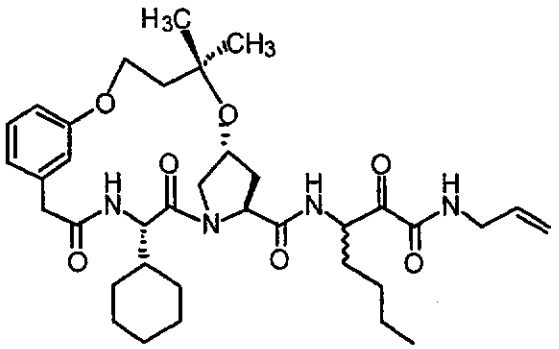
Example 83: Preparation of compound 83:



83

The desired compound **83** was prepared by the same method as described in the preparation of compound **30** in Example 30, except that amine **E** was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 831.1 [calcd for $C_{45}H_{52}N_6O_9$, 830.5].

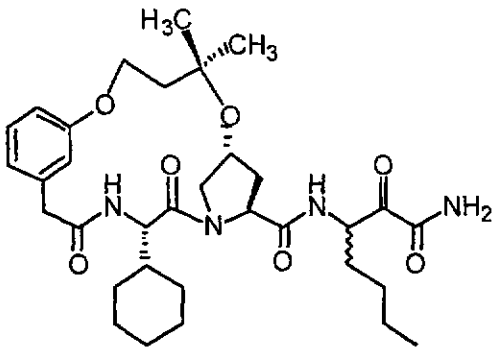
Example 84: Preparation of compound 84:



84

The desired compound **84** was prepared by the same method as described in the preparation of compound **30** in Example 30, except that an appropriate amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 653.1 [calcd for $C_{36}H_{52}N_4O_7$, 652.4].

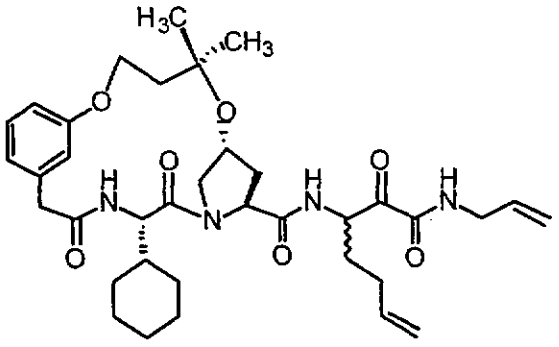
Example 85: Preparation of compound 85:



85

The desired compound **85** was prepared by the same method as described in the preparation of compound **30** in Example 30, except that an appropriate amine was used to substitute amine **A** in Step I, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 613.1 [calcd for $C_{33}H_{48}N_4O_7$, 612.4].

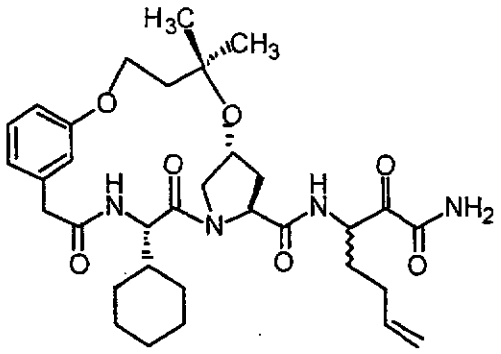
Example 86: Preparation of compound 86:



86

The desired compound **86** was prepared by the same method as described in the preparation of compound **30** in Example 30, except that an appropriate amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 651.1 [calcd for $C_{36}H_{50}N_4O_7$, 650.4].

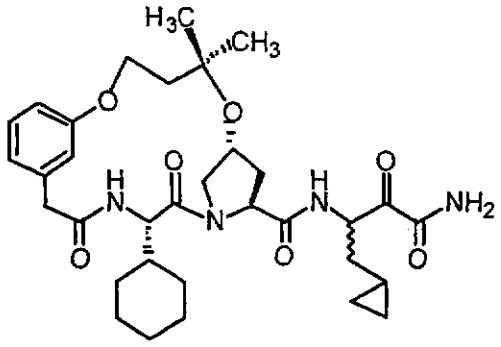
Example 87: Preparation of compound 87:



87

The desired compound **87** was prepared by the same method as described in the preparation of compound **30** in Example 30. Except that an appropriate amine was used to substitute amine **A** in Step I, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 611.1 [calcd for $C_{33}H_{46}N_4O_7$, 610.3].

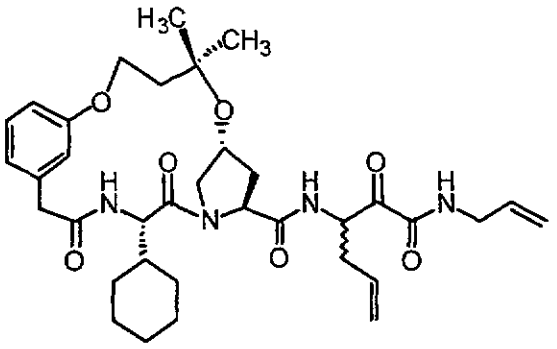
Example 88: Preparation of compound 88:



88

The desired compound **88** was prepared by the same method as described in the preparation of compound **30** in Example 30. Except that an appropriate amine was used to substitute amine **A** in Step I, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 611.1 [calcd for $C_{33}H_{46}N_4O_7$, 610.3].

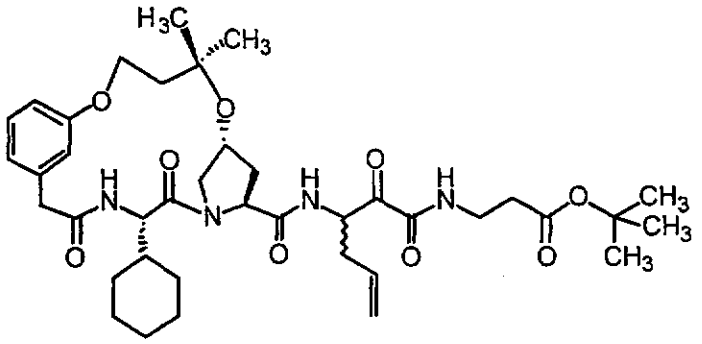
Example 89: Preparation of compound 89:



89

The desired compound **88** was prepared by the same method as described in the preparation of compound **30** in Example 30. Except that an appropriate amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 637.1 [calcd for $C_{35}H_{48}N_4O_7$, 636.4].

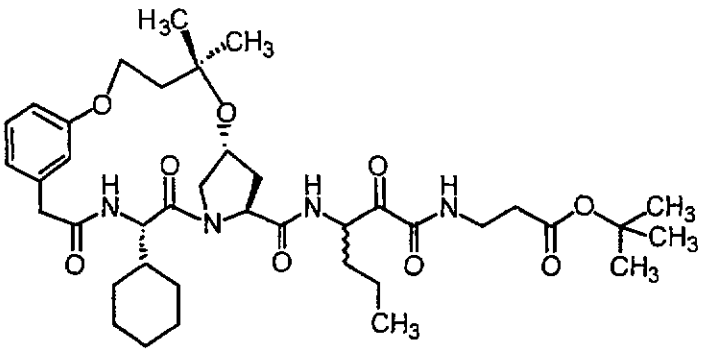
Example 90: Preparation of compound 90:



90

The desired compound **90** was prepared by the same method as described in the preparation of compound **30** in Example 30. Except that an appropriate amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 725.1 [calcd for $C_{39}H_{56}N_4O_9$, 724.4].

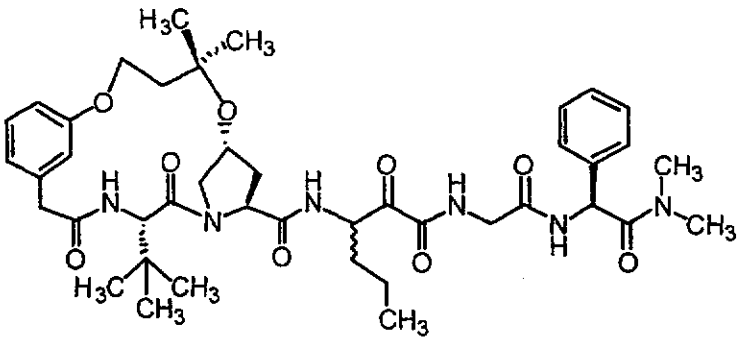
Example 91: Preparation of compound 91:



91

The desired compound **91** was prepared by the same method as described in the preparation of compound **30** in Example 30. Except that an appropriate amine was used to substitute amine **A** in Step I. . LRMS $(M+H)^+$ *m/z* 727.1 [calcd for $C_{39}H_{58}N_4O_9$, 726.4].

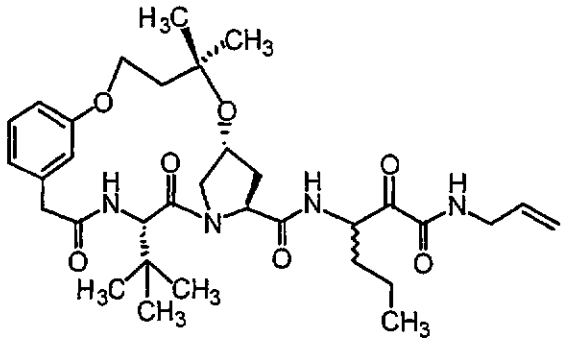
Example 92: Preparation of compound 92:



92

The desired compound **92** was prepared by the same method as described in the preparation of compound **30** Example 30, except that Boc-*tert*-butylglycine was used to substitute Boc-cyclohexylglycine in Step C. LRMS $(M+H)^+$ *m/z* 791.1 [calcd for $C_{42}H_{58}N_6O_9$, 790.4].

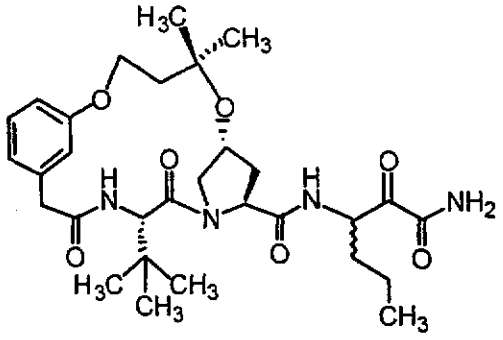
Example 93: Preparation of compound 93:



93

The desired compound **93** was prepared by the same method as described in the preparation of compound **92** in Example 92. Except that an appropriate amine was used to substitute amine **A**. LRMS $(M+H)^+$ *m/z* 613.1 [calcd for $C_{33}H_{48}N_4O_7$, 612.4].

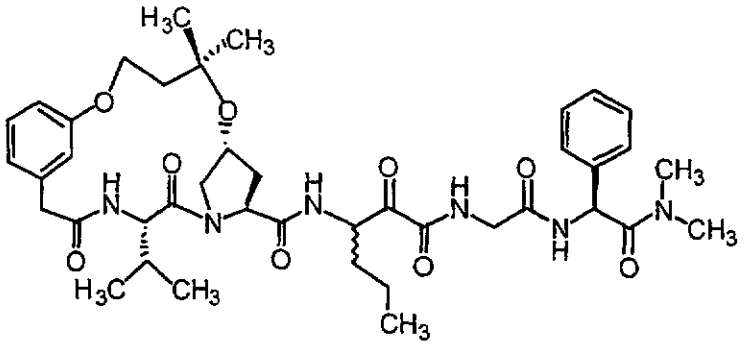
Example 94: Preparation of compound 94:



94

The desired compound **94** was prepared by the same method as described in the preparation of compound **92** in Example 92. Except that an appropriate amine was used to substitute amine **A**, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 573.1 [calcd for $C_{30}H_{44}N_4O_7$, 572.3].

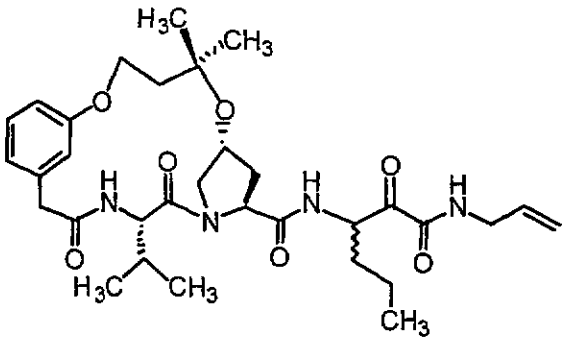
Example 95: Preparation of compound 95:



95

The desired compound **95** was prepared by the same method as described in the preparation of compound **30** Example 30, except that Boc-valine was used to substitute Boc-cyclohexylglycine in Step C. LRMS $(M+H)^+$ *m/z* 777.1 [calcd for $C_{41}H_{56}N_6O_9$, 776.4].

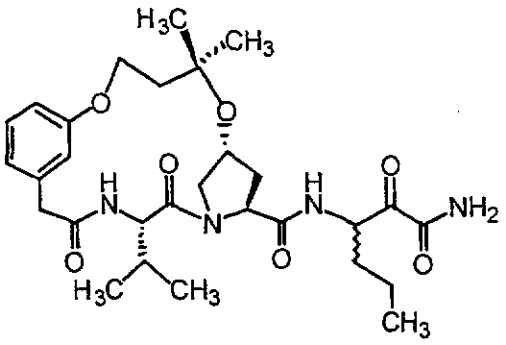
Example 96: Preparation of compound 96:



96

The desired compound **96** was prepared by the same method as described in the preparation of compound **95** in Example 95. Except that an appropriate amine was used to substitute amine **A**. LRMS $(M+H)^+$ *m/z* 599.1 [calcd for $C_{32}H_{46}N_4O_7$, 598.3].

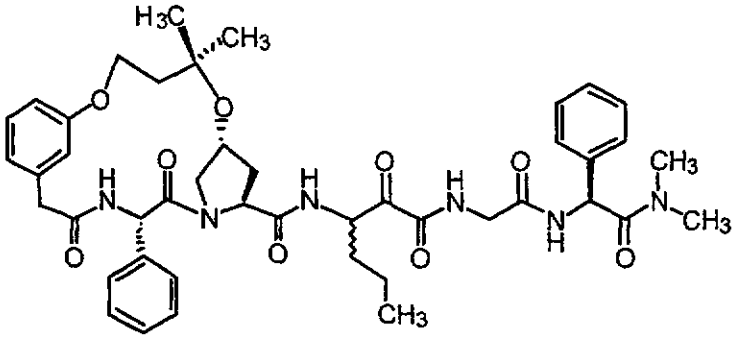
Example 97: Preparation of compound 97:



97

The desired compound **97** was prepared by the same method as described in the preparation of compound **95** in Example 95. Except that an appropriate amine was used to substitute amine **A**, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 559.1 [calcd for $C_{29}H_{42}N_4O_7$, 558.3].

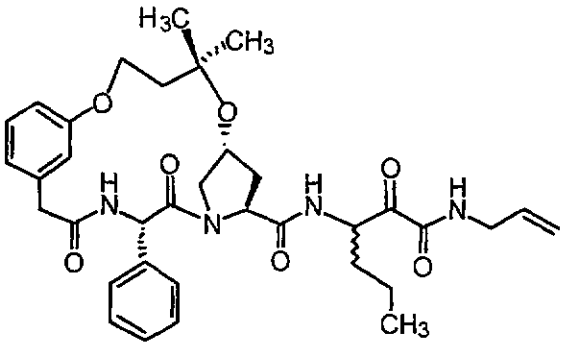
Example 98: Preparation of compound 98:



98

The desired compound **98** was prepared by the same method as described in the preparation of compound **30** Example 30, except that Boc-phenylglycine was used to substitute Boc-cyclohexylglycine in Step C. LRMS $(M+H)^+$ *m/z* 811.1 [calcd for $C_{44}H_{54}N_6O_9$, 810.4].

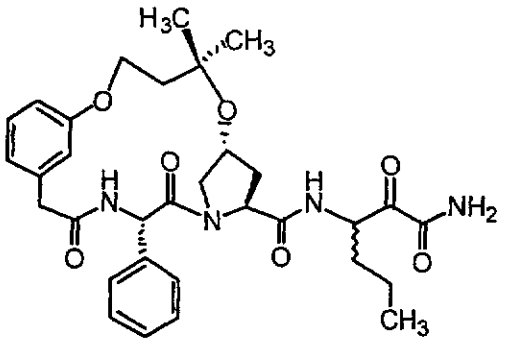
Example 99: Preparation of compound 99:



99

The desired compound **99** was prepared by the same method as described in the preparation of compound **98** in Example 98. Except that an appropriate amine was used to substitute amine **A**. LRMS $(M+H)^+$ *m/z* 633.1 [calcd for $C_{35}H_{44}N_4O_7$, 632.3].

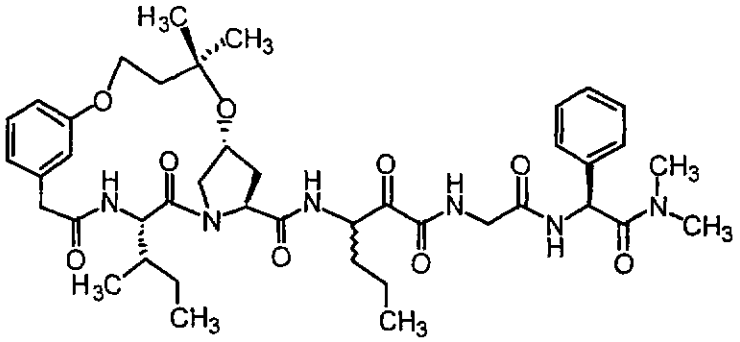
Example 100: Preparation of compound 100:



100

The desired compound **100** was prepared by the same method as described in the preparation of compound **98** in Example 98. Except that an appropriate amine was used to substitute amine **A**, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 593.1 [calcd for $C_{35}H_{40}N_4O_7$, 592.3].

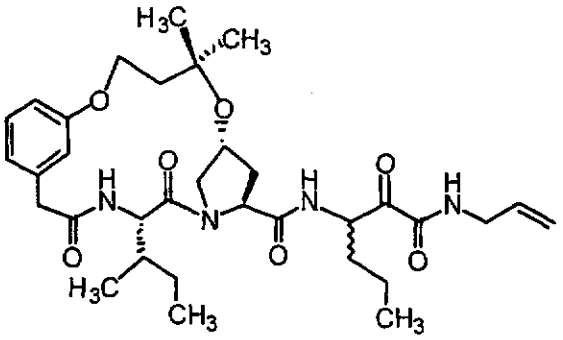
Example 101: Preparation of compound 101:



101

The desired compound **101** was prepared by the same method as described in the preparation of compound **30** Example 30, except that Boc-isoleucine was used to substitute Boc-cyclohexylglycine in Step C. LRMS $(M+H)^+$ *m/z* 791.1 [calcd for $C_{42}H_{56}N_6O_9$, 790.4].

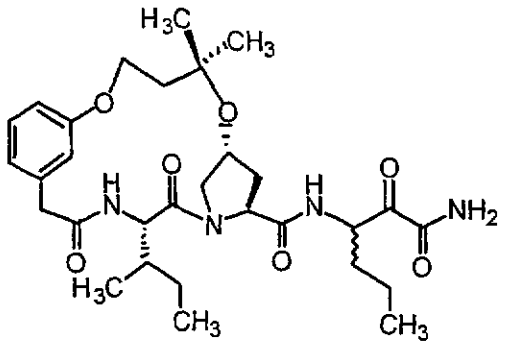
Example 102: Preparation of compound 102:



102

The desired compound **102** was prepared by the same method as described in the preparation of compound **101** in Example 101. Except that an appropriate amine was used to substitute amine **A**. LRMS $(M+H)^+$ *m/z* 613.1 [calcd for $C_{33}H_{48}N_4O_7$, 612.4].

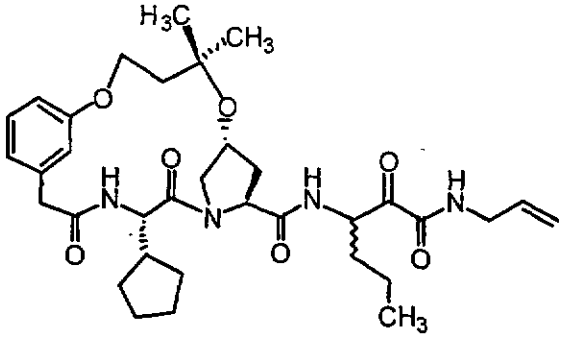
Example 103: Preparation of compound 103:



103

The desired compound **103** was prepared by the same method as described in the preparation of compound **101** in Example 101. Except that an appropriate amine was used to substitute amine **A**, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 573.1 [calcd for $C_{30}H_{44}N_4O_7$, 572.3].

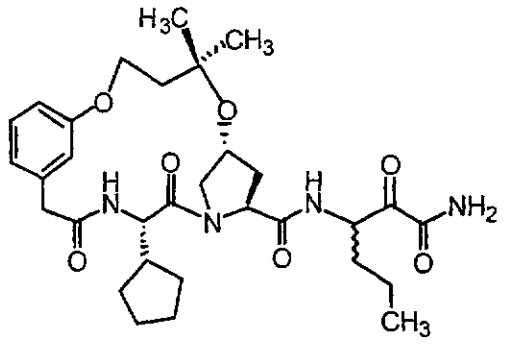
Example 104: Preparation of compound 104:



104

The desired compound **104** was prepared by the same method as described in the preparation of compound **30** Example 30, except that Boc-cyclopentylglycine was used to substitute Boc-cyclohexylglycine in Step C, and that an appropriate amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 625.1 [calcd for $C_{34}H_{48}N_4O_7$, 624.4].

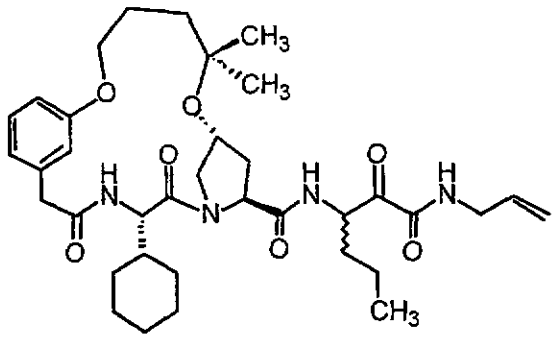
Example 105: Preparation of compound 105:



105

The desired compound **105** was prepared by the same method as described in the preparation of compound **104** in Example 104. Except that an appropriate amine was used to substitute amine **A**, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 585.1 [calcd for $C_{31}H_{44}N_4O_7$, 584.3].

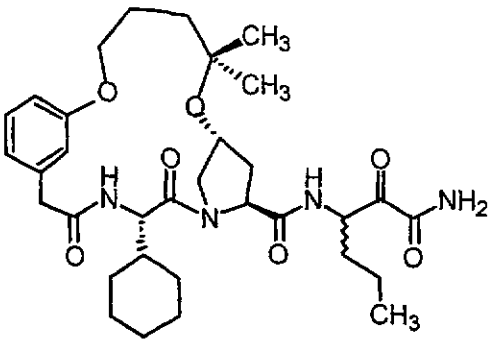
Example 106: Preparation of compound 106:



106

The desired compound **106** was prepared by the same method as described in the preparation of compound **30** Example 30 with the following exceptions: (a). 5-benzyloxy-2-methyl-1-pentene was used to substitute 4-benzyloxy-2-methyl-1-butene in Step A; (b). an appropriate amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 653.1 [calcd for $C_{36}H_{52}N_4O_7$, 652.4].

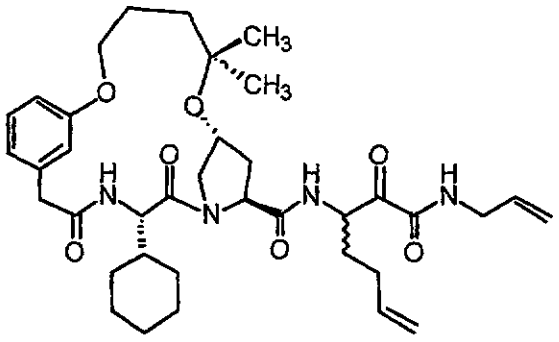
Example 107: Preparation of compound 107:



107

The desired compound **107** was prepared by the same method as described in the preparation of compound **106** in Example 106. Except that an appropriate amine was used to substitute amine **A** in Step I, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 613.1 [calcd for $C_{33}H_{48}N_4O_7$, 612.4].

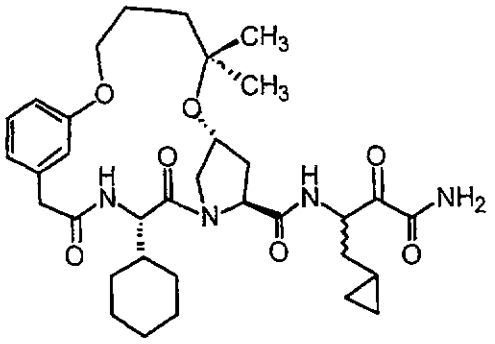
Example 108: Preparation of compound 108:



108

The desired compound **108** was prepared by the same method as described in the preparation of compound **106** Example 106, with the exception that an appropriate amine was used to substitute amine **A** in Step I. LRMS $(M+H)^+$ *m/z* 665.1 [calcd for $C_{37}H_{52}N_4O_7$, 664.4].

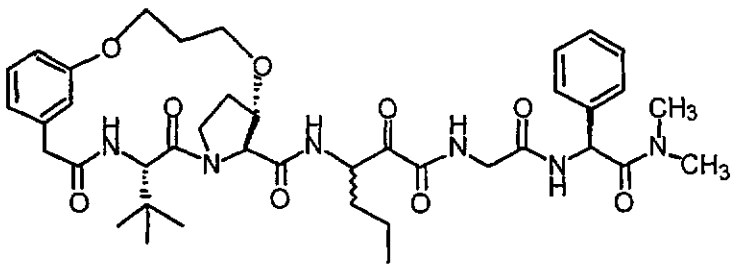
Example 109: Preparation of compound 109:



109

The desired compound **109** was prepared by the same method as described in the preparation of compound **106** Example 106, with the exception that an appropriate amine was used to substitute amine **A** in Step I, and that the oxidation was performed according the procedure in Example **10**, Step J. LRMS $(M+H)^+$ *m/z* 625.1 [calcd for $C_{34}H_{48}N_4O_7$, 624.4].

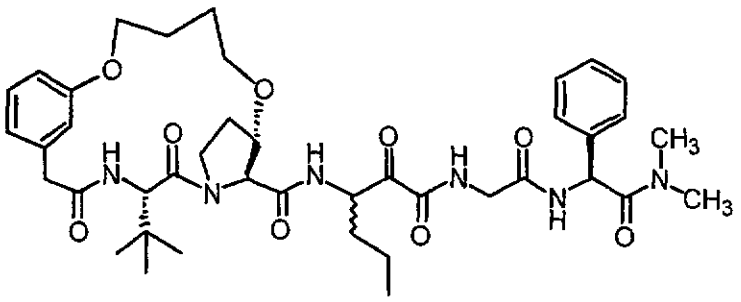
Example 110: Preparation of compound 110:



110

The desired compound **110** was prepared by the same method as described in the preparation of compounds **1A** and **1B**, Example 1, except that Boc-3-hydroxyproline was used to substitute proline **1a** in Step A, and that Boc-*tert*-butylglycine was used to substitute Boc-cyclohexylglycine in Step D. LRMS $(M+H)^+$ *m/z* 763.1 [calcd for $C_{40}H_{54}N_6O_9$, 762.4].

Example 111: Preparation of compound 111:



111

The desired compound **111** was prepared by the same method as described in the preparation of compounds **4A** and **4B** in Example 4, except that Boc-3-hydroxyproline was used to substitute proline **1a** in Step A, and that Boc-*tert*-butylglycine was used to substitute Boc-cyclohexylglycine in Step D. LRMS $(M+H)^+$ *m/z* 777.1 [calcd for $C_{41}H_{56}N_6O_9$, 776.4].

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 (K_i) 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 K_i value.

The obtained K_i values for the various macrocycles of the present invention are given in the afore-mentioned **Table 1** wherein the compounds have been arranged in the order of ranges of K_i values. 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.

Cell Bioassay Method: The cell bioassays for the HCV serine protease was performed on the inventive compounds by following the procedure described by S. Agrawal *et al*, "Development and Characterization of Hepatitis C Virus Serine Protease Cell-based Trans-Cleavage Assay", *Hepatology* Supplement to Volume 30 (No. 4, Part 2, October 1999), *Abstract No. 615* (Proceedings of AASLD 50th Annual Meeting, Dallas, Texas, November 5-9, 1999), the disclosure of which is incorporated herein by reference. The assay was performed in HeLa/Huh7 cells that were co-transfected with a plasmid that expresses a reporter protein substrate containing the NS5A/5B cleavage recognition sequence and an 1BNS4A $_{21-32}$ GS-GSNS $_{3-81}$ I17K expression vector and YFPn1 as a internal standard protein to control cytotoxicity. Protease activity was measured by SDS-PAGE of total cell lysates followed by Western blot detection using a monoclonal antibody directed against the reporter substrate. Quantitation of substrate cleavage was performed by scanning the immunoblot on the phosphoimager.

Materials:

Plasmid DNAs

pBFP-5A/5B-GFP: The reporter gene that expresses the substrate encodes a fusion protein comprised of an N' terminal blue fluorescent protein (BFP) domain and a C' terminal green fluorescent protein (GFP) domain, separated by a 25 amino acids derived from the NS5A/5B cleavage recognition sequence. Both GFP and BFP are essentially homologous autofluorescent proteins that emit green or blue light, respectively, when excited by UV light of the appropriate wavelength. Four amino acid substitutions in the chromophore of GFP alter the emission wavelength and convert the protein to BFP.

The substrate and the resulting GFP and BFP products can be detected in cell lysates by immunologic methods using a monoclonal antibody that recognizes both proteins.

The BFP-5A/5B-GFP reporter gene contains the BFP and GFP autofluorescent protein coding sequences (Quantum Biotechnologies, Inc., Montreal, Canada) separated by the NS5A/5B cleavage recognition sequence, cloned between the Nhe I and Bam HI restriction endonuclease sites of the pQBI25 cloning vector (Quantum Biotechnologies, Inc.). Expression of the fusion protein is under the control of the CMV IE promoter-enhancer. The bovine growth hormone p (A) sequence of the vector provides the polyadenylation signal for the mRNA. The NS5A/5B cleavage sequence is: SSGADTEDVVCCSMSYTWTGALVTP. DNA sequencing was used to validate the clone.

P1BOO2: 1bNS4A21-32GS-GS NS 3-81 I17K: The subtype 1b protease was cloned as an Xba1/Not1 fragment behind the CMV promoter in vector pC1neo.

YFPn1: YFPn1 was purchased from CLONTECH (Palo Alto, California). Addition of third plasmid to the transfection supplies an internal standard protein to control for cytotoxicity and does not affect percentage of protease cleavage.

Plasmid DNAs were maintained and propagated in DH5α cells (obtained from LifeTechnologies) in LB medium under the appropriate antibiotic selection, and purified using QIAfilter Plasmid Kits (Qiagen, Valencia, California).

Cell Culture:

HeLa cells were maintained and propagated in Eagle's Minimum Essential Media (EMEM; BioWhittaker, Walkersville, Maryland) supplemented with 10% fetal calf serum (FCS), 2 mM glutamine, and 100 u/ml penicillin-streptomycin (BioWhitaker), 2% $NaHCO_3$.

Huh7 cells were maintained and propagated in Dulbecco's Modified Eagle's medium (DMEM; BioWhittaker) supplemented with 10% fetal calf serum (FCS), 100u/ml penicillin-streptomycin (BioWhitaker) and 5 ml NEAA(100x; BioWhittaker)/L .

SOP Procedure

Day preceding transfection:

HeLa cells were seeded in 24 well plates (Falcon 3047 plates) at a density of 6 x 10^4 cells/well and grown overnight at 37^{0}C in a 5% CO2 incubator.

Day of transfection:

Plasmid DNAs were diluted to a final concentration of 0.05 µg/µl in nuclease free water (Promega, Madison, Wisconsin, cat # P119C). 0.75 µg BFP-5A/5B-GFP was combined and mixed with 0.175 µg P1B002 (0.23X) and 0.02µg of YFPn1. The DNAs were brought to a final volume of 60 µl with EMEM lacking FBS, glutamine, and antibiotics. A ratio of 5 µl volumes of SuperFect Reagent (Qiagen, cat # 301305) per total µgs of DNA was added and the mixture vortexed about 10 seconds and incubated 10 min. at room temperature to allow complex formation.

While complex formation was taking place, growth medium from cell culture plates was aspirated and cells washed 1X with 1 ml PBS without Ca^{2+}, Mg^{2+} (BioWhitaker). 350 µl EMEM (supplemented with appropriate suplements-compleat medium) was added to the tube containing the transfection complexes and the mixture pipetted up and down 2-3 times. Total volume was transferred to one well of the 24 well culture plate. The HeLa cells were incubated with the transfection complexes for about 3 hr. at 37^{0}C and 5% CO2. The media containing the transfection complexes was removed from the cells by aspiration.

The cells were washed once in about 1 ml PBS, the PBS was aspirated and 495 µl of complete EMEM was added followed by 5 µl compound/well. The cells were incubated 22-24 hr. at 37^{0}C and 5% CO2.

Preparation of Cell Lysates

The medium from each well was aspirated and washed once 1x with DPBS. Cells were harvested in 100 µl of 1x Tris-SDS-BME sample buffer (OWL separation system, Portsmouth, New Hampshire, cat # ER33) and transferred to microcentrifuge tubes. It was then boiled 3-5 min. to lyse cells. Loading was done at 10 µl/well on SDS-PAGE gel. The lysates were resolved by electrophoresis on 10 cm x 10 cm 12.5% SDS-PAGE (Owl Scientific, cat #

OG-0125B) run at 30 mamp in Tris-Glycine-SDS buffer (Owl Scientific). Prior to use, PVDF membrane (Immobilon-P; .45µm pore size; Millipore, Bedford, Massachusetts) was soaked in 100% methanol for 10 seconds and then the blot was placed in distilled water. The proteins were transferred to PVDF filter membranes (0.45µm, Millipore) at
108 mamp per gel for 90 minutes using a semi-dry electroblotter.

Detection of Proteins by ECF Western Blot (Amersham Pharmacia Biotech, Little Chalfont, England), catalog #RPN 5780). The PVDF filter membranes were blocked by 5% blocking reagent (from kit) in ~10 ml PBS containing 0.05% Tween 20, pH 7.4 (Sigma Chemicals, St. Louis, Missouri, cat # 3563) for overnight at 2-4°C in refrigerator. The next day, the membranes were rinsed briefly twice with TPBS containing 0.05% Tween 20 washing buffer, then washed three times each time 5 min. in PBS containing 0.05% Tween 20, pH 7.4. The membranes were incubated in 12 mls of a 1:3000 dilution of anti-GFP monoclonal antibody for 30 minutes (Clontech, Palo Alto, California) in PBS containing 0.05% Tween 20, pH7.4 while at the same time 1% BSA (Albumin, bovine cat # A-2153 from Sigma) was added to reduce background. The membranes were washed briefly twice with TPBS, then thrice, for 5 min. each time, in TPBS washing buffer. The membranes were incubated in 12 mls of a 1:600 dilution anti fluorescein-linked anti mouse Ig in TPBS for 30 minutes. The membranes were washed briefly with TPBS twice, then for 5 min. in TPBS washing buffer thrice. For signal amplification with ECF substrate membranes were incubated in 10 ml of 1:2500 anti fluorescein alkaline phosphatase conjugate for 30 minutes. The membranes were rinsed briefly with TPBS twice, then 5 min. in TPBS washing buffer thrice. The ECF substrate solution was prepared as per manufacturer's instructions (aliquot and freeze), membranes were incubated for 2-3 minutes, excess reagent was drained off, then were blotted with filter papers, air-dried for 9-10 minutes and then scanned.

Scanning the membrane: The blot was placed on the glass of phosphoimager Storm 860. The blue chemiluminiescent was set up, 200 pixcels size, 700

PMT voltage. The file was opened in ImageQuant and quantitated by creating squares around the bands representing the substrate (S), the product (P) and the internal control (IC). The % cleavage of the substrate was measured as P/(S+P)x100. The inhibition in cleavage due to drug was measured compared duplicate to drug controls included on each blot. A report was created in Excel. The results are shown in **Table 2**. 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.

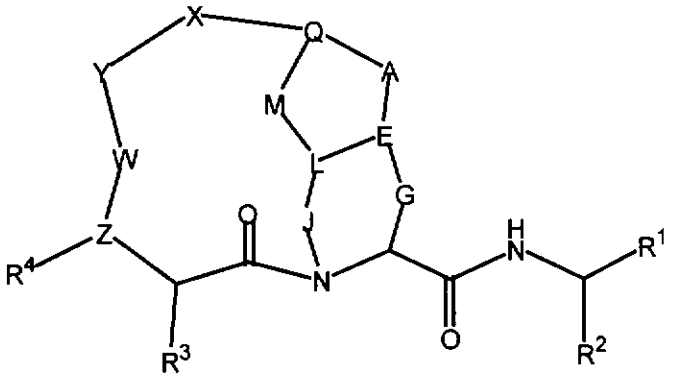
Table 2: HCV Cell-based assay results:

Example Number	Cell-Based Assay (μM)
1B	2
2	2
4A	2.5
4B	1.8
5	0.6
7B	7
8	3.5
12B	5.2
21	2
23	3
30	1
57B	1.5
58	2

It will be apparent to those skilled in the art that many modifications, variations and alterations to the present disclosure, both to materials and methods, may be practiced. Such modifications, variations and alterations are intended to be within the spirit and scope of the present invention.

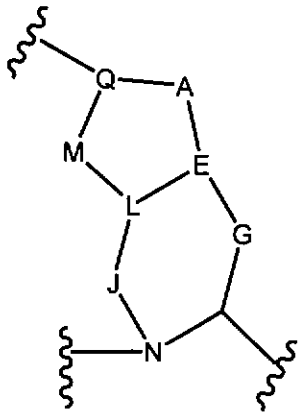
CLAIMS

1. A macrocyclic compound, including enantiomers, stereoisomers, rotomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula I:

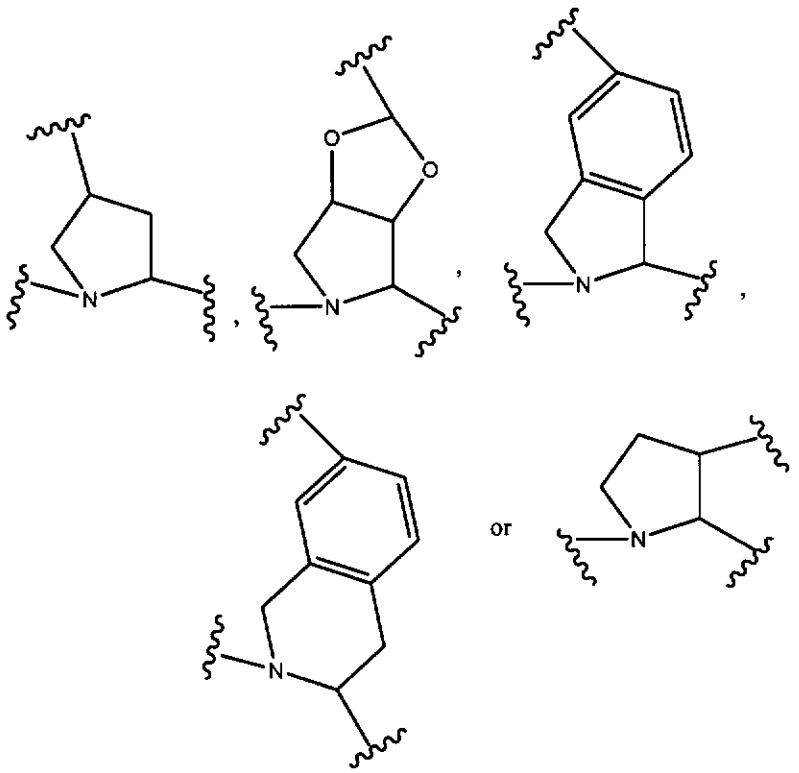


Formula I

wherein the moiety:



represents:



X and Y are independently selected from the moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl sulfide, alkyl-aryl sulfide, aryl sulfide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, or a combination thereof, with the proviso that X and Y may optionally be additionally substituted with moieties selected from the group consisting of aromatic, alkyl, alkyl-aryl, heteroalkyl, and cycloalkyl;

$R^1 = COR^5$, wherein R^5 = H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, or COR^7 wherein R^7 = H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$,

$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$,
$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$,
$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$,
$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$,
$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})\ CONR^{12}R^{13}$,
wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, or CH;

W may be present or absent, and if W is present, W is C=O;

R^4 is H, C1-C10 alkyl, C1-C10 alkenyl or C3-C8 cycloalkyl; and

R^2 and R^3 are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; oxygen, nitrogen, sulfur, or phosphorus atoms with said oxygen, nitrogen, sulfur, or phosphorus atoms numbering zero to six;
(cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;
with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

2. The compound of claim 1, wherein $R^1 = COR^5$, and R^5 is H, OH, $COOR^8$, or $CONR^9R^{10}$.

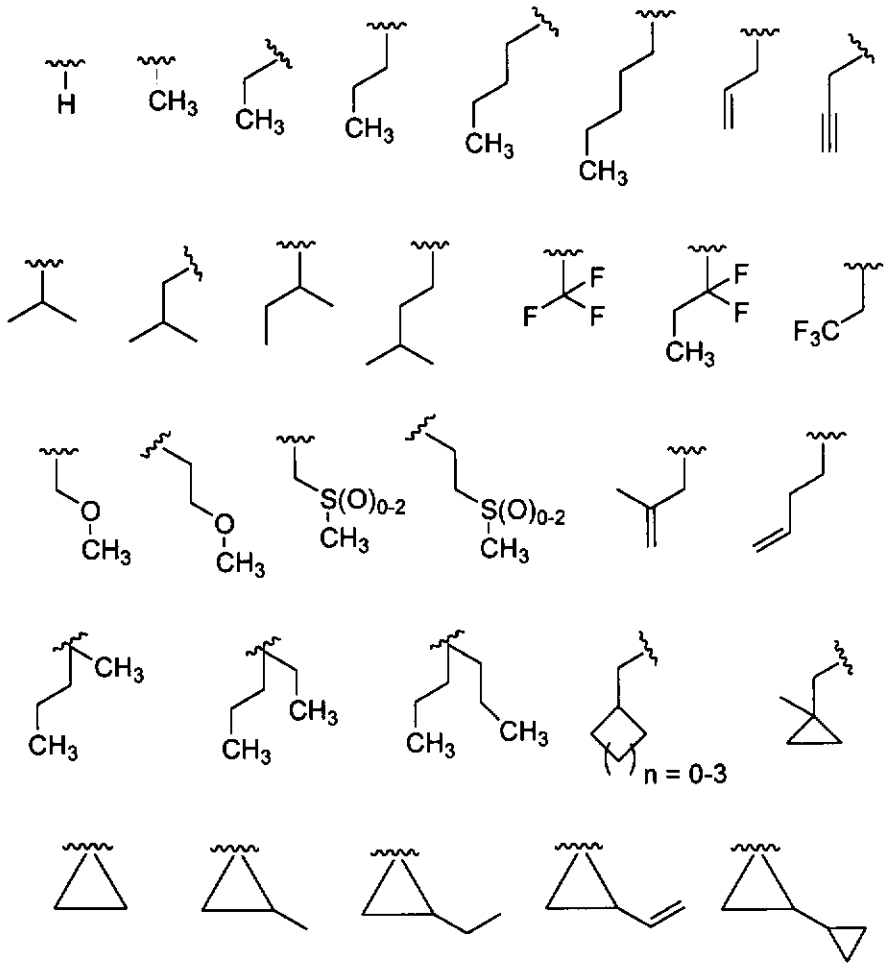
3. The compound of claim 2, wherein R^1 = $COCONR^9R^{10}$, and R^9 is H, R^{10} is H, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})$ $CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$.

4. The compound of claim 3, wherein R^{10} = $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cyclohexyl, cyclopentyl, cyclopropyl, piperidyl, pyridyl and 2-indanyl.

5. The compound of claim 4, wherein $R^{1'}$ is H.

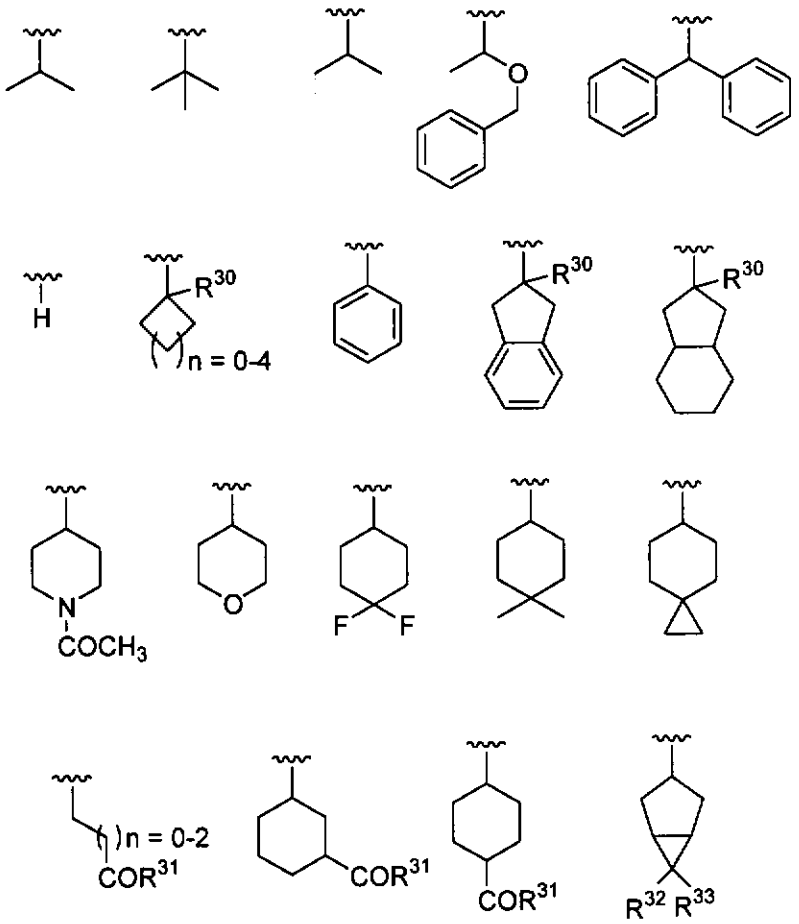
6. The compound of claim 5, wherein $R^{2'}$ = phenyl, thiophenyl, cyclohexyl, 2-indanyl, cyclopentyl, pyridyl, or phenyl(4-$HNSO_2NH_2$), R^{11} is H or *tert*-butyl, R^{12} and R^{13} are methyl, and R' is hydroxymethyl or tert-butoxymethyl.

7. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:



8. The compound of claim 7 wherein $R^1 = COR^5$, and R^5 is H, OH, $COOR^8$, or $CONR^9R^{10}$.

9. The compound of claim 1, wherein R^3 is selected from the group consisting of:



wherein R^{30} = H, CH_3 or other alkyl groups;

R^{31} = OH, O-alkyl, NH_2, N-alkyl; and

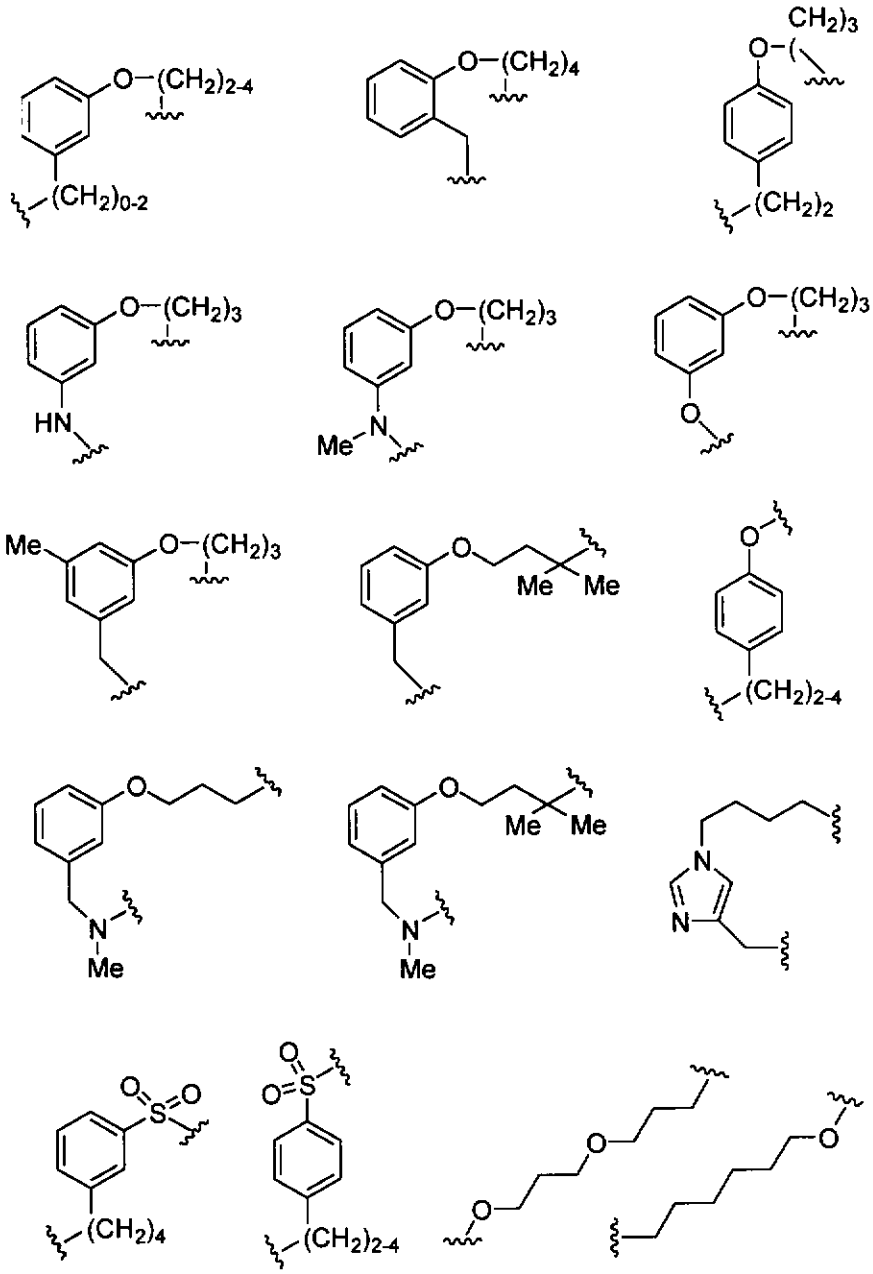
R^{32} and R^{33} may be the same or different and are selected independently from H, F, Cl, Br and CH_3.

10. A compound of claim 9, wherein Z = N and R^4= H.

11. A compound of claim 10, wherein:

X and Y are independently alkyl, alkyl-aryl, heteroalkyl, heteroaryl, alkyl ether or alkyl aryl ether.

12. A compound of claim 10, wherein the moiety X-Y is selected from the group consisting of the following structures:



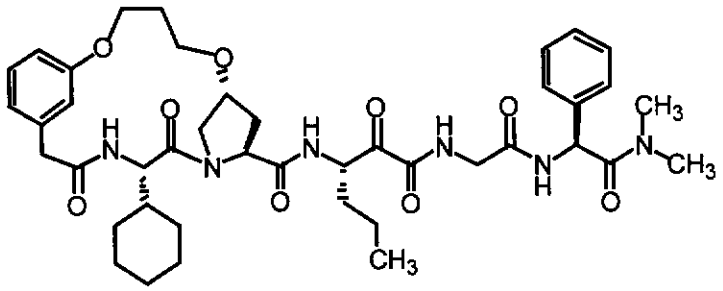
13. A pharmaceutical composition comprising as an active ingredient a compound of claim 1.

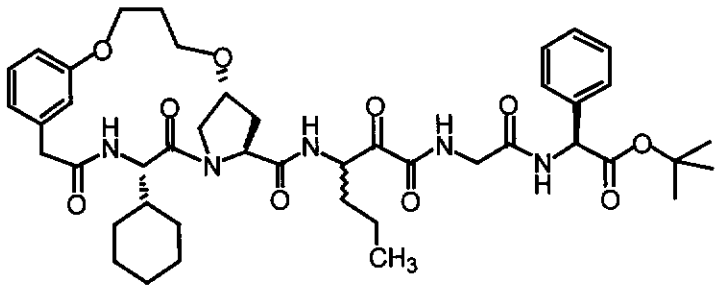
14. The pharmaceutical composition of claim 13 additionally comprising a pharmaceutically acceptable carrier.

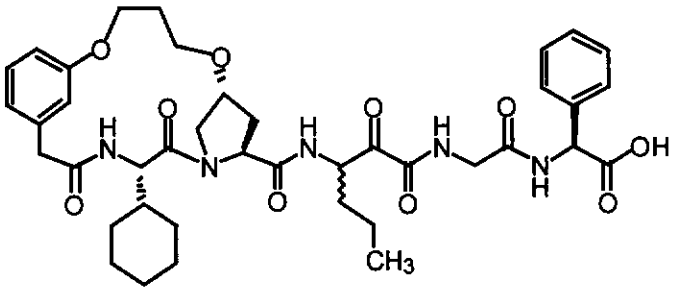
15. Use of therapeutically effective amounts of a compound of claim 1 for the preparation of a medicament for treating disorders associated with the Hepatitis C Virus ("HCV") protease.

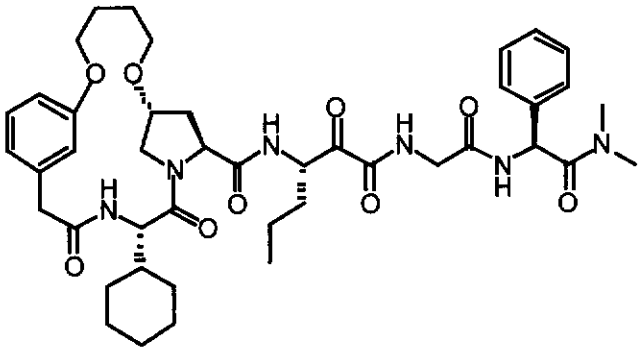
16. A method of preparing a pharmaceutical composition for treating the disorders associated with the Hepatitis C Virus ("HCV") protease, said method comprising bringing into intimate contact a compound of claim 1 and a pharmaceutically acceptable carrier.

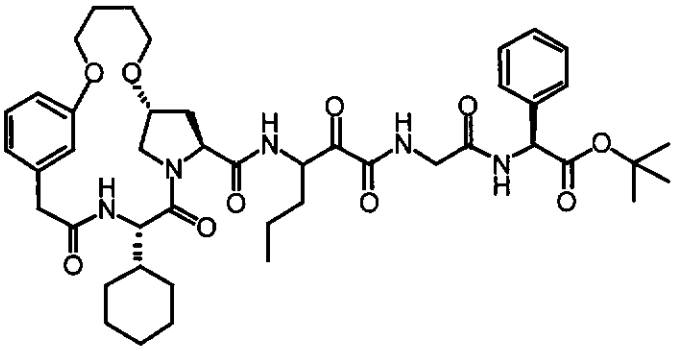
17. A compound exhibiting Hepatitis C Virus ("HCV") protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

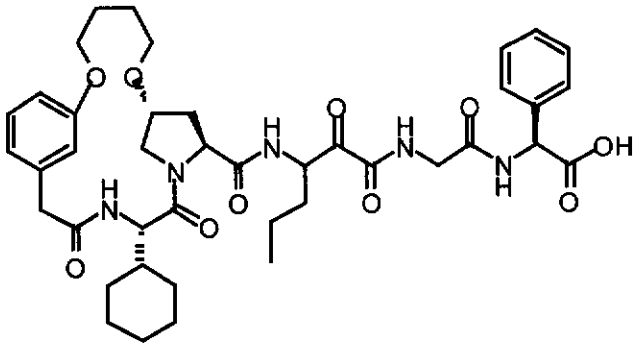


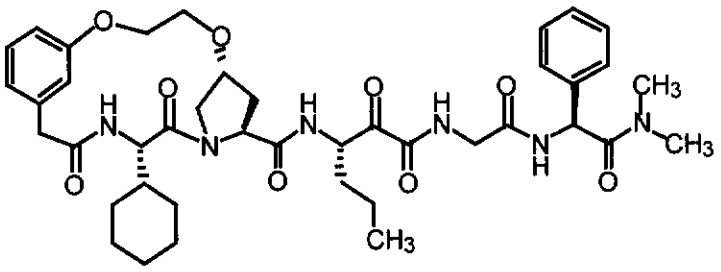


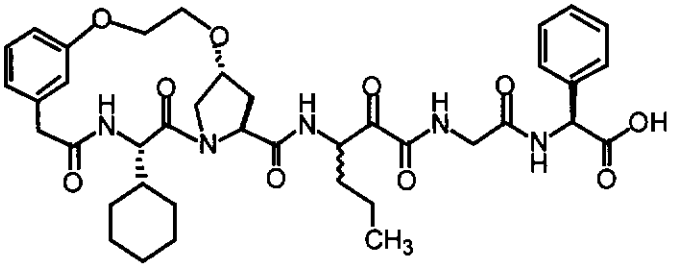


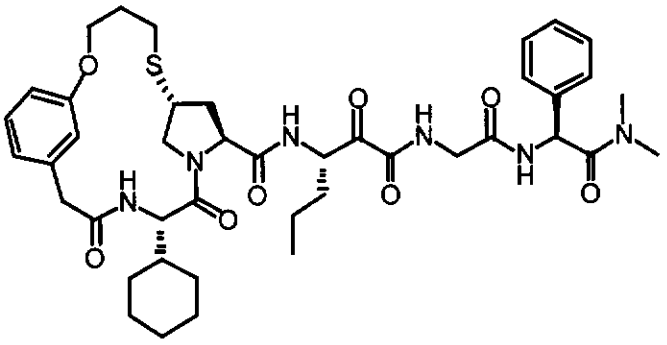


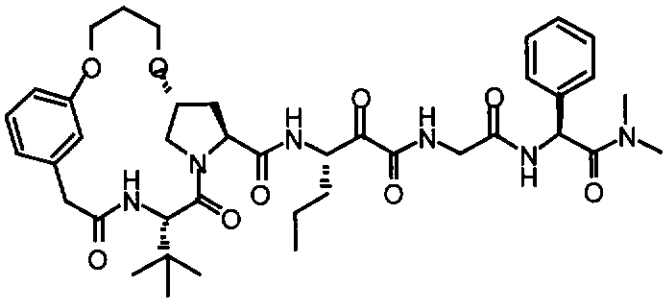


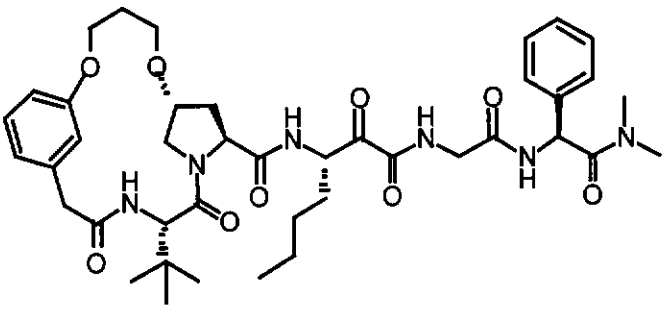


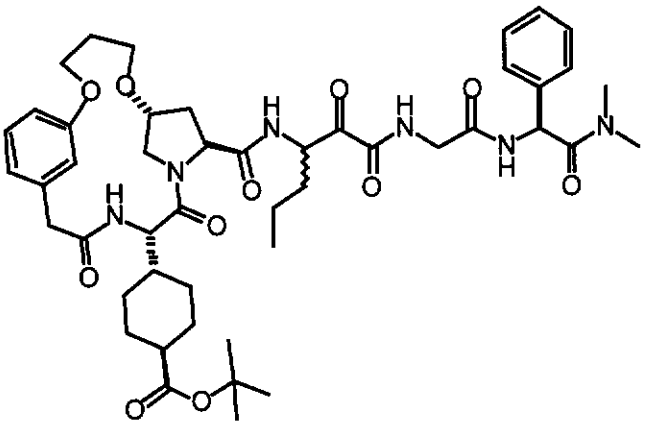


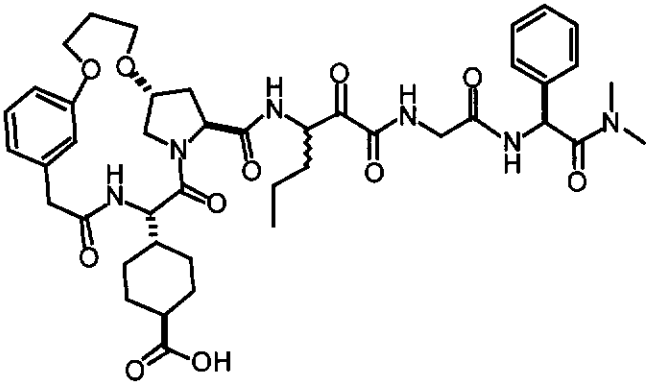


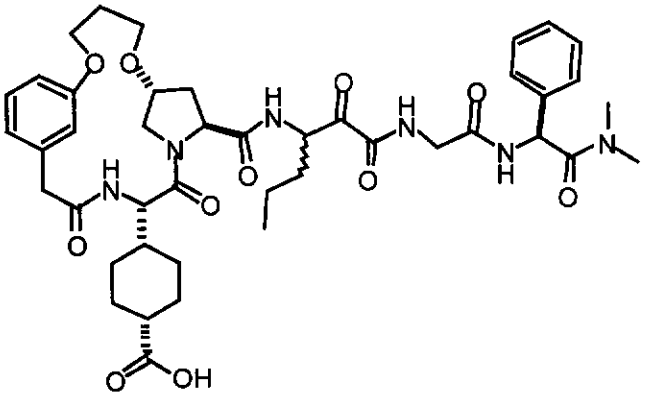


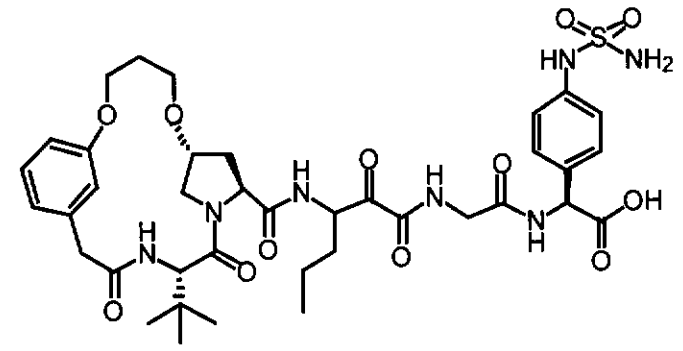


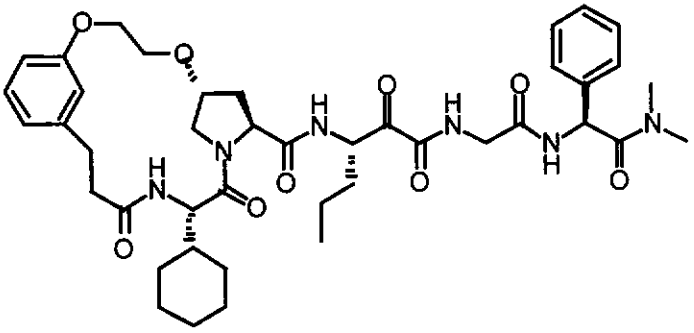


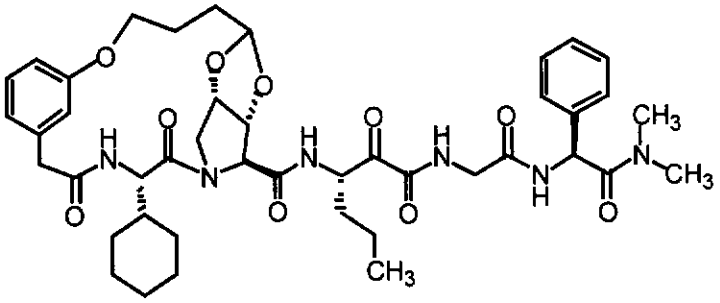


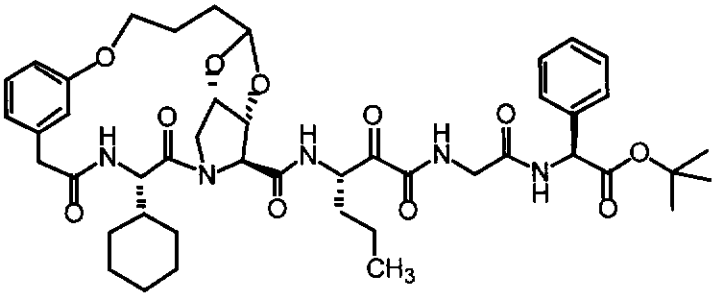


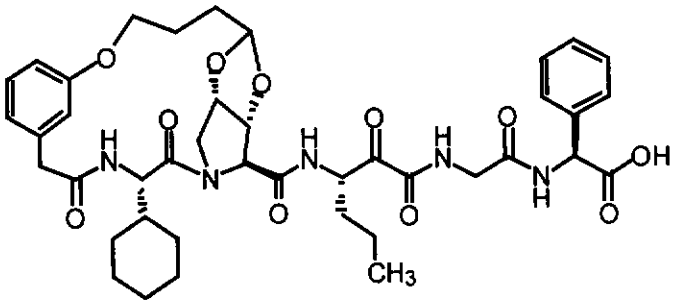


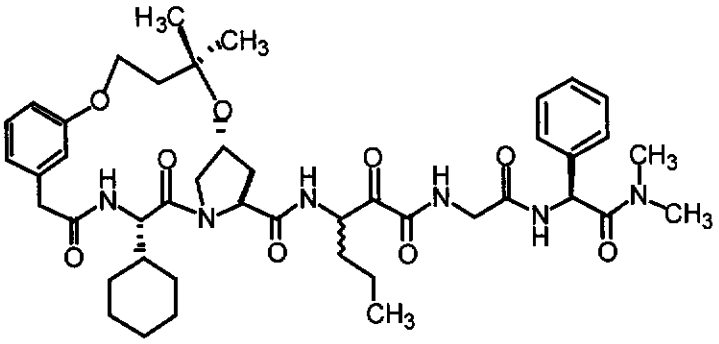


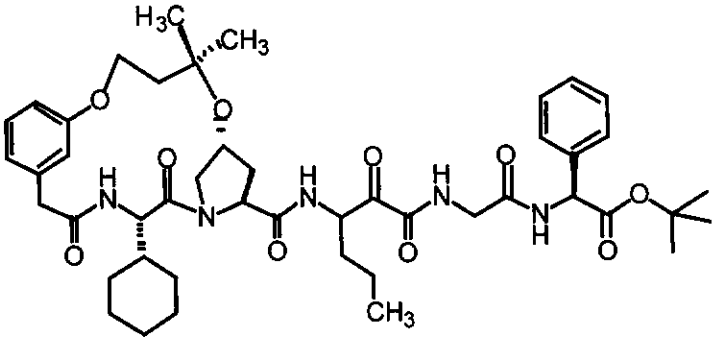


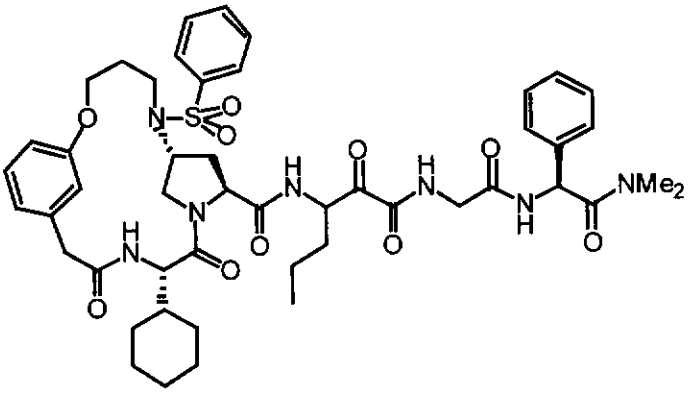


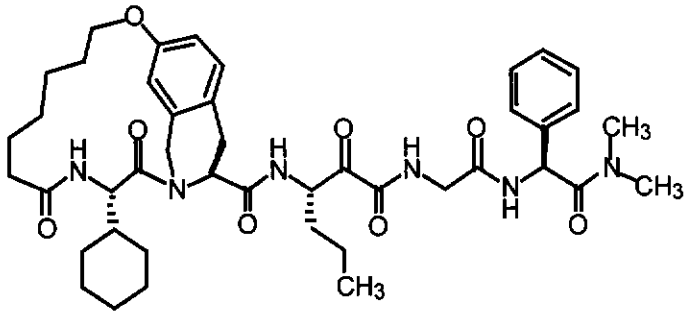


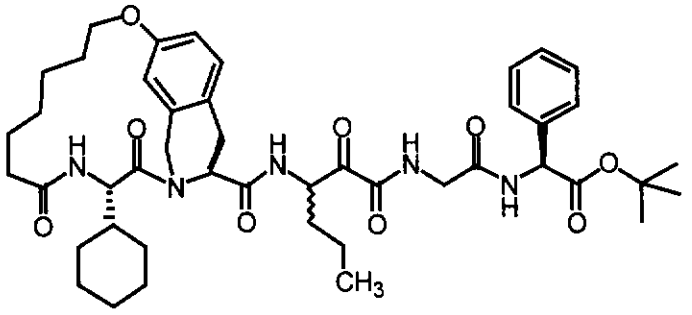


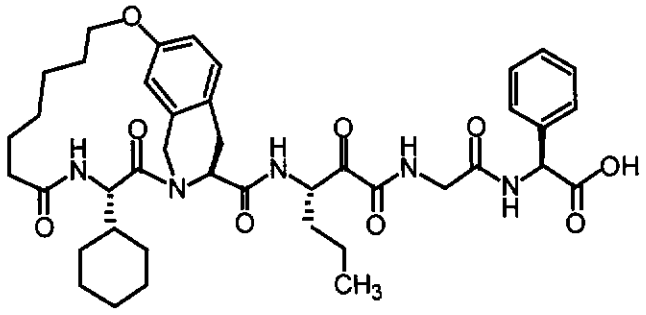


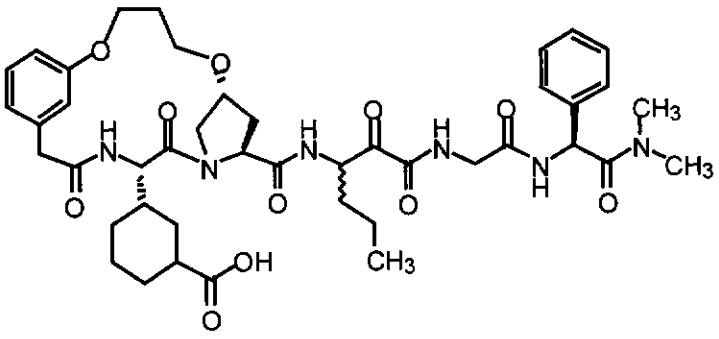


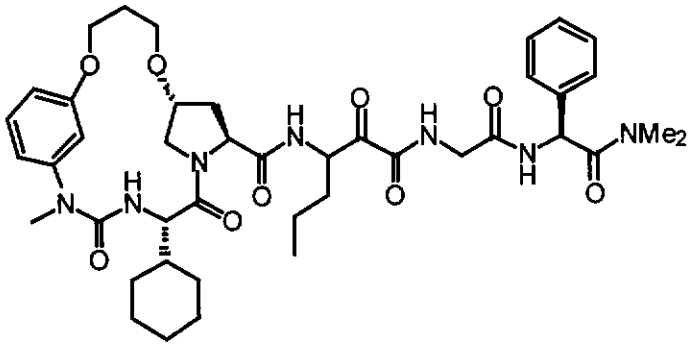


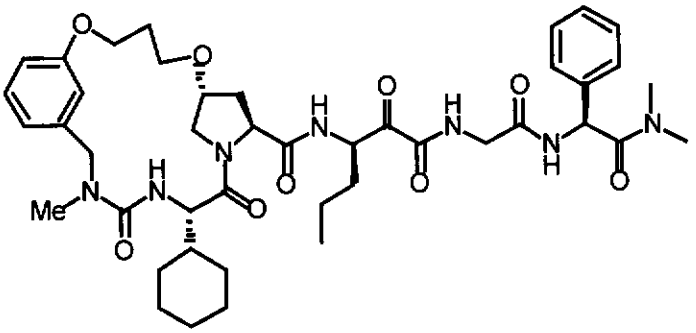


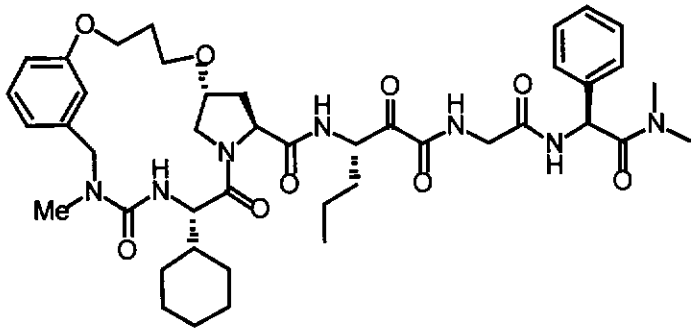


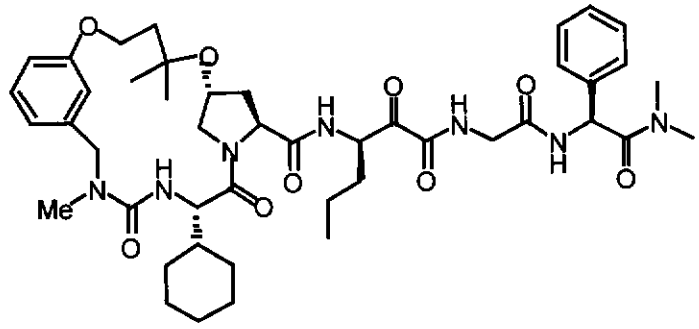


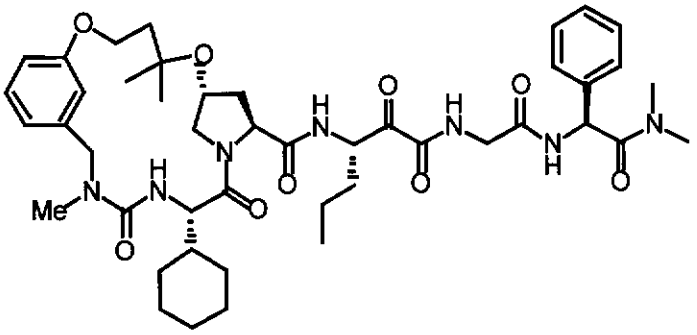


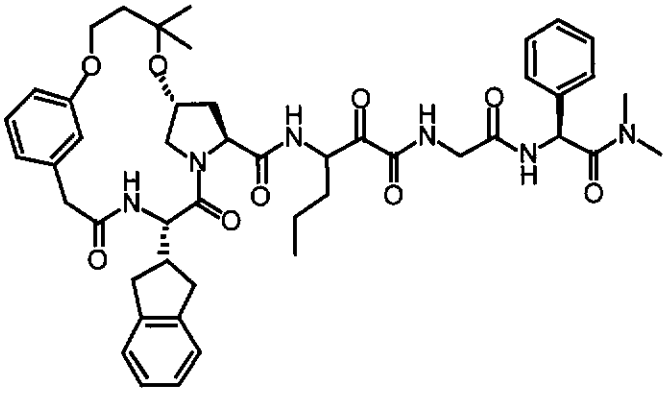

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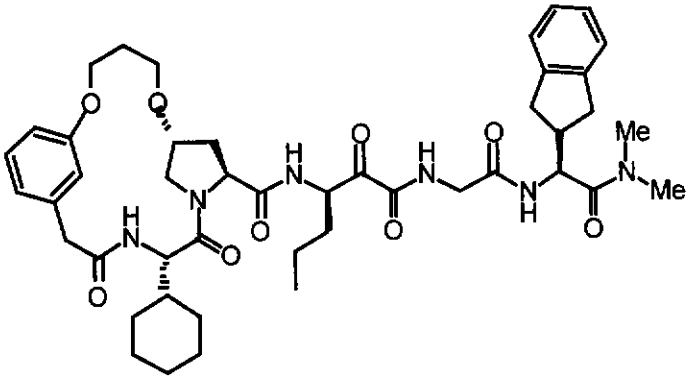

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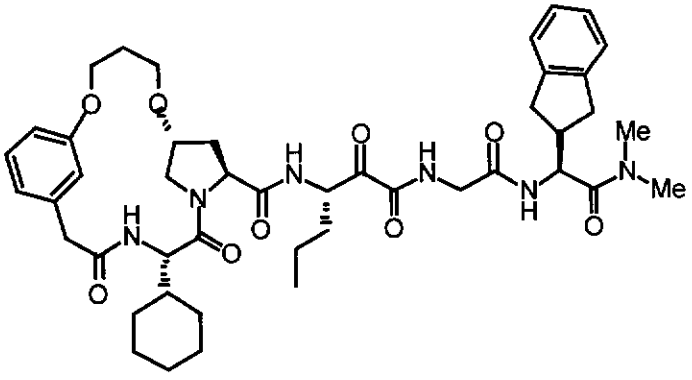

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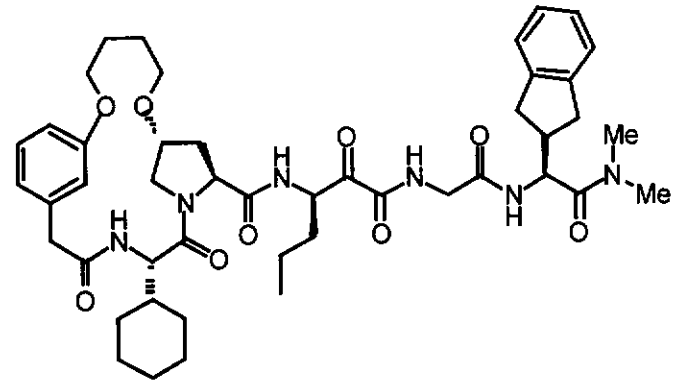

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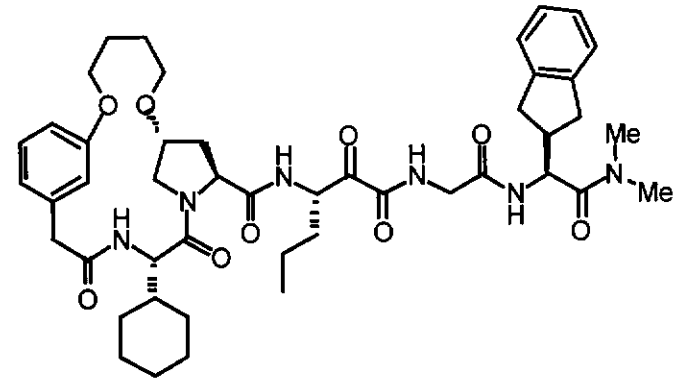


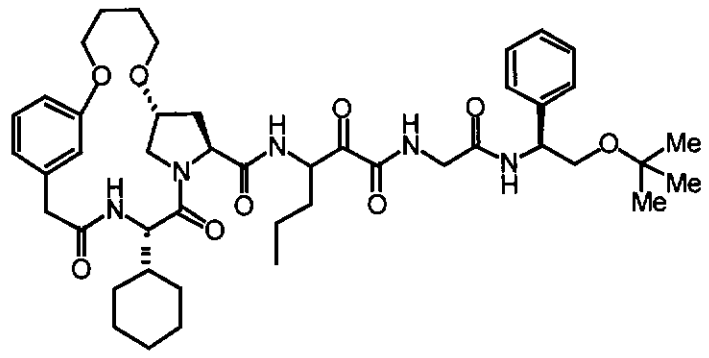


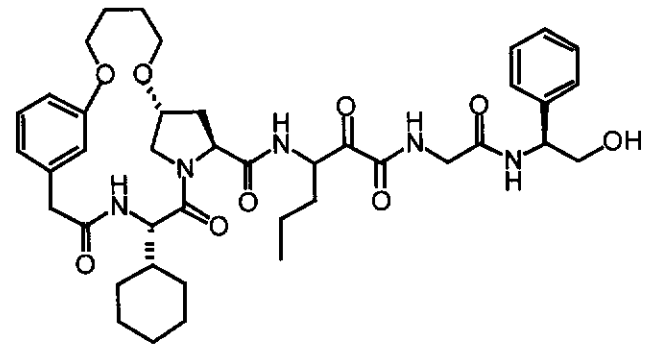


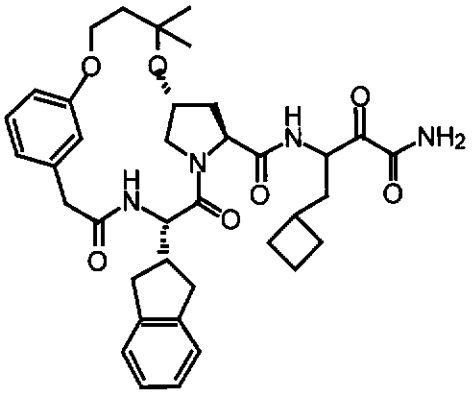


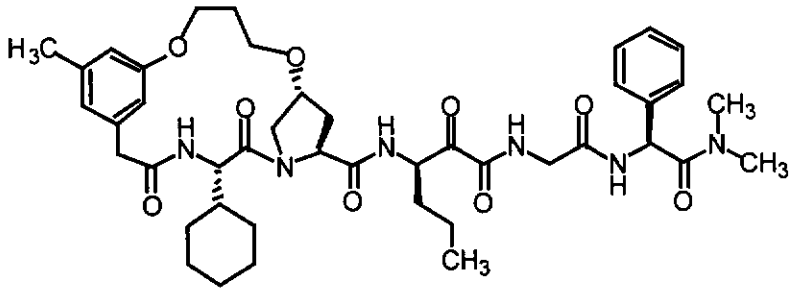


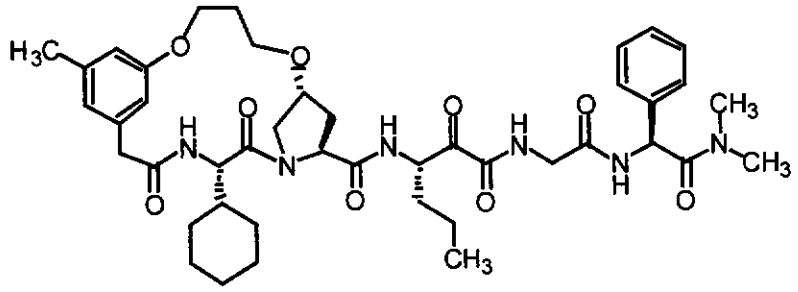


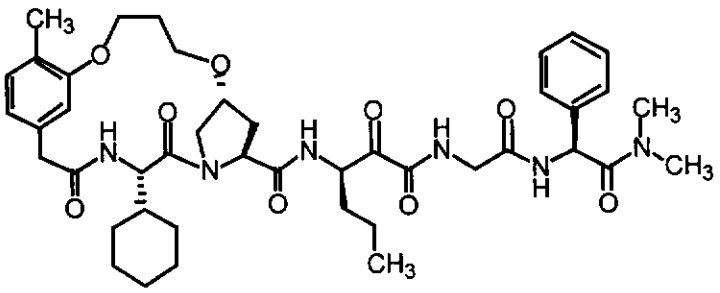


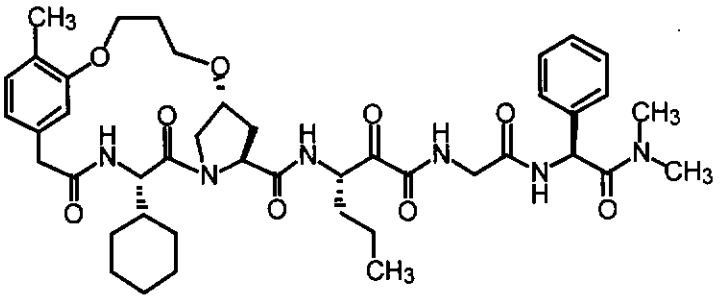


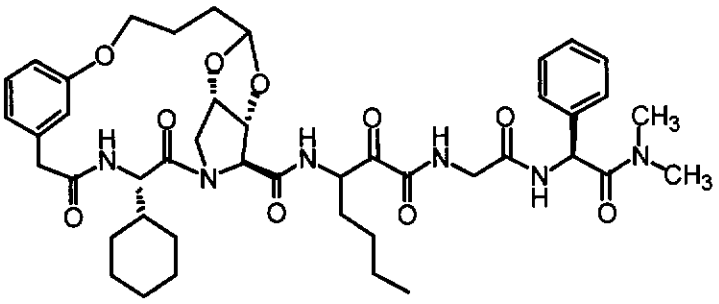


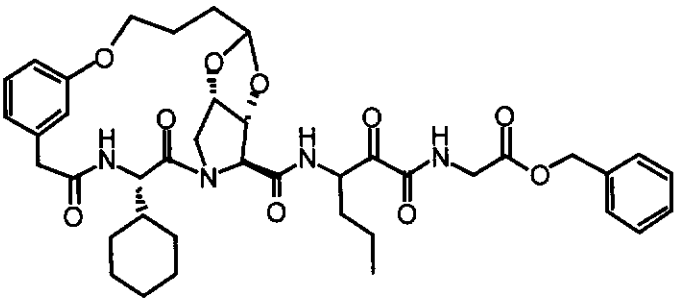


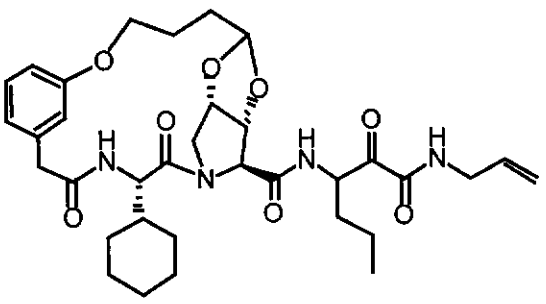


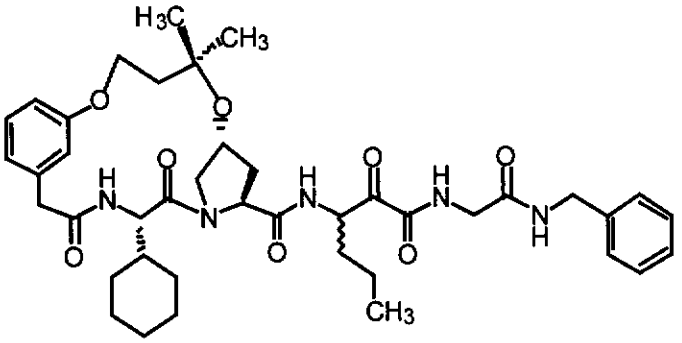


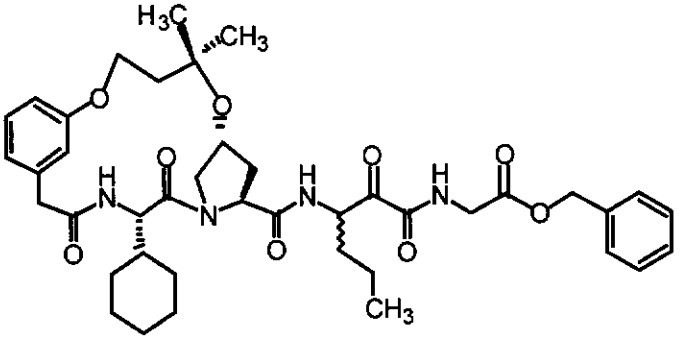


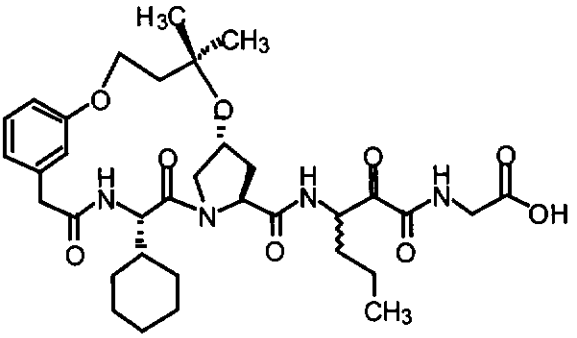


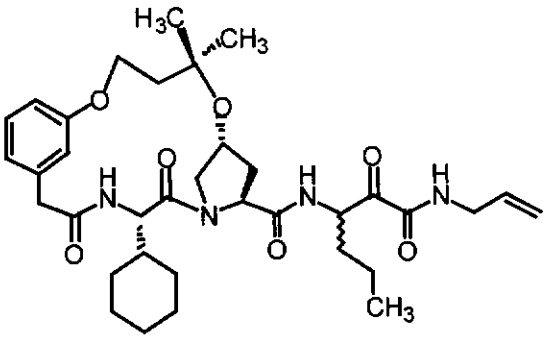


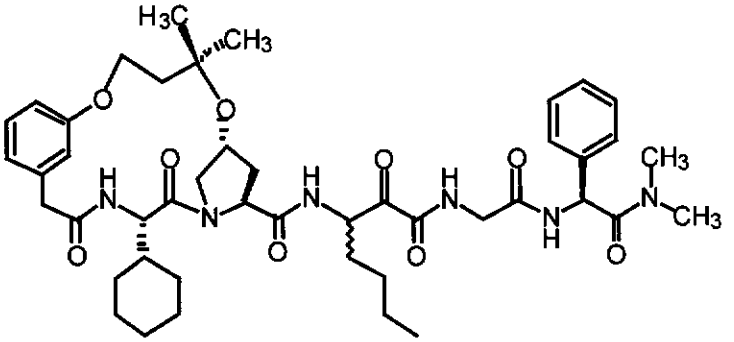


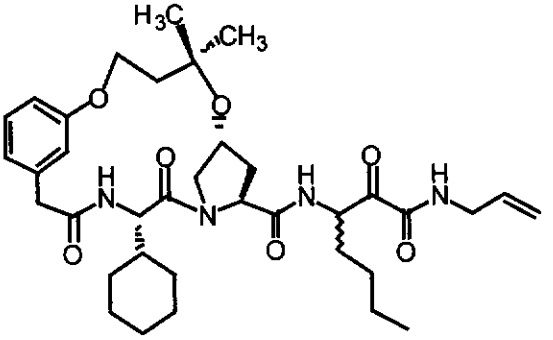


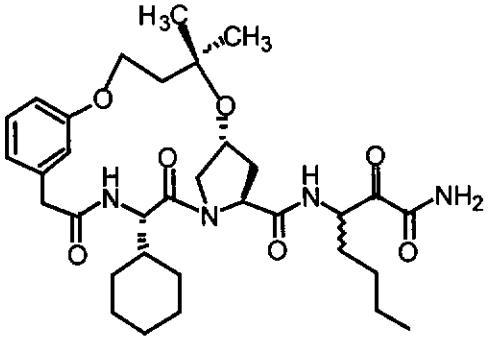


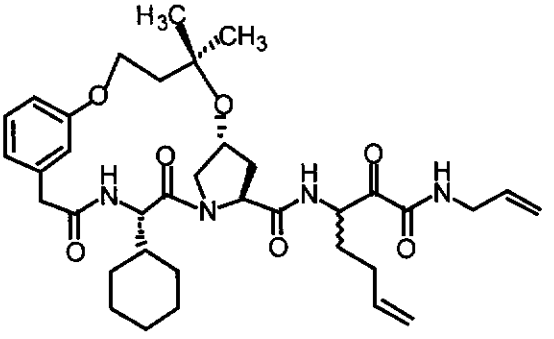


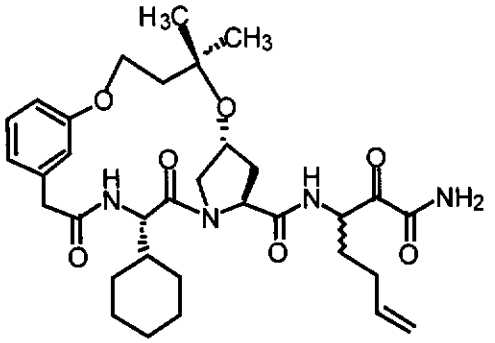


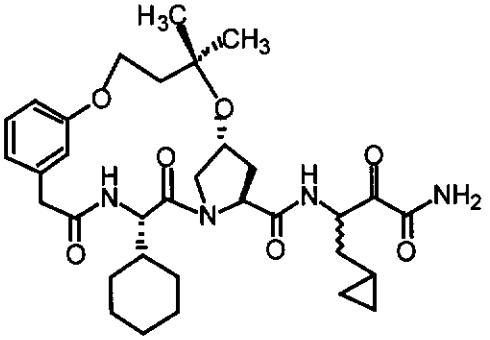


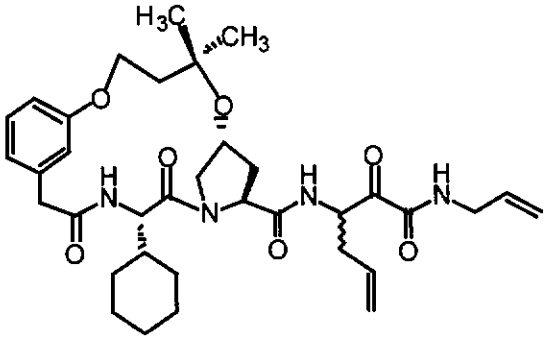


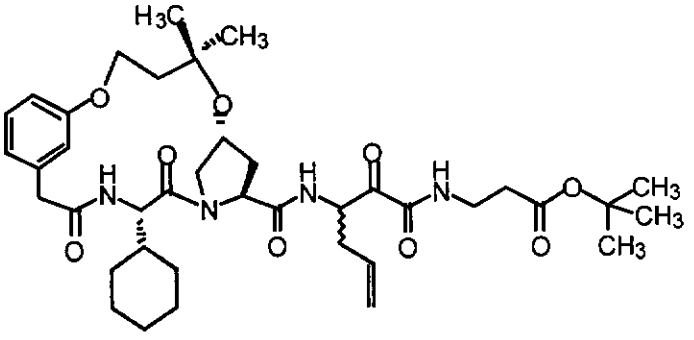


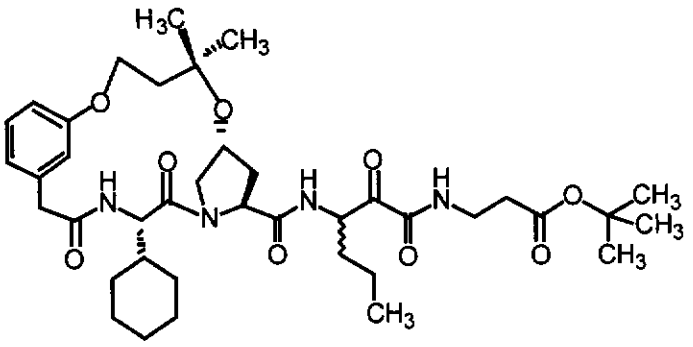


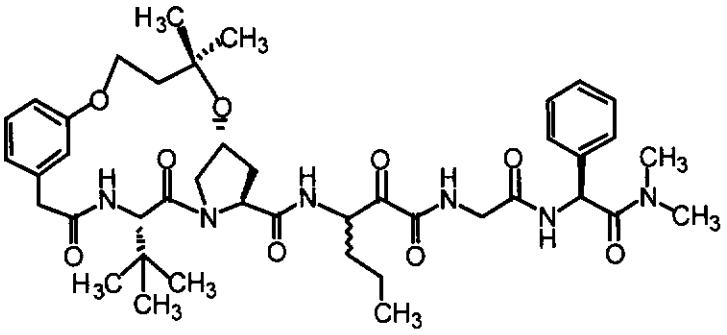


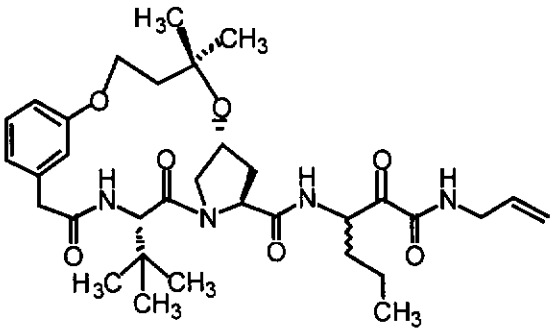


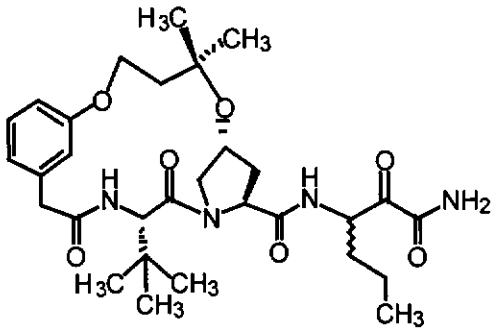


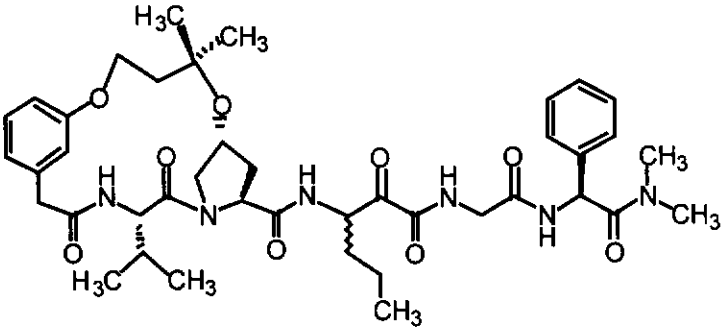


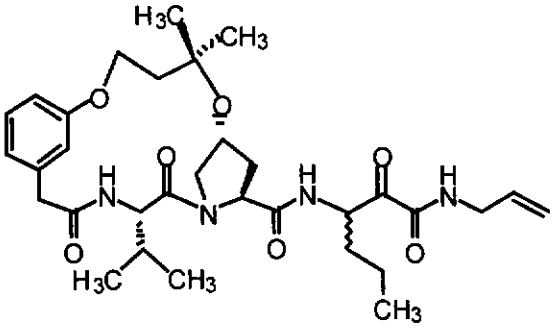


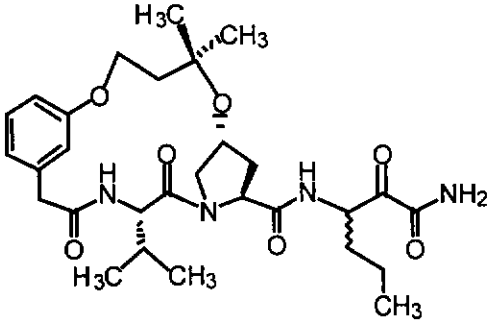


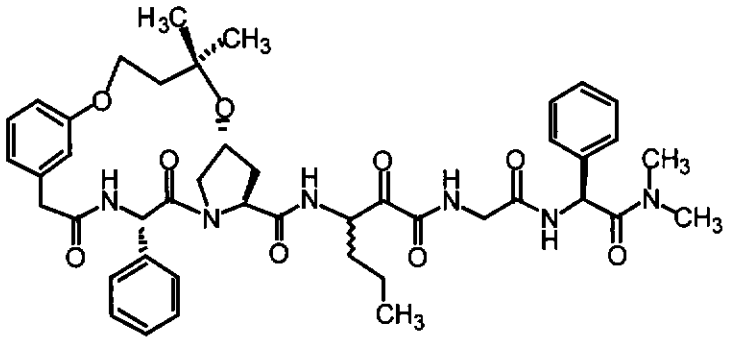


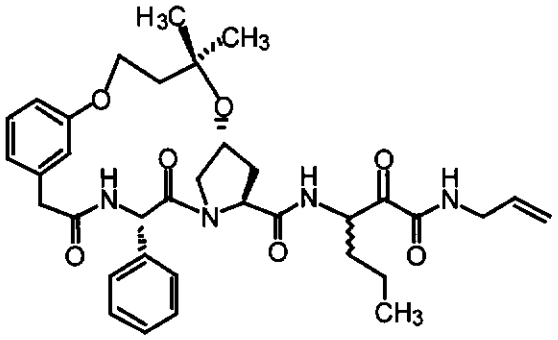


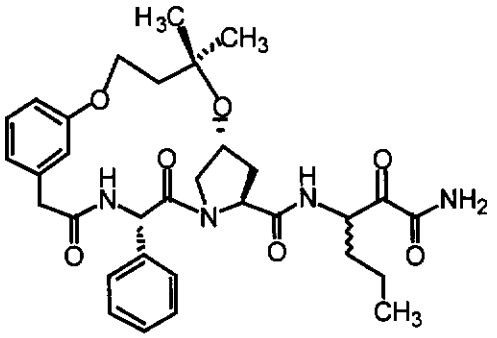


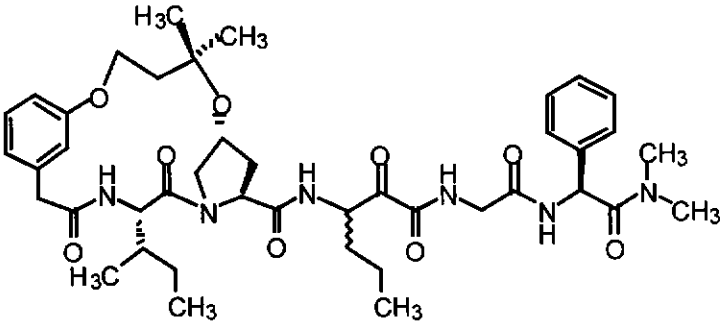


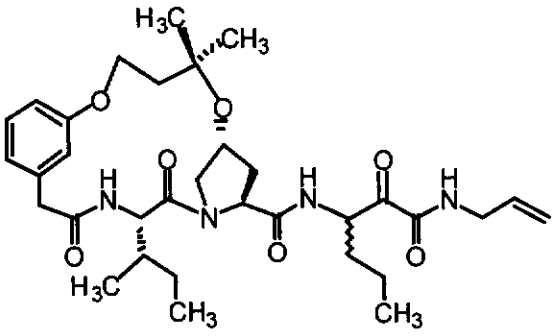


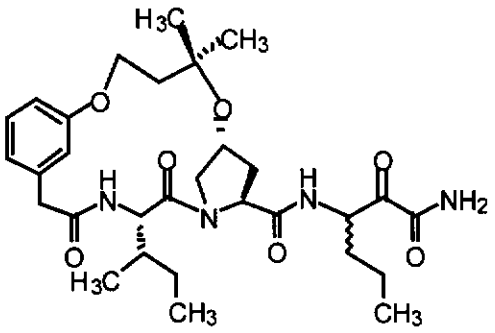


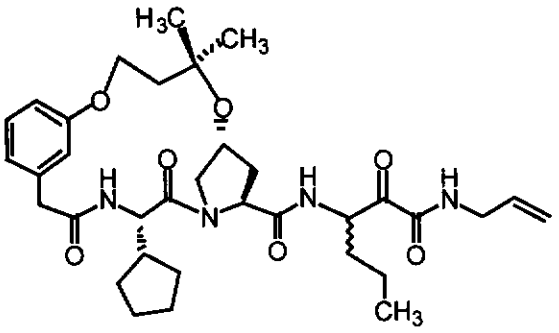


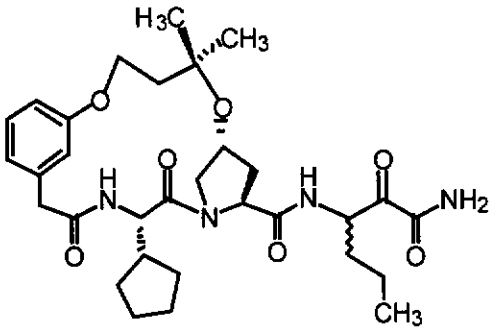


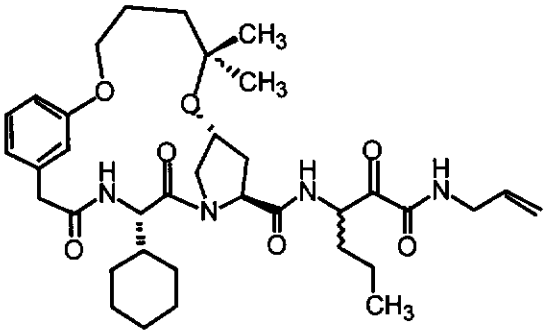


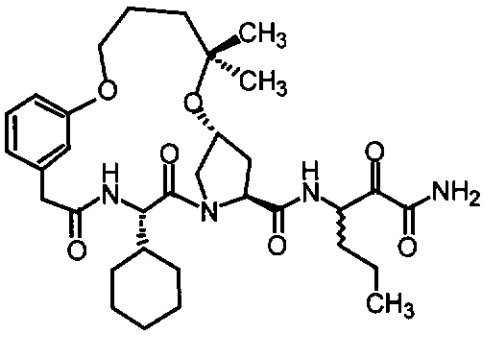


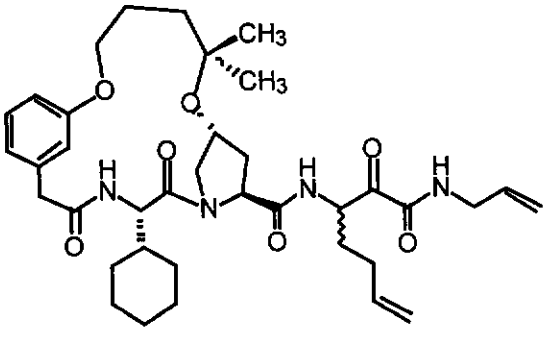


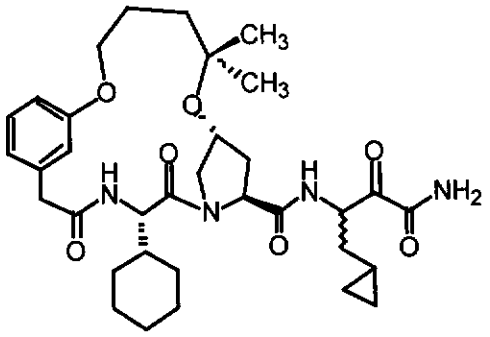


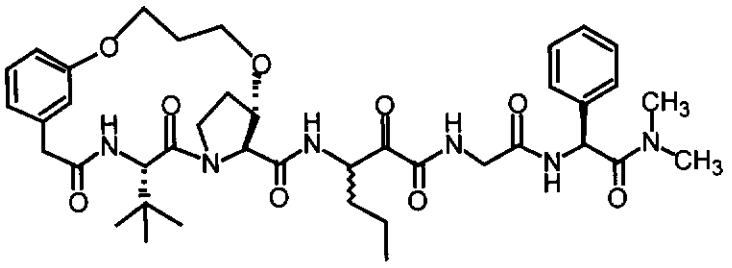


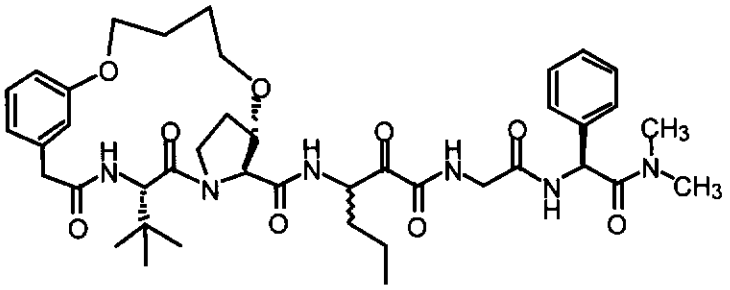












18. A pharmaceutical composition for treating disorders associated with the Hepatitis C Virus ("HCV") protease, said composition comprising therapeutically effective amount of one or more compounds in claim 17 and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of claim 18, additionally containing an antiviral agent.

20. The pharmaceutical composition of claim 18 or claim 19, additionally containing an interferon.

21. The pharmaceutical composition of claim 20, wherein said antiviral agent is ribavirin and said interferon is α-interferon.