Peptidic Compounds

FIELD OF THE INVENTION

This invention relates to novel peptidic compounds, methods for preparing them and their use as antibiotics and in the treatment of HIV infections.

BACKGROUND OF THE INVENTION

Bacteria and the bacterial infections that can be treated by antibiotics include, but are not limited to the following:

Staphylococcus aureus, (or "staph"), are bacteria commonly found on the skin and in the noses of healthy people, (F)and are one of the most common causes of skin infections and can also cause serious and sometimes fatal infections (such as bloodstream infections including toxic shock syndrome, impetigo, surgical wound infections, infections of plastic implants, osteomyelitis and pneumonia).

Enterococci, which have been known as a cause of infective endocarditis for close to a century, more recently have been recognized as a cause of nosocomial infection and "superinfection" in patients receiving antimicrobial agents.

Other Gram positive bacteria that can be treated by antibiotics include staphylococcus epidermitis which causes endocarditis, clostridium difficile which causes diarrhea and pseudomembranous colitis, bacillus anthracis of anthrax and streptococcus pneumoniae which causes pneumonia, meningitis, septicemia, and childhood otitis media (or ear-ache). The family of streptococcus bacteria can also be divided into group A or Pyrogenes, which are involved in blood poisoning, glomerularnephritis and fevers such as puerperal, scarlet and rheumatic fever. Group B or streptococcus agalactiae cause neonatal meningitis and pneumonia.

Bacterial Resistance to Antibiotics

Bacterial Infections can occur while in hospital (noscomial), but an additional problem is the increase of infections that are aquired while the person is in the community. A recent study (C) identified the antimicrobial susceptibility profile and resistance mechanisms of pretreatment MRSA isolates obtained from adult subjects participating in recent clinical treatment trials of community respiratory infections. Out of 465 S. aureus isolates, 43 were identified as MRSA. Antimicrobial susceptibility testing indicated susceptibility rates to: vancomycin (100%), gentamicin (86%), clindamycin (39%), quinolones (49%), and erythromycin (12%). All ciprofloxacin-resistant isolates had an amino acid change in GyrA and GrlA. The results indicate that MRSA from adult subjects with community respiratory infections have similar antimicrobial susceptibility profiles and resistance mechanisms as nosocomial MRSA.

The pathogenic potential of Staphylococcus aureus in nosocomial and community-acquired infections is well known. When penicillin was introduced in mid-1940s, S. aureus was almost 94% susceptible to this drug. Widespread resistance to penicillin developed in the 1950s, followed by resistance to semi-synthetic penicillins in the 1960s and 1970s. Since then, strains of methicillin-resistant S. aureus and methicillin-resistant coagulase-neg. staphylococci have spread worldwide. The prevalence of methicillin-resistant S. aureus varies geographically. In Argentina it reaches nearly 50%. Methicillin resistance in staphylococci develops due to the additional. penicillin binding protein PBP2a encoded by gene mecA and is a serious problem both for microbiologists and physicians(A). The

high prevalence of methicillin-resistant staphylococci compromises the use of semi-synthetic penicillins for clin. treatments in many institutions, thus increasing the use of vancomycin (a glycopeptide). Until 1996, glycopeptides were almost universally active against S. aureus but it was then that the first glycopeptide-intermediate S. aureus (GISA) also known as VISA (vancomycin intermediately resistant S. aureus) was described and isolated in Japan, followed by France and USA. Infections with Staphylococcus aureus with reduced susceptibility to vancomycin continue to be reported, including 2 cases caused by S. aureus isolates with full resistance to vancomycin. (A) There is also vancomycin-resistant S. aureus (VRSA) The worldwide increase in the incidence of S. aureus clinical isolates with reduced susceptibility to vancomycin and teicoplanin means that glycopeptide resistance in S. aureus is becoming an important clinical problem

The exact mechanisms involved have not been elucidated yet, although VISA is associated with increased wall synthesis. Many VISA strains are characterized by increased cell wall biosynthesis and decreased crosslinking of the peptide side chains, leading to accumulation of free D-alanyl-D-alanine termini in the peptidoglycan, which it has been proposed can act as false target sites for vancomycin. (B)

The mechanism of vancomycin resistance in enterococcus is well defined and appears to be different to that of VISA.

Vancomycin resistance in enterococci, known as VRE or glycopeptide-resistant enterococci (GRE), exists as either intrinsic resistance where isolates of Enterococcus gallinarum and E. casseliflavus/E. flavescens demonstrate an inherent, low-level resistance to vancomycin or by acquired resistance where Enterococci become resistant to vancomycin by acquisition of genetic information from another organism. Most commonly, this resistance is seen in E. faecium and E. faecalis, but also has been recognized in E. raffinosus, E. avium, E. durans, and several other enterococcal species.

Several genes, including vanA, vanB, vanC, vanD, and vanE, contribute to resistance to vancomycin in enterococci.

E. faecium is the most frequently isolated species of VRE in hospitals and typically produces high vancomycin (>128 μg/ml) and teicoplanin (>16 μg/ml) minimum inhibitory concentrations (MICs). These isolates typically contain vanA genes. The epidemiology of vancomycin-resistant Enterococcus faecium (VREF) in Europe is characterized by a large community reservoir. In contrast, nosocomial outbreaks and infections (without a community reservoir) characterize VREF in the United States. (G)

In vancomycin-susceptible enterococci, D-alanyl-D-alanine (formed by an endogenous D-alanine-D-alanine ligase) is added to a tripeptide precursor to form a pentapeptide precursor. The D-Ala-D-Ala terminus is the target of vancomycin; once vancomycin has bound, the use of this pentapeptide precursor for further cell-wall synthesis is prevented. In the VanA phenotype, one of the proteins whose synthesis is induced by exposure of bacterial cells to vancomycin is called VanA; VanA is a ligase and resembles the D-alanine-D-alanine ligase from Escherichia coli and other organisms, including vancomycin-susceptible enterococci. VanA generates D-Ala-D-X, where X is usually lactate; the formation of D-lactate is due to the presence of VanH, a dehydrogenase encoded by vanH. The depsipeptide moiety, D-Ala-D-Lac, is then added to a tripeptide precursor, resulting in a depsipentapeptide precursor. Vancomycin does not bind to the D-Ala-D-Lac terminus, so this depsipentapeptide can be used in the remaining steps of cell-wall synthesis. However, when the normal pentapeptide precursor ending in D-Ala-D-Ala is also

present, cells are not fully vancomycin resistant, despite the presence of D-Ala-D-Lac containing precursors. This apparent problem is taken care of in large part by vanX, which encodes a dipeptidase, VanX, that cleaves D-Ala-D-Ala, preventing its addition to the tripeptide precursor. Should any D-Ala-D-Ala escape cleavage and result in a normal pentapeptide precursor, vanY encodes an ancillary or back-up function. That is, it codes for a carboxypeptidase, VanY, which cleaves D-alanine and D-lactate from D-Ala-D-Ala and D-Ala-D-Lac termini, respectively, resulting in tetrapeptide precursors, to which vancomycin does not bind. The other genes involved in the VanA resistance complex include vanR and vanS, whose encoded proteins are involved in sensing the presence of extracellular vancomycin or its effect and signaling intracellularly to activate transcription of vanH, vanA, and vanX. A final gene in the vanA cluster is vanZ, which encodes VanZ, the role of which is not known. (J)

VanB, encoded by vanB in the vanB gene cluster, is also a ligase that stimulates the formation of D-Ala-D-Lac. The VanB phenotype is typically associated with moderate to high levels of vancomycin resistance but is without resistance to teicoplanin. This is explained by the observation that vancomycin, but not teicoplanin, can induce the synthesis of VanB and of VanHB and VanXB. However, because mutants resistant to teicoplanin can readily be selected from VanB strains on teicoplanin-containing agar, clinical resistance would likely occur among VanB strains if teicoplanin were widely used. Most of the proteins encoded by the vanA gene cluster have homologues encoded by the vanB gene cluster, except for VanZ. The vanB gene cluster has an additional gene, vanW, of unknown function.

The acquired gene clusters associated with vanA and vanB are found in different genetic surroundings. These elements have in turn been found on both transferable and nontransferable plasmids, as well as on the chromosome of the host strain. VanB type resistance was initially not found to be transferable, but at least in some instances, the vanB gene cluster has been found on large (90 kb to 250 kb) chromosomally located transferable elements, More recently, vanB has been found as part of plasmids. (I)

In addition to being found in different genetic surroundings, the vanA and vanB gene clusters have also been found in a number of different bacterial species. vanA has been found in multiple enterococcal species as well as in lactococci, Orskovia, and Arcanobacteria (H). The distribution of the vanB gene cluster seems somewhat more restricted, having been found primarily in E. faecium and E. faecalis, although it has recently been found in Streptococcus bovis (H).

The VanC phenotype (low-level resistance to vancomycin, susceptible to teicoplanin) is an inherent (naturally occurring) property of E. gallinarum and E. casseliflavus. This property is not transferable and is related to the presence of species-specific genes vanC-1 and vanC-2, respectively; a third possible species, E. flavescens and its gene vanC-3, are so closely related to E. casseliflavus and vanC-2 that different names are probably not warranted. These species appear to have two ligases; the cell-wall pentapeptide, at least in E. gallinarum, ends in a mix of D-Ala-D-Ala and D-Ala-D-Ser. The genes vanC-1 and vanC-2 apparently lead to the formation of D-Ala-D-Ser containing cell-wall precursors, while D-Ala-D-Ala ligases, also present in these organisms, result in D-Ala-D-Ala. The presence of both D-Ala-D-Ala and D-Ala-D-Ser precursors may explain why many isolates of these species test susceptible to vancomycin and why even those isolates with decreased susceptibility display only low-level resistance. (J)

VanD-type glycopeptide resistance has been recently described in an E. faecium isolate from the United States (I). The organism was constitutively resistant to vancomycin (MIC > 64 μg/ml) and to low levels (4 μg/ml) of teicoplanin. Following polymerase chain reaction amplification with primers that amplify many D-Ala-D-Ala ligases, a 605-bp fragment was identified whose deduced amino acid sequence showed 69% identity to VanA and VanB and 43% identify to VanC.

Bacterial Resistance to Different classes of antibiotics.

As well as resistance to approved beta-lactam, glycopeptide antibiotics (including vancomycin, trade name vancocin), and the macrolide-lincosamide-streptogramins (including quinupristin-dalfopristin, trade name synercid)(D) various recent findings have also underlined the importance of biocide resistance as a clin. relevant phenomenon. (D) Outbreaks of biocide-resistant organisms in hospitals have been described and the genetic mechanism for resistance to quaternary ammonium compds. (QACs) in Staphylococcus aureus has now been elucidated.

Some strains of MRSA which have intermediate resistance to glycopeptides were demonstrated to have decreased susceptibility to some biocides including triclosan for which minimal bactericidal concns. (MBCs) increased from 0.002 to 3.12 mg l-1. Biocide resistance amongst enterococci has also been demonstrated although there was no clear correlation between biocide and antibiotic resistance. The exact mechanisms of resistance in these strains are still being studied but it is clear that biocide resistance is an important clin. phenomenon.

Vancomycin is a cyclic compound. Disclosed herein by reference, WO 03/002545 teaches that 'peptoid compounds' made from a peptide chain covalently linked in a cyclic form through a heterocyclic or aromatic ring system have antibacterial activity. The reaction know to those skilled in the art variously as 'ring closing metathesis', 'Grubbs metathesis' or 'olefin metathesis' is taught in W0 03/00254 to join the ends of the molecule which therefore need to terminate in allyl groups (-CH_2-CH=CH_2) that react in that chemical processes described. The literature (J.Bremner et al New J.Chem, 2002, 26, 1549-1551) teaches that cyclic compounds so made based on a 1,1-binaphthyl scaffold linked in a ring through the 3,3'-positions can have antibacterial activity. Further this literature describes cyclic molecules made from 1,1'-binaphthyl linked through the 2,2' positions.

Additionally the prior art (J.Bremner et al Tetrahedron, 2003, 59, 8741-8755) teaches that related cyclic compounds (therein known as 'carbazole linked cyclic peptoids') can have antibacterial activity.

There is a need for new compounds which are useful in the treatment of bacterial infections, especially those caused by vancomycin resistant organisms.

(A) Staphylococcus aureus with reduced susceptibility to vancomycin. Cosgrove, S. E.; Carroll, K. C.; Perl, T. M. Clinical Infectious Diseases (2004), 39(4), 539-545.

(B) Morphological and genetic differences in two isogenic Staphylococcus aureus strains with decreased susceptibilities to vancomycin. Reipert, A; Ehlert, Kn; Kast, T; Bierbaum, G. . Antimicrobial Agents and Chemotherapy (2003), 47(2), 568-576.

(C) Antimicrobial susceptibility and molecular characterization of community-acquired methicillin-resistant Staphylococcus aureus. Almer, L.S.; Shortridge, V.D.; Nilius, A.M.; Beyer, Jill M.; Soni, Niru B.; Bui, Mai H.; Stone, G.G.; Flamm, R.K Diagnostic Microbiology and Infectious Disease (2002), 43(3), 225-232.

(D) Methicillin-resistant, quinupristin-dalfopristin-resistant Staphylococcus aureus with reduced sensitivity to glycopeptides. Werner, G.; Cuny, C.; Schmitz, F.-J.; Witte, W. Journal of Clinical Microbiology (2001), 39(10), 3586-3590.

(E) Susceptibility of antibiotic-resistant cocci to biocides. Fraise, A. P. Society for Applied Microbiology Symposium Series (2002), 31(Antibiotic and Biocide Resistance in Bacteria).

(F) WWW.CDC.gov VISA/VRSA Vancomycin-Intermediate/Resistant Stapylococcus aureus

(G) Epidemic and nonepidemic multidrug-resistant Enterococcus faecium. Leavis HL, Willems RJL, Top J, Spalburg E, Mascini EM, Fluit AC, et al. Emerg Infect Dis. 2003 Sept. Available from: URL: http://www.cdc.gov/ncidod/EID/vol9no9/02-0383.htm

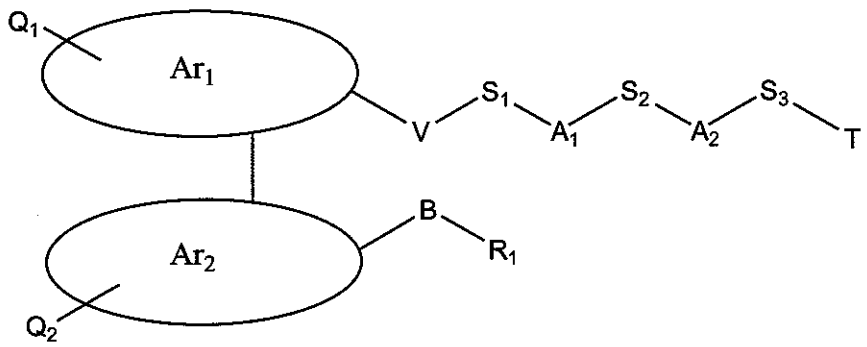
(H) Power EGM, Abdulla YH, Talsania HG, Spice W, Aathithan S, French GL. vanA genes in vancomycin-resistant clinical isolates of Oerskovia turbata and Arcanobacterium (Corynebacterium) haemolyticum. J Antimicrob Chemother 1995;36:595-606.

(I) Perichon B, Reynolds P, Courvalin P. VanD-type glycopeptide-resistant Enterococcus faecium BM4339. Antimicrob Agents Chemother 1997;41:2016-8.

(J) Diversity among Multidrug-Resistant Enterococci Barbara E. Murray, M.D. Emerg Infect Dis. 2003 Sept. Available from: URL: http://www.cdc.gov/ncidod/EID/vol4no1/murray.htm

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a compound of formula I,



I

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

B is selected from –O-, -S-, -S(O)-, -$S(O)_2$-, -NH-, and –N(C_1-C_6alkyl)-;

R_1 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkylC_6-C_{10}aryl, C_2-C_6alkenyl, C_2-C_6alkynyl, a polyoxyalkylene having from 2 to 6 carbon atoms, and when B is -S-, -S(O)-, -$S(O)_2$-, -NH- or –N(C_1-C_6alkyl)- then R_1 may be hydroxyl;

V is a linker group selected from –O-,–O-L-C(O), -O-L-NR_6-, -C(O)-, -NR_6-, -S(O)-, -$S(O)_2$-, -O-L-S(O)-, -$S(O)_2$-L-C(O)-, -$S(O)_2$-L-NR_6-, $P(O)_2O$-;

wherein L is selected from C_1-C_{12}alkyl, C_2-C_8 alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10}aryl and C_1-C_6alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12}alkyl;

A_1 and A_2 are the same or different and are basic amino acid residues;

each of S_1, S_2 and S_3 is either present or absent and is an independently selected amino acid residue;

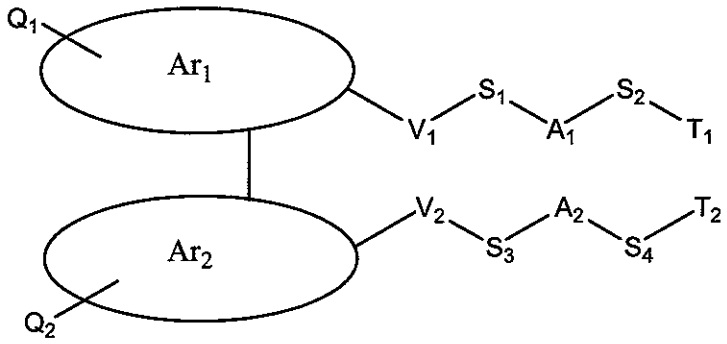
T is present or absent and is selected from –C(O)R_8, –C(O)OR_8, -OR_8, -NHR_8, NHOR_8, -NH-C_6aryl-CO-R_8, -NH-C_6aryl-CO-NHR_8, -NH-C_6aryl-CONHOR_8, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

In a second aspect, there is provided a compound of formula II,



(II)

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

each of V_1 and V_2 is a linker group independently selected from –O-,–O-L-C(O), -O-L-NR_6-, -C(O)-, -NR_6-, -S(O)-, -$S(O)_2$-, -O-L-S(O)-, -$S(O)_2$-L-C(O)-, -$S(O)_2$-L-NR_6-, $P(O)_2O$-;

wherein L is selected from C_1-C_{12}alkyl, C_2-C_8alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10}aryl and C_1-C_6alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12}alkyl;

A_1 and A_2 are the same or different and are basic amino acid residues;

each of S_1, S_2, S_3 and S_4 is either present or absent and is an independently selected amino acid residue;

T_1 is either present or absent and is independently selected from -C(O)R_8, -C(O)OR_8, -OR_8, -NHR_8, -NHOR_8, -NH-C_6aryl-COR_8, -NH-C_6aryl-CONHR_8, -NH-C_6aryl-CONHOR_8, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T_1 forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T1 is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T1 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene;

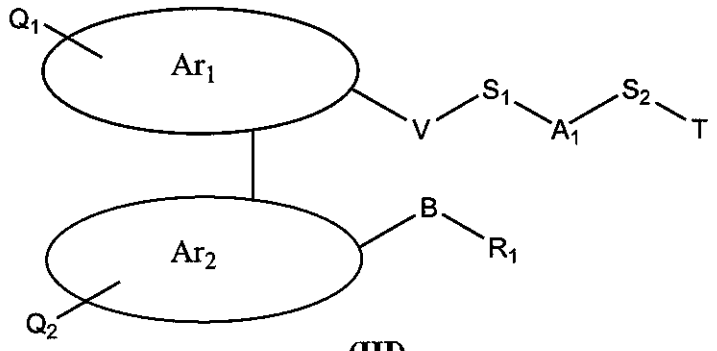
T_2 is either present or absent and is independently selected from -C(O)OR_9, -OR_9, -NHR_9, $NHOR_9$, -NH-C_6aryl-CO-R_9, -NH-C_6aryl-CO-NHR_9, -NH-C_6aryl-$CONHOR_9$, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T_2 forms a carboxylate isostere, optionally substituted with R_9, which replaces the carboxylic acid group of the amino acid to which T_2 is connected;

wherein R_9 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T_2 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

In a third aspect, there is provided a compound of formula III,



(III)

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

B is selected from –O-, -S-, -S(O)-, -$S(O)_2$-, -NH-, and –N(C_1-C_6alkyl)-;

R_1 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkylC_6-C_{10}aryl, C_2-C_6alkenyl, C_2-C_6alkynyl, a polyoxyalkylene having from 2 to 6 carbon atoms, and when B is -S-, -S(O)-, -$S(O)_2$-, -NH- or –N(C_1-C_6alkyl)- then R_1 may be hydroxyl;

V_1 is a linker group selected from selected from –O-, –O-L-C(O), -O-L-NR_6-, -C(O)-NR_6-, -S(O)-, -$S(O)_2$-, -O-L-S(O)-;,-$S(O)_2$-L-C(O)-, -$S(O)_2$-L-NR_6-, -$P(O)_2$O-;

wherein L is selected from C_1-C_{12}alkyl, C_2-C_8alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10} aryl and C_1-C_6alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12} alkyl;

A_1 is a basic amino acid residue;

each of S_1 and S_2 is either present or absent and is an independently selected amino acid residue;

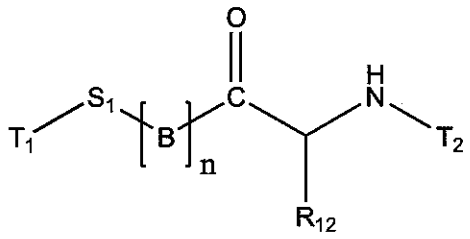
T is present or absent and is selected from -C(O)R_8, -C(O)OR_8, -OR_8, -NHR_8, -NHOR_8, -NH-C_6aryl-COR_8, -NH-C_6aryl-CONHR_8, -NH-C_6aryl-CONHOR_8, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

In a fourth aspect, there is provided a compound of formula IV,



IV

or pharmaceutically acceptable derivatives thereof, wherein

R_{12} is an alkylaromatic or alkylpolyaromatic group optionally substituted with -OC_{1-6}alkyl or -OC_{2-6}alkenyl;

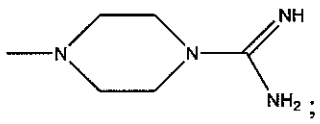
each B is an independently basic amino acid residue;

n = 1 or 2;

S_1 is present or absent and is an independently selected amino acid residue;

T_1 is selected

from $-NHR_{13}$, $-NHOR_{13}$, $-NH-C_6$aryl$-COR_{13}$, $-NH-C_6$aryl$-CONHR_{13}$, $-NH-C_6$aryl$-CONHOR_{13}$,



$-NH-C_6$aryl$-CONHOH$, $-(NH)-SO_2C_6$aryl, $-(NH)COR_{13}$ or ;

or T1 forms a carboxylate isostere, optionally substituted with R_{13}, which replaces the carboxylic acid group of the amino acid to which T_1 is connected;

wherein R_{13} is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T_1 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene;

T_2 is selected from $-C(O)R_{14}$, $-C(O)OR_{14}$, $-OR_{14}$, $-C(O)NHR_{14}$;

wherein R_{14} is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, and CH_2-fluorene;

wherein the optional substituent of R_{12} and the side-chain of S_1 may together form a $-OC_{1-6}$alkylene linking group.

In a fifth aspect, there is a provided a compound of Example 2.

In a sixth aspect, there is provided a composition comprising a compound according to any one of the first to fifth aspects, a salt or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers or adjuvants.

In a seventh aspect, there is provided a method of treating a bacterial infection in a mammal comprising administering an effective amount of compound according to any one of the first to fifth aspects, a salt or a pharmaceutically acceptable derivative thereof.

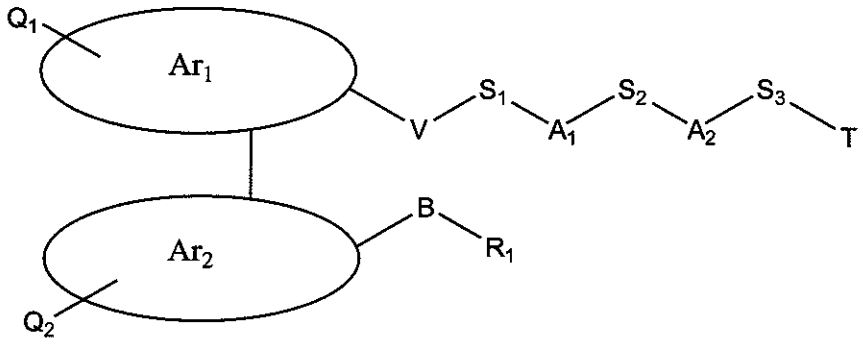
In an eighth aspect, there is provided a method for treatment or prophylaxis of HIV in a subject comprising administering to said subject an effective amount of a compound according to any one of the first to fifth aspects, a salt or a pharmaceutically acceptable derivative thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. shows a diagramatic representation of the antibacterial screening assay design using a 96-well microtitre plate.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention provides a compound of formula I,



I

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

B is selected from –O-, -S-, -S(O)-, $-S(O)_2$-, -NH-, and $-N(C_1$-C_6alkyl)-;

R_1 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkylC_6-C_{10}aryl, C_2-C_6alkenyl, C_2-C_6alkynyl, a polyoxyalkylene having from 2 to 6 carbon atoms, and when B is -S-, -S(O)-, $-S(O)_2$-, -NH- or $-N(C_1$-C_6alkyl)- then R_1 may be hydroxyl;

V is a linker group selected from –O-,–
O-L-C(O), -O-L-NR_6-, -C(O)-, -NR_6-, -S(O)-, $-S(O)_2$-, -O-L-S(O)-, $-S(O)_2$-L-C(O)-, $-S(O)_2$-L-NR_6-, $P(O)_2O$-;

wherein L is selected from C_1-C_{12}alkyl, C_2-C_8 alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10}aryl and C_1-C_6alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12}alkyl;

A_1 and A_2 are the same or different and are basic amino acid residues;

each of S_1, S_2 and S_3 is either present or absent and is an independently selected amino acid residue;

T is present or absent and is selected from –C(O)OR_8, -OR_8, -NHR_8, NHOR_8, -NH-C_6aryl-CO-R_8, -NH-C_6aryl-CO-NHR_8, -NH-C_6aryl-$CONHOR_8$, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T is connected;

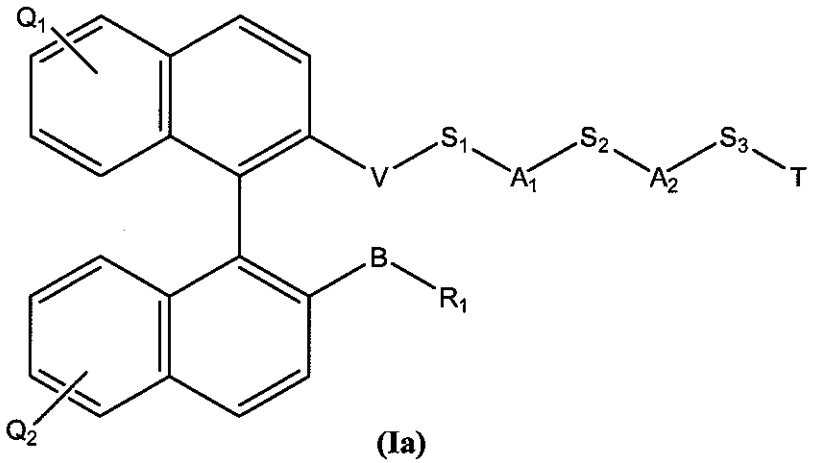
wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

Preferably, A_1 and A_2 are each independently selected from the group consisting of lysine, arginine and ornithine. More preferably A_1 is selected from lysine and ornithine and A_2 is selected from arginine.

Preferably, S_1 and S_2 are absent.

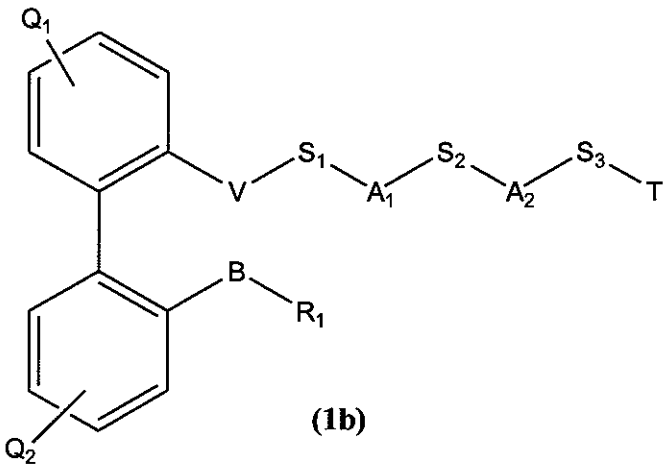
In a preferred embodiment, the compound of formula I is of formula Ia:



(Ia)

wherein Q_1, Q_2, V, S_1, A_1, S_1, A_2, S_3, T, B and R_1 are as defined above.

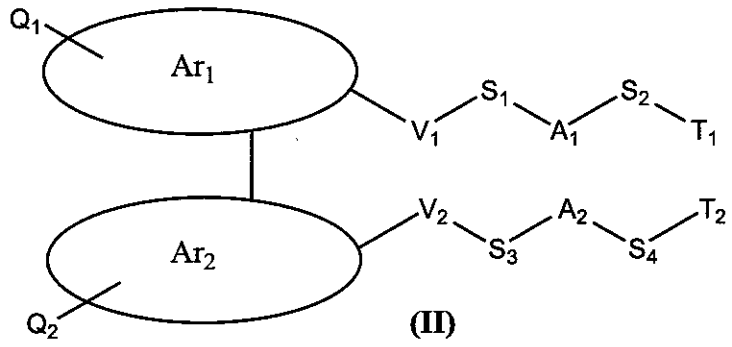
In a further preferred embodiment, the compound of formula I is of formula Ib:



(1b)

wherein Q_1, Q_2, V, S_1, A_1, S_1, A_2, S_3, T, B and R_1 are as defined above.

In a second aspect, there is provided a compound of formula II,



(II)

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

each of V_1 and V_2 is a linker group independently selected from –O-,–O-L-C(O), -O-L-NR_6-, -C(O)-, -NR_6-, -S(O)-, -$S(O)_2$-, -O-L-S(O)-, -$S(O)_2$-L-C(O)-, -$S(O)_2$-L-NR_6-, -$P(O)_2O$-;

wherein L is selected from C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10}aryl and C_1-C_{16}alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12}alkyl;

A_1 and A_2 are the same or different and are basic amino acid residues;

each of S_1, S_2, S_3 and S_4 is either present or absent and is an independently selected amino acid residue;

T_1 is either present or absent and is independently selected from -C(O)OR_8, -OR_8, -NHR_8, -$NHOR_8$, -NH-C_6aryl-COR_8, -NH-C_6aryl-$CONHR_8$, -NH-C_6aryl-$CONHOR_8$, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T1 forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T1 is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T1 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene;

T_2 is either present or absent and is independently selected from -C(O)OR_9, -OR_9, -NHR_9, $NHOR_9$, -NH-C_6aryl-CO-R_9, -NH-C_6aryl-CO-NHR_9, -NH-C_6aryl-$CONHOR_9$, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T_2 forms a carboxylate isostere, optionally substituted with R_9, which replaces the carboxylic acid group of the amino acid to which T_2 is connected;

wherein R_9 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

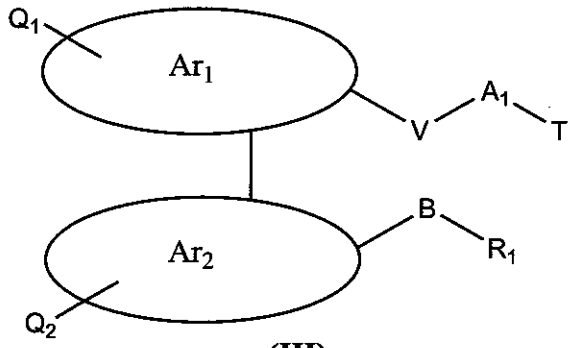
wherein when T_2 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

Preferably, A_1 and A_2 are each independently selected from the group consisting of lysine, arginine and ornithine.

Preferably, A_1 and A_2 are the same.

Preferably, S_1, S_2, S_3 and S_4 are absent.

In a third aspect, there is provided a compound of formula III,



(III)

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

B is selected from –O-, -S-, -S(O)-, $-S(O)_2$-, -NH-, and $-N(C_1$-C_6alkyl)-;

R_1 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkylC_6-C_{10}aryl, C_2-C_6alkenyl, C_2-C_6alkynyl, a polyoxyalkylene having from 2 to 6 carbon atoms, and when B is -S-, -S(O)-, $-S(O)_2$-, -NH- or $-N(C_1$-C_6alkyl)- then R_1 may be hydroxyl;

V_1 is a linker group selected from selected from –O-, –O-L-C(O), -O-L-NR_6-, -C(O)-NR_6-, -S(O)-, $-S(O)_2$-, -O-L-S(O)-;,$-S(O)_2$-L-C(O)-, $-S(O)_2$-L-NR_6-, $P(O)_2$O-

wherein L is selected from C_1-C_{12}alkyl, C_2-C_8alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10} aryl and C_1-C_6alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12} alkyl;

A_1 is a is a basic amino acid residue;

each of S_1 and S_2 is either present or absent and is an independently selected amino acid residue;

T is present or absent and is selected from – C(O)OR_8, -OR_8, -NHR_8, -NHOR_8, -NH-C_6aryl-COR_8, -NH-C_6aryl-CONHR_8, -NH-C_6aryl-CONHOR_8, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

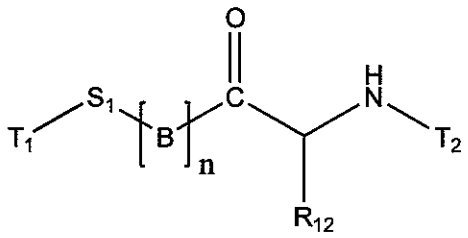
or T forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

Preferably, A_1 is selected from lysine, arginine and ornithine.

In a fourth aspect, there is provided a compound of formula IV,



IV

or pharmaceutically derivatives thereof, wherein

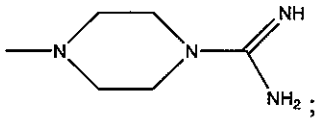
R_{12} is an alkylaromatic or alkylpolyaromatic group optionally substituted with -OC_{1-6}alkyl or -OC_{2-6}alkenyl;

each B is an independently selected basic amino acid residue;

n = 1 or 2;

S_1 is present or absent and is an independently selected amino acid residue;

T_1 is selected
from -NHR_{13}, -$NHOR_{13}$, -NH-C_6aryl-COR_{13}, -NH-C_6aryl-$CONHR_{13}$, -NH-C_6aryl-$CONHOR_{13}$,



-NH-C_6aryl-CONHOH, -(NH)-SO_2C_6aryl, -(NH)COR_{13} or ;

or T_1 forms a carboxylate isostere, optionally substituted with R_{13}, which replaces the carboxylic acid group of the amino acid to which T_1 is connected;

wherein R_{13} is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T_1 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene;

T_2 is selected from $-C(O)R_{14}$, $-C(O)OR_{14}$, $-OR_{14}$, $-C(O)NHR_{14}$;

wherein R_{14} is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, and CH_2-fluorene;

wherein the optional substituent of R_{12} and the side-chain of S_1 may together form a $-OC_{1-6}$alkylene linking group.

Preferably, R_{12} is selected from–CH_2-phenyl-$OCH_2CH{=}CH_2$ and $-CH_2$-phenylanthracene. Preferably, S_1 is selected from allylglycine. Preferably, T_2 is $-C(O)CH_3$. Preferably, T_1 is CH_3O-. Preferably, B is arginine or lysine.

In a fifth aspect, there is provided a compound of Example 2.

Preferably the compound of Example 2 is selected from **69**, **70**, **71**, **72**, **73**, **74**, **75**, **76**, **83**, **32**, **37**, **65**, **56**, **118**, **119**, **120**, **121**, **132**, **90**, **134**, **135**, **136**, **137**, **139**, **140**, **141**, **159**, **160**, **163**, **164**, **78**, **81**, **88**, **87**, **89**, **165**, **166**, **167**, and **168**.

It would be understood by the person skilled in the art the peptide chain formed by the combination of the amino acid residues of the compounds of the present invention could be a peptide or a reverse peptide depending on the nature of the linker group V: for example, where the group V is of the form –O-L-C(O)- then the peptide will be a peptide chain with its N-terminus bound to V whereas if the group V is of the form –O-L-NH- then the peptide will be a reverse peptide chain with its C-terminus bound to V.

As is well known to those skilled in the art, the term carboxylate isostere includes any moiety capable of replacing the carboxylate group of an amino acid. Suitable carboxylate isosteres include tetrazole (ref: e.g JOC 1992, 57, 202-209; JACS 1998, 110, 5875-5880 or Tet.Lett, 1993, 34, 1757-1760.), isoxazole, oxazole and thiazole.

As used herein, the term "halo" or "halogen" refers to fluorine (fluoro), chlorine (chloro), bromine (bromo) or iodine (iodo).

As used herein, the term "alkyl" either used alone, having 1 to 12, preferably 1 to 8, more preferably 1 to 6, carbon atoms, or in compound terms such as NH(alkyl) or $N(alkyl)_2$, refers to monovalent straight chain or branched hydrocarbon groups having 1 to 12 carbon atoms, including their stereoisomeric forms if applicable. For example, suitable alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 2-, 3- or 4-methylpentyl, 2-ethylbutyl, n-hexyl, and 2-, 3-, 4- or 5-methylpentyl.

As used herein, the term "alkenyl" refers to straight chain or branched hydrocarbon groups having one or more double bonds between carbon atoms. Suitable alkenyl groups include, but are not limited to ethenyl, propenyl, isopropenyl, butenyl, pentenyl and hexenyl.

The term "alkynyl" as used herein, refers to straight chain or branched hydrocarbon groups containing one or more triple bonds. Suitable alkynyl groups include, but are not limited to ethynyl, propynyl, butynyl, pentynyl and hexenyl.

The term "cycloalkyl" as used herein, refers to cyclic hydrocarbon groups. Suitable cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "aryl" as used herein, refers to a C_6-C_{10} aromatic hydrocarbon group, for example phenyl or naphthyl.

The term "heterocycle" when used alone or in compound words includes monocyclic, polycyclic, fused or conjugated hydrocarbon residues, preferably C_{3-6},wherein one or more carbon atoms (and where appropriate, hydrogen atoms attached thereto) are replaced by a heteroatom so as to provide a non-aromatic or aromatic residue. Suitable heteroatoms include, O, N and S. Where two or more carbon atoms are replaced, this may be by two or more of the same heteroatom or by different heteroatoms. Suitable examples of heterocyclic groups may include pyrrolidinyl, pyrrolinyl, piperidyl, piperazinyl, morpholino, indolinyl, indazolyl, quinolinyl, isoquinolinyl, imidazolidinyl, pyrazolidinyl, thiomorpholino, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrrolyl etc.

Each alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclyl group may be optionally substituted with C_1-C_6alkyl, OH, OC_1-C_6alkyl, halo, CN, NO_2, CO_2H, CO_2C_1-C_6alkyl, $CONH_2$, CONH(C_1-C_6alkyl), CON(C_1-C_6alkyl)$_2$, trifluoromethyl, C_6aryl, C_3-C_6cycloalkyl, hetrocyclyl, NH_2, NH(C_1-C_6alkyl) or N(C_1-C_6alkyl)$_2$. For example, an optionally substituted aryl group may be 4-methylphenyl or 4-hydroxyphenyl group, and an optionally substituted alkyl group may be 2-hydroxyethyl, trifluoromethyl, or difluoromethyl. Futher, methyl substituents (C_1alkyl) may be substituted with an optionally sustitued aryl to form a benzyl substituent.

As used herein, the term "amino acid residue" refers to an amino acid which is bound by means of amide bonds or suitable replacements thereof to one or more of the linker group V, other amino acid residues and the terminal group T. The amino acid may be an α-amino acid or a β-amino acid. A suitable replacement for the amide bond can be any replacement that is known in the art as it is well known that where two amino acids or a combination of natural and unnatural amino acids are joined together to form an amide bond between them the bond can be replaced by a suitable link, which may be called a peptoid (discussion of this may be found in PM Fischer 'The design, synthesis and application of stereochemical and directional peptide isosteres a critical review' *Curr. Protein and Peptide Science*, 2003, 4(5), 339-356 and references therein). Examples of suitable replacements include, but are not limited to:

reduced amide: amino methylene: CH_2NH; (Szelke, M., Leckie, B.; Hallet A., Jones, D.M., Sueiras, J.; Atrash.B.; Lever, A., Nature, 19821982, 299, 555-557.; Ambo A, Adachi T, Sasaki Y. Synthesis and opioid activities of [D-Leu-8]Dynorphin(1-8) analogs containing a reduced peptide bond, psi(CH_2-NH). Chem Pharm Bull (Tokyo). 1995, 43(9), 1547-50)

ether bond : CH_2O; (Hedenstrom M, Yuan Z, Brickmann K, Carlsson J, Ekholm K, Johansson B, Kreutz E, Nilsson A, Sethson I, Kihlberg j. Conformations and receptor activity of desmopressin analogues, which contain gamma-turn mimetics or a psi[$CH_{(2)}$O] isostere. J Med Chem. 2002, 45(12), 2501-11)

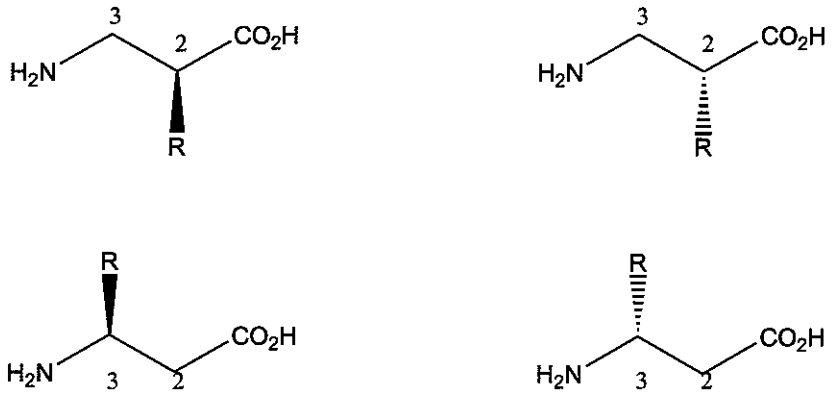
hydroxy ethylene $CHOHCH_2$- and ketomethylene $COCH_2$; (Harbeson SL, Rich DH. Inhibition of aminopeptidases by peptides containing ketomethylene and hydroxyethylene amide bond replacements. J Med Chem. 1989, 32(6), 1378-92)

urea NHCONH; (Dales NA, Bohacek RS, Satyshur KA, Rich DH. Design and synthesis of unsymmetrical peptidyl urea inhibitors of aspartic peptidases Org Lett. 2001, 3(15), 2313-6)

The amino acid may be a L- or D- isomer and may have a naturally occurring side chain or a non-naturally occurring side chain. The amino acid may also be further substituted in the α-position or the β-position with a group selected from -C_1-C_{12}alkyl, -C_2-C_6alkenyl, -C_2-C_6alkynyl, -$(CH_2)_nCOR_a$, -$(CH_2)_nR_b$, -PO_3H, -$(CH_2)_n$heterocyclyl or -$(CH_2)_n$aryl where R_a is -OH, -NH_2, -NHC_1-C_6alkyl, -OC_1-C_{12}alkyl or -C_1-C_{12}alkyl and R_b is -OH, -SH, -SC_1-C_6alkyl, -OC_1-C_{12}alkyl, -C_3-C_6cycloalkyl, -C_3-C_6cycloalkenyl, -NH_2, -NHC_1-C_6alkyl or -$NHC(C{=}NH)NH_2$, n is 0 or an integer from 1 to 6 and where each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclyl group may be substituted with one or more groups selected from -OH, -NH_2, -NHC_1-C_6alkyl, -OC_1-C_{12}alkyl, -SH, -SC_1-C_6alkyl, -CO_2H, -CO_2C_1-C_6alkyl, -$CONH_2$ or -$CONHC_1$-C_6alkyl.

The term "α-amino acid" as used herein, refers to a compound having an amino group and a carboxyl group in which the amino group and the carboxyl group are separated by a single carbon atom, the α-carbon atom. An α-amino acid includes naturally occurring and non-naturally occurring L-amino acids and their D-isomers and derivatives thereof such as salts or derivatives where functional groups are protected by suitable protecting groups. The α-amino acid may also be further substituted in the α-position with a group selected from -C_1-C_{12}alkyl, -C_2-C_{10}alkenyl, -C_2-C_{12}alkynyl, -$(CH_2)_nCOR_1$, -$(CH_2)_nR_2$, -PO_3H, -$(CH_2)_n$heterocyclyl or -$(CH_2)_n$aryl where R_1 is -OH, -NH_2, -NHC_1-C_{12}alkyl, -OC_1-C_{12}alkyl or C_1-C_{12}alkyl and R_2 is -OH, -SH, -SC_1-C_6alkyl, -OC_1-C_{12}alkyl, -C_3-C_6cycloalkyl, -C_3-C_6cycloalkenyl, -NH_2, -NHC_1-C_3alkyl or -$NHC(C{=}NH)NH_2$, n is 0 or an integer from 1 to 10 and where each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclyl group may be substituted with one or more groups selected from -OH, -NH_2, -NHC_1-C_6alkyl, -OC_1-C_{12}alkyl, -SH, -SC_1-C_6alkyl, -CO_2H, -CO_2C_1-C_6alkyl, -$CONH_2$ or -$CONHC_1$-C_6alkyl.

As used herein, the term "β-amino acid" refers to an amino acid that differs from an α-amino acid in that there are two (2) carbon atoms separating the carboxyl terminus and the amino terminus. As such, β-amino acids with a specific side chain can exist as the *R* or *S* enantiomers at either of the α (C2) carbon or the β (C3) carbon, resulting in a total of 4 possible isomers for any given side chain. The side chains may be the same as those of naturally occurring α-amino acids or may be the side chains of non-naturally occurring amino acids.



Furthermore, the β-amino acids may have mono-, di-, tri- or tetra-substitution at the C2 and C3 carbon atoms. Mono-substitution may be at the C2 or C3 carbon atom. Di-substitution includes two substituents at the C2 carbon atom, two substituents at the C3 carbon atom or one substituent at each of the C2 and C3 carbon atoms. Tri-substitution includes two substituents at the C2 carbon atom and one substituent at the C3 carbon atom or two substituents at the C3 carbon atom and one substituent at the C2 carbon atom. Tetra-substitution provides for two substituents at the C2 carbon atom and two substituents at the C3 carbon atom. Suitable substituents include -C_1-C_{12}alkyl, -C_2-C_6alkenyl, -C_2-C_6alkynyl, -$(CH_2)_nCOR_a$, -$(CH_2)_nR_b$, -PO_3H, -$(CH_2)_n$heterocyclyl or -$(CH_2)_n$aryl where R_a is -OH, -NH_2, -NHC_1-C_6alkyl, -OC_1-C_{12}alkyl or -C_1-C_{12}alkyl and R_b is -OH, -SH, -SC_1-C_6alkyl, -OC_1-C_{12}alkyl, -C_3-C_6cycloalkyl, -C_3-C_6cycloalkenyl, -NH_2, -NHC_1-C_6alkyl or -$NHC(C{=}NH)NH_2$, n is 0 or an integer from 1 to 6 and where each alkyl, alkenyl, alkynyl cycloalkyl, cycloalkenyl, aryl or heterocyclyl group may be substituted with one or more groups selected from -OH, -NH_2, -NHC_1-C_6alkyl, -OC_1-C_{12}alkyl, -SH, -SC_1-C_6alkyl, -CO_2H, -CO_2C_1-C_6alkyl, -$CONH_2$ or -$CONHC_1$-C_6alkyl.

The term "non-naturally occurring amino acid" as used herein, refers to amino acids having a side chain that does not occur in the naturally occurring L-α-amino acids. Examples of non-natural amino acids and derivatives include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids.

The term "basic amino acid" includes any amino acid having a side chain that can act as a base and generally includes amino acids having a side chain bearing one or more nitrogen atoms. Included within the definition are the naturally occurring basic L-amino acids lysine, arginine, and histidine and their D-isomers. Further included are the L- and D- forms of ornithine; 2-,3- and 4- amidinophenylglycine; 2,3, and 4 amidinophenylalanine; 2-, 3- and 4-guanidinophenylglycine; pyridylalanine; cysteic- and homocysteic acid-S-(aminoiminomethyl) amides; and amidinopiperidinylalanine. Preferably, the side-chain comprises an amino group (NH_2) or an amino group substituted on the nitrogen atom with up to two substituents. Examples of optional substituents include C_1-C_{12}alkyl, C_3-C_7cycloalkyl, C_6-C_{10}aryl, benzyl, and suitable nitrogen protecting groups (see "Protective Groups in Organic Synthesis" Theodora Greene and Peter Wuts, third edition, Wiley Interscience, 1999). Preferably, the amino group

is capable of carrying a positive charge at physiological pH. In a preferred form of the invention, the side chain comprises a substituent selected from a group consisting of: $-N(R_{10})_2$, $-N(R_{10})-COR_{11}$, $-NR_{10}C(=NR_{10})N(R_{10})_2$, $-C(=NR_{10})N(R_{10})_2$, $-NR_{10}C(=O)N(R_{10})_2$, $-N=NC(=NR_{10})N(R_{10})_2$, $NR_{10}NR_{10}C(=O)NHN(R_{10})_2$, $-NR_{10}CC=NHN(R_{10})_2$ wherein each R_{10} is independently selected from hydrogen and C_1-C_6alkyl and R11 is selected from hydrogen, hydroxy, C_1-C_{12}alkyl, C_1-C_6alkoxy and NR_{10}; and 3-8-membered N-containing heterocyclic group such as piperidinyl, pyrollodinyl, imidazolinyl, pyrazolidinyl or piperazinyl, wherein the 3-8-membered N-containing heterocyclic group can be attached via a nitrogen or carbon atom. Preferred substituents include optionally substituted guanidine [$-NHC(=NH)NH_2$], amidino [$-C(=NH)NH_2$], ureido [$-NHC(=O)NH_2$], carbazono [$-N=NC(=)NHNH_2$], carbazido [$-NHNHC(=O)NHNH_2$] and semicarbazido [$-NHC(=O)NHNH_2$] and amino ([NH_2].

The compounds of the present invention include binaphthyl derivatives. Substituted binaphthyl derivatives are chiral compounds. The present invention encompassed both enantiomeric forms. Preferably, when the compound of the present invention is a 2,2'-binapthyl derivative then the binapthyl group is in the S configuration.

The term "pharmaceutically acceptable derivative" may include any pharmaceutically acceptable salt, hydrate or prodrug, or any other compound which upon administration to a subject, is capable of providing (directly or indirectly) a compound of the present invention or a pharmaceutically active metabolite or residue thereof.

The salts of the compound of formulae (I) to (IV) are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include, but are not limited to, salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, malic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, zinc, ammonium, alkylammonium such as salts formed from triethylamine, alkoxyammonium such as those formed with ethanolamine and salts formed from ethylenediamine, choline or amino acids such as arginine, lysine or histidine. General information on types of pharmaceutically acceptable salts and their formation is known to those skilled in the art and is as described in general texts such as "*Handbook of Pharmaceutical salts*" P.H.Stahl, C.G.Wermuth , 1st edition, 2002, Wiley-VCH.

Basic nitrogen-containing groups may be quarternised with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds in which a free hydroxy group is converted into a group, such as an ester, carbonate or

carbamate, which is capable of being converted *in vivo* back to a hydroxy group. A prodrug may include modifications of one or more of the functional groups of a compound of formula (1). In particular, compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (eg, two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy and carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvlin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methioine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include phosphate derivatives of compounds of the present invention (such as acids, salts of acids, or esters) joined through a phosphorus-oxygen bond to a free hydroxyl of the compoundI.

It will also be recognised that the compounds of the first to fifth aspects may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres eg., greater than about 90% ee, such as about 95% or 97% ee or greater than 99% ee, as well as mixtures, including racemic mixtures, thereof. Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediates, or by chiral resolution.

In a sixth aspect, there is provided a composition comprising a compound according to any one of the first to fifth aspects, a salt or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers or adjuvants.

The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

In a seventh aspect, there is provided a method of treating a bacterial infection in a mammal comprising administering an effective amount of compound according to any one of the first to fifth aspects, a salt or a pharmaceutically acceptable derivative thereof.

Yet another aspect of the present invention provides a use of a compound of the first to fifth aspects in the preparation of a medicament for treating or preventing bacterial infection. They are particularly useful for treating infections caused by Gram positive bacteria such as enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermis, Klebsiella pneumoniae, Streptococcus pneumoniae, including multi-resistant strains such as vancomycin resistant Staphylococcus aureus and methicillin-resistant Staphylococcus aureus.

Accordingly the invention provides the use of a compound of the first to fifth aspects for treatment or prophylaxis of bacterial infections and provides method comprising of administering an suitable amount of a compound according to one of the first to fifth aspects.

Suitable dosages may lie within the range of about 0.1 ng per kg of body weight to 1 g per kg of body weight per dosage. The dosage is preferably in the range of 1 μg to 1 g per kg of body weight per dosage, such as is in the range of 1 mg to 1 g per kg of body weight per dosage. In one embodiment, the dosage is in the range of 1 mg to 500 mg per kg of body weight per dosage. In another embodiment, the dosage is in the range of 1 mg to 250 mg per kg of body weight per dosage. In yet another preferred embodiment, the dosage is in the range of 1 mg to 100 mg per kg of body weight per dosage, such as up to 50 mg per kg of body weight per dosage. In yet another embodiment, the dosage is in the range of 1μg to 1mg per kg of body weight per dosage.

Suitable dosage amounts and dosing regimens can be determined by the attending physician and may depend on the severity of the condition as well as the general age, health and weight of the subject.

The active ingredient may be administered in a single dose or a series of doses. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a composition, preferably as a pharmaceutical formulation.

This invention thus further provides pharmaceutical formulation comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carriers(s) must be "acceptable' in the sense of being compatible with other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The compounds of the invention, together with a conventional adjuvant, carrier or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids as solutions, suspensions, emulsions, elixirs or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

The subjects treated in the above method are mammals, including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species, and preferably a human being, male or female.

As used herein, the term "effective amount" relates to an amount of compound which, when administered according to a desired dosing regimen, provides the desired treatment of the bacterial infection or therapeutic activity, or disease prevention. Dosing may occur at intervals of minutes, hours, days, weeks, months or years or continuously over any one of these periods. A therapeutic, or treatment, effective amount is an amount of the compound which,

when administered according to a desired dosing regimen, is sufficient to at least partially attain the desired therapeutic effect, or delay the onset of, or inhibit the progression of or halt or partially or fully reverse the onset or progression of the bacterial infection. A prevention effective amount is an amount of compound which when administered according to the desired dosing regimen is sufficient to at least partially prevent or delay the onset of a particular disease or condition.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds which are usually applied in the treatment of the above mentioned pathological conditions. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

When other therapeutic agents are employed in combination with the compounds of the present invention they may be used for example in amounts as noted in the Physician Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

In addition to the antibacterial properties of compounds of the present invention, the present inventors have also found that compounds of the present invention are also effective in treating HIV. Accordingly, in an eighth aspect the present invention provides a method for treatment or prophylaxis of HIV in a subject comprising administering to said subject an effective amount of a compound according to any one of the first to fourth aspects, a salt or a pharmaceutically acceptable derivative thereof.

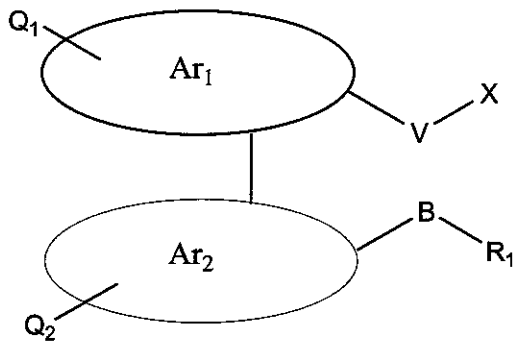
Preferably, the compound is selected from one or more of the following compounds of Example 2: **78**, **81**, **88**, **89**, **165**, **166**, **167**, **168**, **83**, **119**, **164**, **163**, **158**.

In order that the nature of the present invention may be more clearly understood, preferred forms thereof will now be described with reference to the following non-limiting examples.

EXPERIMENTAL

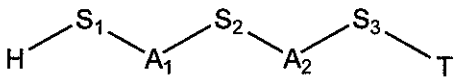
Compounds of Formulae (I) to (III) may be prepared using the methods depicted or described herein or known in the art for the preparation of compounds of analogous structure. It will be understood that minor modifications to methods described herein or known in the art may be required to synthesise particular compounds of Formula (1). General synthetic procedures applicable to the synthesis of compounds may be found in standard references such as *Comprehensive Organic Transformations*, R. C. Larock, 1989, VCH Publishers, *Advanced Organic Chemistry*, J. March, 4th edition, 1992, Wiley InterScience, *Amino Acid and Peptide Synthesis*, J.Jones, (Oxford Chemistry Primers) 2nd edition 2002, Oxford university press, *The practice of peptide synthesis*, 2003, 2nd edition, M. Bodansky and A. Bodansky, Springer-Verlag, New York and references therein. It will also be recognised that certain reactive groups may require protection and deprotection during the synthetic process. Suitable protecting and deprotecting methods for reactive functional groups are known in the art for example in *Protective Groups in Organic Synthesis*, T. W. Greene & P. Wutz, John Wiley & Son, 3rd Edition, 1999.

Compounds of formula (I) as described above, may be prepared by reacting a compound of formula (A):



A

wherein X is OH or an activating group; with a compound of formula (B) under appropriate conditions.



B

wherein B, R_1, Ar_1, Ar_2, V, Q_1, Q_2, S_1, A_1, S_2, A_2, S_3, T are as defined in formula (I).

Conveniently the reaction between compounds formulae (A) and (B) is based upon forming an amide bond and may be conducted using approaches routinely used in peptide synthesis. For example, the coupling reaction of an amine with a carboxylic acid (X=OH) or an activated carbonyl carbon such as an acyl chloride , acyl azide , acyl-succinimide or an anhydride (X= Cl, N3, O-succinimde, OC(O)R).

Compounds of the formula (A) may be conveniently prepared from an aromatic or heteroaromatic ring system carrying any of;

desired substituents

functional groups which may be converted into desired substituents using conventional approaches known to those skilled in the art; or

appropriately activated positions on the nucleus of the ring system such that desired substituents may be placed on the ring system using conventional approaches known to those skilled in the art.

In addition the ring system Ar_1-Ar_2 includes a position that may be converted into the group BR1. This position may be a functional group or may be an appropriately activated position on the ring to allow conversion into functional groups using conventional approaches known to those skilled in the art. For example functional groups include hydroxyl, amino and suitably protected derivatives of these. Examples of suitably activated positions include those which may be alkylated or acylated such as phenoxide.

The compound of formula (B) can be prepared using any suitable approach readily ascertainable to those skilled in the art. Preferably compound (B) can be formed by reactions of suitably protected amino acids in a suitable sequence. In one preferred approach this is based upon formation of amide bonds and may be conducted using approaches routinely used in peptide synthesis, for example, the reaction of an amine with an appropriately activated carbonyl group. Preferably compound (B) may have a protecting group on the amino terminus of S1 or S2 which is removed once the group S1A1S2A2S3T has been formed to allow coupling of S1 or A1 to V of compound (A). Those skilled in the art can readily determine the appropriate methodology to build the desired group (B).

Where appropriate , protecting groups may be used to mask certain positions on the compounds of formulae (A) and (B) so as to avoid or limit unwanted side reactions.

Suitable aromatic or heteraromatic ring systems may be commercially available or be readily prepared from commercially available ring systems or ring system precursors.

The compounds of the present invention may be prepared according to the general procedure of Scheme 1. Although this process is illustrated using specific reagents and compounds, it will be appreciated by one of skill in the art that suitable analogous reagents may be used to prepare analogous products, as depicted, for example, in scheme 1.

As would be understood by persons skilled in the art compounds of formulae II and III can be prepared by similar methods (after appropriate modification) to those used to produce compounds of formula I.

Example 1 Preparation and Biological Activity of Compounds according to the Present Invention

General Synthetic Procedures

Protocol 1: Peptide Coupling

To a stirred solution of an acid (1 equiv.) and an amine (1 equiv.) in dry acetonitrile or DMF (5-10 mls) was added EDCI (1.2 equiv.) and HObt (1.2 equiv.). If the amine was a HCl salt then 1 equivalent of DIPEA was also added. The reaction mixture was stirred overnight before the solvent was removed and the resultant residue subjected to flash silica gel column chromatography (normally using 2%MeOH/DCM as the eluant) to afford the desired compound

Protocol 2: *N*-Fmoc Deprotection

To a stirring solution of the Fmoc-protected peptide in dry acetonitrile (5-10 mls) was added piperidine (0.1 ml). The resultant solution was then stirred at room temperature for 3 hours. The solvent was then removed and the resultant residue subjected to flash silica gel chromatography using a short column (using 2%MeOH/DCM then 5%MeOH/DCM upon removal of Fmoc byproducts) to afford the desired compound.

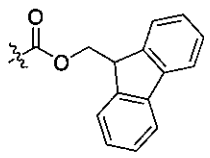
Protocol 3: *N*-Boc & PMC/PBF Deprotection

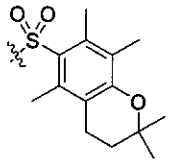
To a stirring solution of the protected peptide in DCM (2 mls) was added TFA (2 mls). The reaction mixture was stirred at room temperature for three hours before the solvent was removed. After triturating twice more with DCM (2 mls), the residue was taken up in DCM (2 ml) and treated with a HCl/ether solution (2 ml, 1M), stirred for a minute and evaporated to dryness. This treatment with HCl was repeated twice more. For BOC-deprotection this is the final step, for PMC/PBF-deprotection the following is completed. The residue is taken up in DCM (or dry MeOH if insoluble in DCM), precipitated by the addition of ether and the solid collected by centrifugation. This step is repeated once more to remove the protecting group byproduct. The resultant solid is then dried to yield the desired compound as its hydrochloride salt.

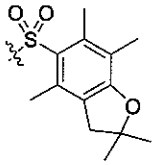
Protocol 4

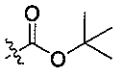
To a stirring solution of the acid, alcohol, and triphenylphosphine in THF at 0°C under a nitrogen atmosphere was added DIAD dropwise. The solution was allowed to warm to room temperature and stirred overnight. The solvent was then removed in *vacuo* and the resulting residue purified by flash column chromatography over silica to yield the desired product.

Protecting Groups

Fmoc = 

PMC = 

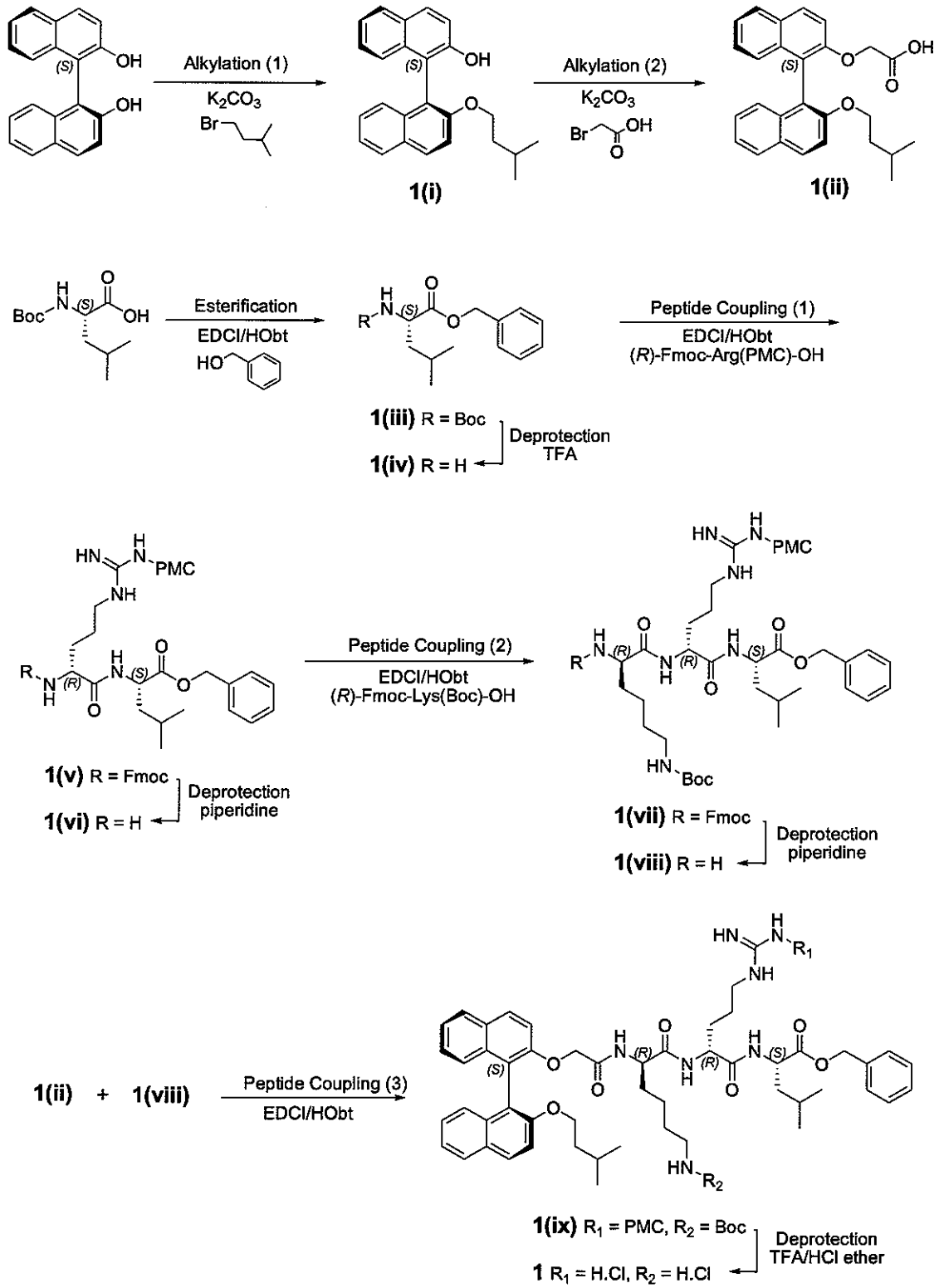
PBF = 

Boc = 

General Notes

Melting point determinations were carried out on a Gallenkamp melting point apparatus. Chemical ionization (CI) and electron impact (EI) mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer by a direct insertion technique with an electron beam energy of 70 eV. Electrospray (ES) *m/z* mass spectra were obtained on a VG Autospec spectrometer. High-resolution mass spectra (HRMS) were determined on a micromass QTof2 spectrometer using polyethylene glycol or polypropylene glycol as the internal standard. The *m/z* values are stated with their peak intensity as a percentage in parentheses. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained as specified on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer. Spectra were recorded in the specified deuterated solvent, and referenced to the residual non-deuterated solvent signal. Chemical shifts (δ) in ppm were measured relative to the internal standard. Multiplet (m) signals are reported from the centre of the peak. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} pre-coated aluminium plates with a thickness of 0.2 mm. All column chromatography was performed under 'flash' conditions on Merck silica gel 60 (230-400 mesh). Chromatography solvent mixtures were measured by volume. All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and TLC analysis. Starting materials and reagents were purchased from Sigma-Aldrich Pty Ltd or Auspep Pty Ltd and were used as received.

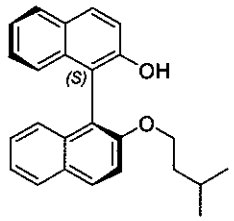
General Synthetic Scheme (Example – Compound 1)



Compounds of Formula I

Synthesis of Compound 1

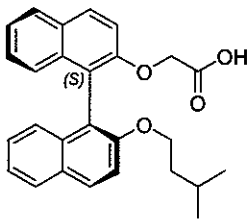
1(i)



To a solution of 1,1'-binaphth-2,2'-diol (1 g, 3.49 mmol) in dry acetone (100 ml) was added anhydrous potassium carbonate (5g). A solution of 1-bromo-3-methylbutane (0.52 ml, 4.19 mmol) in acetone (30 ml) was added dropwise over a 90 min period. The mixture was then heated at reflux for 3 hrs and left to sit overnight before being cooled and filtered. The solid residue was then washed twice more with acetone (10 ml) before the combined organic extracts were evaporated to dryness to yield a honey coloured oil. Subsequent flash column chromatography with 1:1 DCM/Hexane as the eluant affords the desired product **1(i)** as a yellow oil (705 mg, 57%). R_f = 0.64 (1:1 hexane/DCM). Starting diol was also recovered (357 mg, 36%) indicating the reaction had not gone to completion.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61, d, J = 6.5 Hz, 3H; 0.65, d, J = 6.5 Hz, 3H; 1.32, m, 3H; 3.98, m, 2H; 4.95, s, OH; 7.04, dist d, J = 7.8 Hz, 1H; 7.25, m, 7H; 7.42, d, J = 9.1 Hz, 1H; 7.84, d, J = 7.8 Hz, 1H; 7.87, d, J = 8.7 Hz, 1H; 7.99, d, J = 9.0, Hz, 1H.

1(ii)

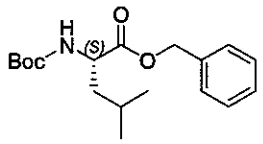


To **1(i)** (532 mg, 1.49 mmol) in dry MeOH (25 ml) was added potassium carbonate (2.06 g, 14.9 mmol) and bromoacetic acid (1.03 g, 7.45 mmol). The resultant solution was then heated at reflux for 8 hrs over which time a white ppte had fallen out of solution. The reaction mixture was then evaporated to dryness and the residue dissolved in water (50 ml). This was then washed with ether (3 x 30 ml) before the aqueous layer was acidified with 3M HCl. This acidified solution was then extracted with DCM (3 x 30 ml) to yield a yellow solution. This yellow solution was then dried ($MgSO_4$) and evaporated to dryness to yield the product **1(ii)** as a yellow oil (325 mg, 53%). Starting material was also recovered (135 mg, 25%) indicating the reaction had not gone to completion.

^{1}H NMR (300MHz, $CDCl_3$) δ 0.54, d, J = 6.5 Hz, 3H; 0.64, d, J = 6.5 Hz, 3H; 1.19, m, 1H; 1.30, m, 2H; 3.94, m, 1H; 4.13, m, 1H; 4.57, ABq, J = 16.8 Hz, 1H; 4.69, ABq, J = 16.8 Hz, 1H; 7.26, m, 4H; 7.37, m, 3H; 7.48, d, J =

8.8 Hz, 1H; 7.90, d, J = 8.2 Hz, 2H; 7.97, d, J = 8.8 Hz, 1H; 8.00, d, J = 8.8, Hz, 1H; 8.06, br s, COOH. MS (EI +ve) 414 (100%) $[M+H]^+$.

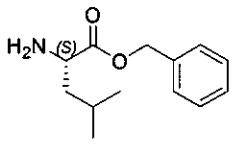
1(iii)



This compound was prepared *via* Protocol 1, using BOC-(*L*)-leu-OH (600 mg, 2.59 mmol) and BzOH (0.41 ml, 4.0 mmol) to yield the desired product **1(iii)** as an off white solid (512 mg, 62%). R_f = 0.78 (5%MeOH/DCM), staining with Mo dip.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91, d, J = 6.5 Hz, 6H; 1.44, m, 2H; 1.45, s, 9H; 1.66, m, 1H; 4.36, m, 1H; 5.08, ABq, J = 12.3 Hz, 1H; 5.17, ABq, J = 12.3 Hz, 1H; 5.27, d, J = 8.4 Hz, NH; 7.31, m, 5H. MS (ES +ve) *m/z* 322 (100%) $[M+H]^+$.

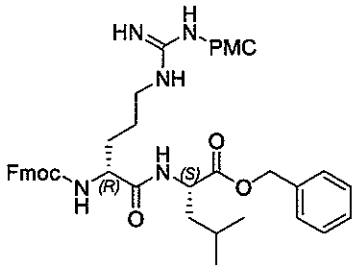
1(iv)



To **1(iii)** (510 mg, 1.59mmol) dissolved in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 1 hr. Ethyl acetate (15 ml) was then added and the solution washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$) and evaporated to dryness to yield the desired product **1(iv)** as a colourless oil (172 mg, 49%). R_f = 0.37 (5% MeOH/DCM), staining with Mo dip.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, d, J = 6.4 Hz, 3H; 0.90, d, J = 6.4 Hz, 3H; 1.43, m, 2H; 1.54, m, 1H; 1.72, m, 1H; 1.74, m, NH_2; 3.48, m, 1H; 5.12, s, 2H; 7.32, m, 5H. MS (ES +ve) *m/z* 222 (100%) $[M+H]^+$.

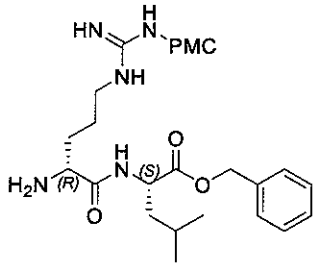
1(v)



This compound was prepared *via* Protocol 1 using **1(iv)** (160 mg, 0.723 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (662.8 mg, 1.00 mmol) to yield the desired product **1(v)** as an off white solid (460 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81, m, 6H; 1.21, s, 6H; 1.58, m, 5H; 1.67, m, 3H; 1.85, m, 1H; 2.04, s, 3H; 2.49, m, 2H; 2.54, s, 3H; 2.58, s, 3H; 3.21, m, 2H; 4.04, m, 1H; 4.23, m, 3H; 4.52, m, 1H; 5.02, ABq, J = 12.3 Hz, 1H; 5.08, ABq, J = 12.3 Hz, 1H; 6.22, br s, NH; 6.36, bs , NH; 7.25, m, 9H; 7.50, d, J = 7.3 Hz, 2H; 7.69, d, J = 7.3 Hz, 2H. MS (ES +ve) *m/z* 888 (100%) $[M+Na]^+$; 866 (10) $[M+H]^+$.

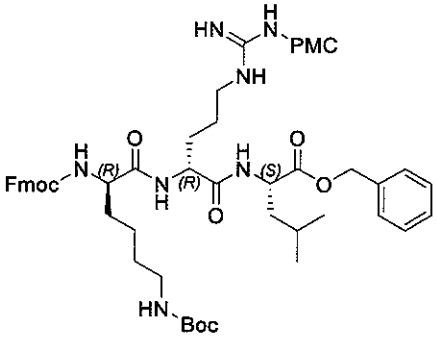
1(vi)



This compound was prepared *via* Protocol 2, using **1(v)** (450 mg, 0.520 mmol) to yield the desired product **1(vi)** as an off white solid (244 mg, 73%). R_f = 0.07 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, m, 6H; 1.28, s, 6H; 1.57, m, 5H; 1.77, m, 2H; 1.86, m, 2H; 2.08, s, 3H; 2.54, s, 3H; 2.58, s, 3H; 2.60, m, 2H; 3.14, m, 2H; 3.38, m, 1H; 4.51, m, 1H; 5.05, ABq, J = 12.3 Hz, 1H; 5.13, ABq, J = 12.3 Hz, 1H; 6.33, br s, NH; 6.38, br s, NH; 7.29, m, 5H; 7.78, d, J = 7.6 Hz, NH. MS (ES +ve) *m/z* 644 (100%) $[M+H]^+$.

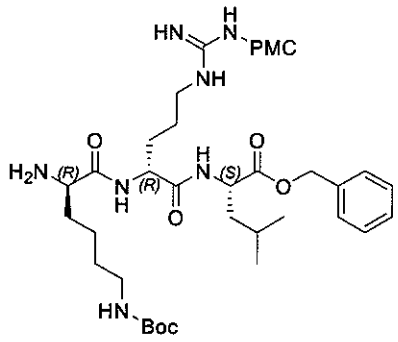
1(vii)



This compound was prepared *via* Protocol 1, using **1(vi)** (240 mg, 0.373 mmol) and Fmoc-(*D*)-lys(BOC)-OH (187 mg, 0.4 mmol) to yield the desired product **1(vii)** as an off white solid (336 mg, 82%). R_f = 0.28 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83, m, 6H; 1.17, m, 2H; 1.18, s, 6H; 1.40, s, 9H; 1.40, m, 2H; 1.60, m, 11H; 2.02, s, 3H; 2.51, m, 2H; 2.52, s, 3H; 2.55, s, 3H; 3.02, m, 2H; 3.18, m, 2H; 3.91, m, 1H; 4.18, m, 3H, 4.52, m, 1H; 5.00, m, 2H; 6.48, br s, NH; 7.25, m, 9H; 7.43, d, J = 7.6 Hz, NH; 7.52, m, 2H; 7.69, d, J = 7.6 Hz, 2H. MS (ES +ve) *m/z* 1116 (80%) $[M+Na]^+$; 1094 (100) $[M+H]^+$.

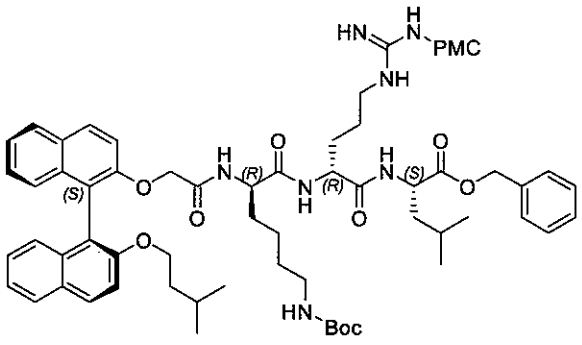
1(viii)



This compound was prepared *via* Protocol 2, using **1(vii)** (330 mg, 0.302 mmol) to yield the desired product **1(viii)** as an off white solid (239 mg, 91%). R_f = baseline (5% MeOH/ DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82, d, J = 5.8 Hz, 3H; 0.84, d, J = 5.8 Hz, 3H; 1.23, m, 2H; 1.27, s, 6H; 1.38, s, 9H; 1.40, m, 2H; 1.60, m, 11H; 2.07, s, 3H; 2.52, s, 3H; 2.54, s, 3H; 2.58, m, 2H; 3.01, m, 2H; 3.19, m, 2H; 3.29, m, 1H; 4.52, m, 2H; 4.92, m, NH; 5.03, ABq, J = 12.3 Hz, 1H; 5.09, ABq, J = 12.3 Hz, 1H; 6.39, br s, NH; 7.28, m, 5H; 7.58, d, J = 7.9 Hz, NH; 7.95, d, J = 7.3 Hz, NH. MS (ES +ve) *m/z* 872 (100%) $[M+H]^+$.

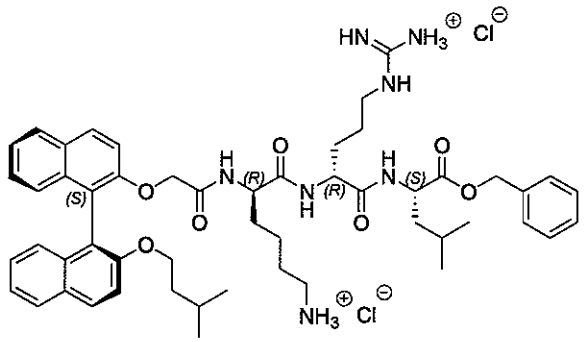
1(ix)



This compound was prepared *via* Protocol 1, using **1(ii)** (50 mg, 0.121 mmol) and **1(viii)** (110 mg, 0.126 mmol) to yield the product **1(ix)** as a white solid (114 mg, 74%). R_f = 0.16 (5% MeOH/ DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.46, d, J = 6.2 Hz, 3H; 0.52, d, J = 6.2 Hz, 3H; 0.89, m, 9H; 1.20, m, 5H; 1.28, s, 6H; 1.39, m, 2H; 1.41, s, 9H; 1.70, m, 7H; 2.09, s, 3H; 2.55, s, 3H; 2.57, s, 3H; 2.61, m, 2H; 2.89, m, 2H; 3.10, m, 2H; 3.86, m, 1H; 4.04, m, 2H; 4.48, m, 4H; 4.82, m, NH; 5.07, ABq, J = 12.6 Hz, 1H; 5.16, ABq, J = 12.6 Hz, 1H; 6.18, d, J = 7.0 Hz, NH; 6.29, br s, NH; 6.48, br s, NH; 7.20, m, 4H; 7.31, m, 7H; 7.45, d, J = 9.1 Hz, 2H; 7.85, m, 2H; 7.95, m, 2H; 8.06, d, J = 8.8 Hz, NH. MS (ES +ve) *m/z* 1291 (70%) $[M+Na]^+$; 1268 (100) $[M+H]^+$.

Compound 1

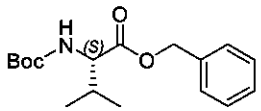


This compound was prepared *via* Protocol 3, using **1(ix)** (104 mg, 0.082 mmol) to yield the desired compound **1** as a white solid (78 mg, 98%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.38, d, J = 6.2 Hz, 3H; 0.43, d, J = 6.2 Hz, 3H; 0.80, m, 9H; 1.07, m, 3H; 1.52, m, 10H; 2.69, m, 2H; 3.05, m, 2H; 3.82, m, 1H; 4.01, m, 2H; 4.35, m, 4H; 5.03, m, 2H; 6.94, m, 2H; 7.06, m, 2H; 7.21, m, 7H; 7.34, d, J = 9.1 Hz, 1H; 7.42, d, J = 9.1 Hz, 1H; 7.85, m, 4H. MS (ES +ve) *m/z* 902 (10%) $[M+H]^+$; 452 (100) $[M+H]^{2+}$.

Synthesis of Compound 2

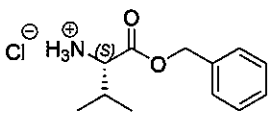
2(i)



To BOC-(*L*)-val-OH (100 mg, 0.48 mmol) and potassium carbonate (160 mg, 1.16 mmol) in acetone (10 ml) was added benzyl bromide (0.1 ml, 0.84 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was then subjected to flash column chromatography over silica, using initially 1:1 hexane/DCM to remove benzyl bromide, then DCM to yield the product **2(i)** as a colourless oil (110 mg, 75%). R_f = 0.38 (DCM) staining with Mo dip.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84, d, J = 7.0 Hz, 3H; 0.93, d, J = 7.0 Hz, 3H; 1.43, s, 9H; 2.14, m, 1H; 4.27, dd, J_1 = 9.1 Hz, J_2 = 4.7 Hz, 1H; 5.05, obscured d, NH; 5.07, ABq, J = 12.3 Hz, 1H; 5.20, ABq, J = 12.3 Hz, 1H; 7.34, m, 5H. MS (ES +ve) *m/z* 308 (60%) $[M+H]^+$; 208 (100) $[M+H\text{-}Boc]^+$.

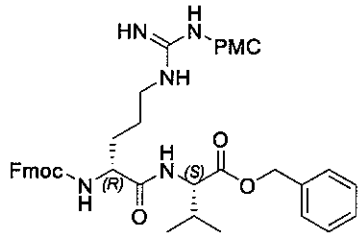
2(ii)



This compound was prepared *via* Protocol 3 using **2(i)** (105 mg, 0.34 mmol) to give the product **2(ii)** as an off white solid (65 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06, m, 6H; 2.44, m, 1H; 4.09, m, 1H; 5.13, ABq, J = 12.0 Hz, 1H; 5.26, ABq, J = 12.0 Hz, 1H; 7.32, m, 5H; 8.51, br s, NH_3^+.

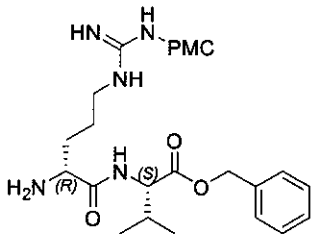
2(iii)



This compound was prepared *via* Protocol 1 using **2(ii)** (136 mg, 0.800 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (530 mg, 0.800 mmol) to yield the desired product **2(iii)** as an off white solid (659 mg, 97%). R_f = 0.40 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79, d, J = 7.0 Hz, 3H; 0.83, d, J = 7.0 Hz, 3H; 1.23, s, 6H; 1.60, m, 2H; 1.68, m, 3H; 1.87, m, 1H; 2.04, s, 3H; 2.11, m, 1H; 2.52, m, 2H; 2.53, s, 3H; 2.56, s, 3H; 3.20, m, 2H; 4.05, m, 1H; 4.25, m, 3H; 4.45, dd, J_1 = 8.5 Hz, J_2 = 5.6 Hz, 1H; 5.00, ABq, J = 12.3 Hz, 1H; 5.10, ABq, J = 12.3 Hz, 1H; 6.27, m, NH; 7.21, m, 2H; 7.26, m, 5H; 7.31, m, 2H; 7.50, d, J = 7.3 Hz, 2H; 7.69, d, J = 7.6 Hz, 2H. MS (ES +ve) *m/z* 852 (100%) $[M+H]^+$.

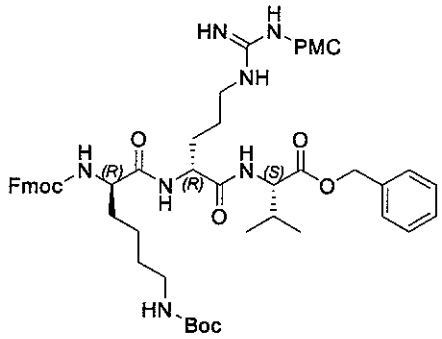
2(iv)



This compound was prepared *via* Protocol 2, using **2(iii)** (604 mg, 0.709 mmol) to yield the desired product **2(iv)** as a colourless oil (361 mg, 81%). R_f = baseline (5% MeOH /DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85, d, J = 7.0 Hz, 3H; 0.88, d, J = 7.0 Hz, 3H; 1.28, s, 6H; 1.53, m, 3H; 1.77, m, 3H/NH_2; 2.08, s, 3H; 2.17, m, 1H; 2.53, s, 3H; 2.55, s, 3H; 2.59, m, 2H; 3.13, m, 2H; 3.38, m, 1H; 4.40, dd, J_1 = 8.5 Hz, J_2 = 5.3 Hz, 1H; 5.15, ABq, J = 12.3 Hz, 1H; 5.15, ABq, J = 12.3 Hz, 1H; 6.38, br s, NH; 7.30, m, 5H; 7.87, d, J = 8.5 Hz, NH. MS (ES +ve) *m/z* 630 (100%) $[M+H]^+$.

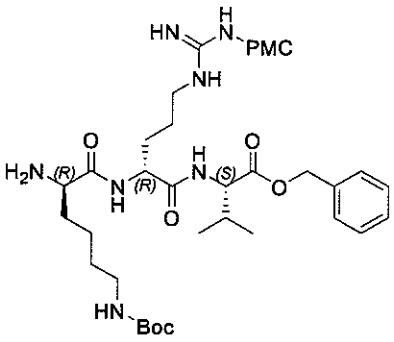
2(v)



This compound was prepared *via* Protocol 1, using **2(iv)** (350 mg, 0.556 mmol) and Fmoc-(*D*)-lys(BOC)-OH (260 mg, 0.555 mmol) to yield the desired product **2(v)** as an off white solid (592mg, 99%). R_f = 0.25 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87, m, 6H; 1.21, s, 3H; 1.22, s, 3H; 1.41, m, 13H; 1.67, m, 4H; 1.75, m, 3H; 1.88, m, 1H; 2.05, s, 3H; 2.18, m, 1H; 2.52, m, 2H; 2.54, s, 3H; 2.57, s, 3H; 3.03, m, 2H; 3.19, m, 2H; 4.01, m, 1H; 4.28, m, 3H; 4.52, m, 1H; 4.61, m, 1H; 4.98, ABq, *J* = 12.3 Hz, 1H; 5.04, m, NH; 5.12, ABq, *J* = 12.3 Hz, 1H; 6.48, br m, NH; 7.27, m, 7H; 7.33, m, 2H; 7.45, d, *J* = 8.2 Hz, NH; 7.55, m, 2H; 7.70, d, *J* = 7.0 Hz, 2H; 7.89, m, NH. MS (ES +ve) *m/z* 1080 (20%) $[M+H]^+$; 559.8 (100) $[M+H+K]^{2+}$.

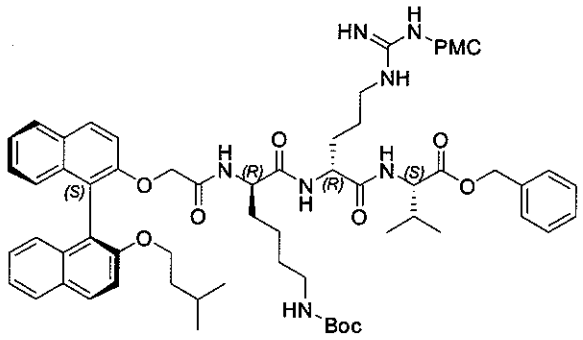
2(vi)



This compound was prepared *via* Protocol 2, using **2(v)** (350 mg, 0.324 mmol) to yield the desired product **2(vi)** as an off white solid (204 mg, 79%). R_f = baseline (5% MeOH/ DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82, δ, *J* = 6.7 Hz, 3H; 0.86, d, *J* = 6.7 Hz, 3H; 1.27, s, 6H; 1.30, m, 4H; 1.38, s, 9H; 1.52, m, 2H; 1.69, m, 2H; 1.76, dist t, 2H; 1.85, m, 2H; 2.07, s, 3H; 2.12, m, 1H; 2.52, s, 3H; 2.54, s, 3H; 2.58, m, 2H; 3.01, m, 2H; 3.18, m, 2H; 3.30, m, 1H; 4.46, m, 1H; 4.61, m, NH; 5.02, ABq, *J* = 12.3 Hz, 1H; 5.12, ABq, *J* = 12.3 Hz, 1H; 6.40, br s, NH; 7.28, m, 5H; 7.52, d, *J* = 8.5 Hz, NH; 7.99, d, *J* = 7.0 Hz, NH. MS (ES +ve) *m/z* 858 (100%) $[M+H]^+$.

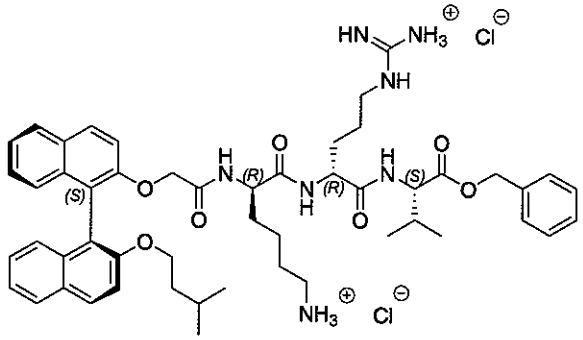
2(vii)



This compound was prepared *via* Protocol 1, using **1(ii)** (92 mg, 0.222 mmol) and **2(vi)** (190 mg, 0.222 mmol) to yield the product **2(vii)** as a white solid (180 mg, 65%). R_f = 0.11 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48, d, *J* = 6.4 Hz, 3H; 0.53, d, *J* = 6.4 Hz, 3H; 0.82, m, 2H; 0.87, t, *J* = 7.0 Hz, 6H; 1.18, m, 6H; 1.28, s, 6H; 1.41, s, 9H; 1.60, m, 1H; 1.76, dist t, 2H; 1.85, m, 1H; 2.08, s, 3H; 2.20, m, 1H; 2.54, s, 3H; 2.56, s, 3H; 2.58, m, 2H; 2.89, m, 2H; 3.14, m, 2H; 3.87, m, 1H; 4.06, m, 2H; 4.45, m, 4H; 4.82, m, NH; 5.08, ABq, *J* = 12.3 Hz, 1H; 5.19, ABq, *J* = 12.3 Hz, 1H; 6.22, m, NH; 7.13, m, 2H; 7.25, m, 2H; 7.35, m, 8H; 7.46, d, *J* = 9.1 Hz, 1H; 7.83, d, *J* = 7.6 Hz, 1H; 7.85, d, *J* = 7.9 Hz, 1H; 7.93, d, *J* = 8.8 Hz, 1H; 7.94, d, *J* = 9.1 Hz, 1H. MS (ES +ve) *m/z* 1255 (100%) $[M+H]^+$.

Compound 2

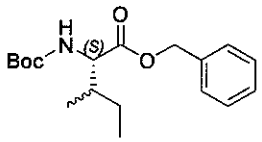


This compound was prepared *via* Protocol 3, using **2(vii)** (100 mg, 0.080 mmol) to yield the product **2** as a white solid (49 mg, 64%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.51, d, *J* = 6.5 Hz, 3H; 0.56, d, *J* = 6.5 Hz, 3H; 0.92, d, *J* = 6.7 Hz, 6H; 0.94, m, 1H; 1.18, m, 3H; 1.61, m, 6H; 2.18, m, 1H; 2.79, m, 2H; 3.16, m, 2H; 3.94, m, 1H; 4.10, m, 2H; 4.48, m, 4H; 5.13, ABq, *J* = 12.3 Hz, 1H; 5.20, ABq, *J* = 12.3 Hz, 1H; 7.06, m, 2H; 7.20, dist t, 2H; 7.35, m, 7H; 7.46, d, *J* = 8.8 Hz, 1H; 7.55, d, *J* = 9.1 Hz, 1H; 7.89, d, *J* = 7.9 Hz, 1H; 7.91, d, *J* = 8.2 Hz, 1H; 8.00, d, *J* = 9.1 Hz, 2H. MS (ES +ve) *m/z* 888 (10%) $[M+H]^+$; 445 (100) $[M+2H]^{2+}$.

Synthesis of Compound 3

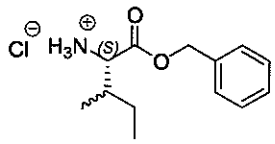
3(i)



To BOC-(*L*)-Ile-OH (200 mg, 0.86 mmol) and potassium carbonate (300 mg, 2.16 mmol) in acetone (20 ml) was added benzyl bromide (0.2 ml, 1.72 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting first with 1:1 hexane/DCM to remove benzyl bromide, then with DCM. The product **3(i)** was isolated as a colourless oil (253 mg, 91%). R_f = 0.28 (DCM) using Mo stain.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, m, 6H; 1.12, m, 1H; 1.38, m, 1H; 1.43, s, 9H; 1.86, m, 1H; 4.31, m, 1H; 5.05, m, NH; 5.10, ABq, *J* = 12.3 Hz, 1H; 5.20, ABq, *J* = 12.3 Hz, 1H; 7.33, m, 5H.

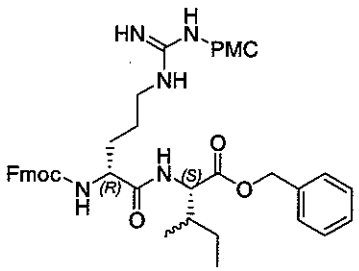
3(ii)



This compound was prepared *via* Protocol 3, using **3(i)** (115 mg, 0.358 mmol) to yield the desired product **3(ii)** as an off white solid hydrochloride salt (80 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90, t, *J* = 7.1 Hz, 3H; 1.03, d, *J* = 6.8 Hz, 3H; 1.43, m, 2H; 2.16, m, 1H; 4.14, m, 1H; 5.13, ABq, *J* = 12.0 Hz, 1H; 5.26, ABq, *J* = 12.0 Hz, 1H; 7.33, m, 5H, 8.62, br s, NH_3^+.

3(iii)

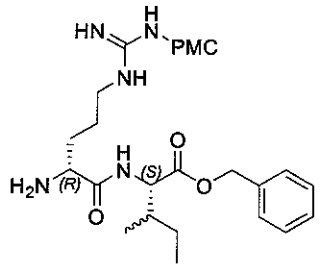


This compound was prepared *via* Protocol 1 using **3(ii)** (173 mg, 0.778 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (520 mg, 0.785 mmol) to yield the desired product **3(iii)** as an off white solid (452 mg, 79%). R_f = 0.40 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, m, 6H; 1.11, m, 1H; 1.23, s, 6H; 1.30, m, 1H; 1.60, m, 2H; 1.70, dist t, 2H; 1.86, m, 2H; 1.99, m, 1H; 2.05, s, 3H; 2.50, m, 2H; 2.53, s, 3H; 2.56, s, 3H; 3.20, m, 2H; 4.06, dist t, 1H; 4.25, m, 3H; 4.50, dd, J_1 = 8.3 Hz, J_2 = 5.3 Hz, 1H; 5.01, ABq, *J* = 12.0 Hz, 1H; 5.12, ABq, *J* = 12.3 Hz, 1H; 6.13, br s, NH; 6.27,

s, NH; 7.19, dist t, 2H; 7.26, m, 5H; 7.33, dist t, 2H; 7.51, d, J = 7.5 Hz, 2H; 7.6, dist t, NH; 7.70, d, J = 7.8 Hz, 2H. MS (ES +ve) *m/z* 866 (100%) $[M+H]^+$.

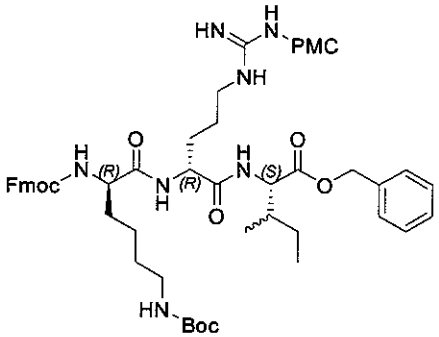
3(iv)



This compound was prepared *via* Protocol 2, using **3(iii)** (540 mg, 0.623 mmol) to yield the desired product **3(iv)** as a white solid (338 mg, 84%). R_f = baseline (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85, m, 6H; 1.13, m, 1H; 1.28, s, 6H; 1.34, m, 1H; 1.54, m, 3H; 1.66, m, 1H; 1.77, dist t, 2H; 1.90, m, 1H; 2.08, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.60, dist t, 2H; 3.13, m, 2H; 3.37, m, 1H; 4.45, dd, J_1 = 8.5 Hz, J_2 = 5.3 Hz, 1H; 5.04, ABq, J = 12.3 Hz, 1H; 5.16, ABq, J = 12.3 Hz, 1H; 6.31, br s, NH; 6.38, br s, NH; 7.30, m, 5H; 7.87, d, J = 8.5 Hz, NH. MS (ES +ve) *m/z* 644 (100%) $[M+H]^+$.

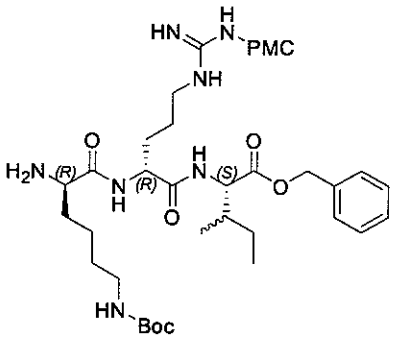
3(v)



This compound was prepared *via* Protocol 1, using **3(iv)** (300 mg, 0.466 mmol) and Fmoc-(*D*)-lys(BOC)-OH (218 mg, 0.465 mmol) to yield the desired product **3(v)** as an off white solid (388 mg, 76%). R_f = 0.25 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83, m, 6H; 1.16, m, 1H; 1.21, s, 3H; 1.22, s, 3H; 1.38, m, 4H; 1.40, s, 9H; 1.67, m, 8H; 1.92, m, 2H; 2.04, s, 3H; 2.52, m, 2H; 2.53, s, 3H; 2.56, s, 3H; 3.03, m, 2H; 3.18, m, 2H; 4.01, dist t, 1H; 4.26, m, 3H; 4.54, m, 2H; 4.95, m, NH; 4.98, ABq, J = 12.3 Hz, 1H; 5.13, ABq, J = 12.3 Hz, 1H; 6.20, br s, NH; 6.41, br s, NH; 7.27, m, 9H; 7.54, m, 2H; 7.70, d, J = 7.3 Hz, 2H. MS (ES +ve) *m/z* 1116 (80%) $[M+Na]^+$; 1094 (100) $[M+H]^+$.

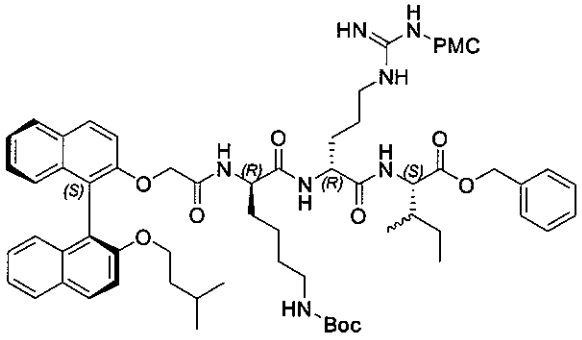
3(vi)



This compound was prepared *via* Protocol 2, using **3(v)** (388 mg, 0.355 mmol) to yield the desired product **3(vi)** as an off white solid (268 mg, 87%). R_f = baseline (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82, m, 6H; 1.15, m, 1H; 1.26, s, 6H; 1.31, m, 2H; 1.37, m, 2H; 1.38, s, 9H; 1.51, m, 2H; 1.71, m, 6H; 1.86, m, 2H; 2.07, s, 3H; 2.52, s, 3H; 2.54, s, 3H; 2.59, m, 2H; 3.02, m, 2H; 3.18, m, 2H; 3.30, m, 1H; 4.51, m, 1H; 4.58, m, 1H; 4.93, m, NH; 5.01, ABq, J = 12.3 Hz, 1H; 5.13, ABq, J = 12.3 Hz, 1H; 6.39, br s, NH; 7.28, m, 5H; 7.49, d, J = 8.5 Hz, NH; 7.98, d, J = 7.9 Hz, NH. MS (ES +ve) *m/z* 872 (100%) $[M+H]^+$.

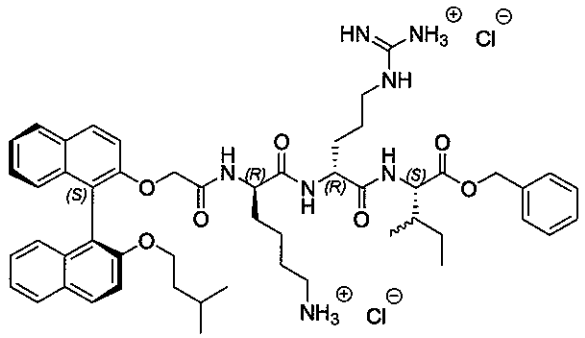
3(vii)



This compound was prepared *via* Protocol 1, using **1(ii)** (119 mg, 0.287 mmol) and **3(vi)** (250 mg, 0.287 mmol) to yield the product **3(vii)** as a white solid (171 mg, 47%). R_f = 0.07 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48, d, J = 6.4 Hz, 3H; 0.53, d, J = 6.4 Hz, 3H; 0.87, m, 7H; 0.96, m, 1H; 1.20, m, 11H; 1.27, s, 6H; 1.41, s, 9H; 1.59, m, 1H; 1.75, m, 2H; 1.84, m, 1H; 1.92, m, 1H; 2.08, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.57, m, 2H; 2.88, m, 2H; 3.11, m, 2H; 3.87, m, 1H; 4.09, m, 2H; 4.49, m, 4H; 5.07, ABq, J = 12.3 Hz, 1H; 5.19, ABq, J = 12.3 Hz, 1H; 6.24, br s, NH; 7.31, m, 12H; 7.44, d, J = 9.1 Hz, 1H; 7.84, m, 2H; 7.92, m, 2H. MS (ES +ve) *m/z* 1269 (100%) $[M+H]^+$.

Compound 3

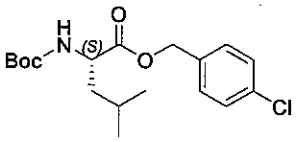


This compound was prepared *via* Protocol 3, using **3(vii)** (170 mg, 0.134 mmol) to yield the product **3** as a white solid (127 mg, 97%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.48, d, J = 6.2 Hz, 3H; 0.53, d, J = 6.2 Hz, 3H; 0.87, m, 7H; 0.96, m, 1H; 1.17, m, 5H; 1.57, m, 8H; 1.79, m, 1H; 1.91, m, 1H; 2.81, m, 2H; 3.16, m, 2H; 3.92, m, 1H; 4.10, m, 1H; 4.19, m, 1H; 4.43, m, 4H; 5.10, ABq, J = 12.3 Hz, 1H; 5.19, ABq, J = 12.3 Hz, 1H; 7.05, m, 2H; 7.16, m, 2H; 7.33, m, 7H; 7.43, d, J = 9.1 Hz, 1H; 7.53, d, J = 9.1 Hz, 1H; 7.85, m, 2H; 7.99, m, 2H. MS (ES +ve) *m/z* 902 (10%) $[M+H]^+$; 452.0 (100) $[M+2H]^{2+}$.

Synthesis of Compound 4

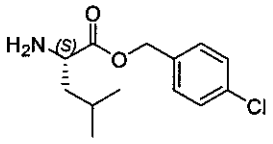
4(i)



To BOC(*L*)-Leu-OH (250 mg, 1.08 mmol) and potassium carbonate (747 mg, 5.40 mmol) in acetone (50 ml) was added 4-chlorobenzyl bromide (333 mg, 1.62 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 1:4 hexane/DCM to first remove 4-chlorobenzyl bromide, then with DCM to yield the product **4(i)** as a colourless oil (366 mg, 95%). Rf = 0.55 (DCM) using Mo dip.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89, d, J = 6.4 Hz, 3H; 0.90, d, J = 6.4 Hz, 3H; 1.41, s, 9H; 1.48, m, 2H; 1.64, m, 1H; 4.31, m, 1H; 4.95, d, J = 8.2 Hz, NH; 5.06, ABq, J = 12.3 Hz, 1H; 5.13, ABq, J = 12.3 Hz, 1H; 7.25, ABq, J = 8.4 Hz, 2H; 7.30, ABq, J = 8.2 Hz, 2H. MS (ES +ve) *m/z* 356 (100%) $[M+H]^+$.

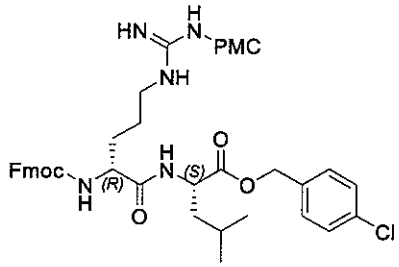
4(ii)



This compound was prepared *via* Protocol 4, using **4(i)** (366 mg, 1.03 mmol) to yield the desired product **4(ii)** as a colourless oil (235 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, d, J = 6.4 Hz, 3H; 0.91, d, J = 6.4 Hz, 3H; 1.43, m, 1H; 1.55, m, 1H; 1.56, m, NH_2; 1.74, m, 1H; 3.48, m, 1H; 5.09, s, 2H; 7.27, ABq, J = 8.5 Hz, 2H; 7.32, ABq, J = 8.5 Hz, 2H. MS (ES +ve) *m/z* 256 (100%) $[M+H]^+$.

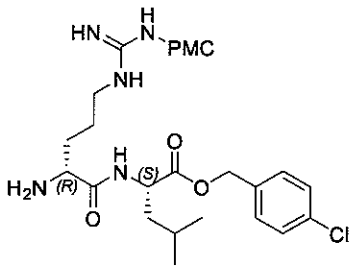
4(iii)



This compound was prepared *via* Protocol 1 using **4(ii)** (235 mg, 0.919 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (609 mg, 0.919 mmol) to yield the desired product **4(iii)** as an off white solid (806 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79, dist d, 6H; 1.28, s, 6H; 1.65, m, 8H; 1.89, m, 1H; 2.03, s, 3H; 2.49, m, 2H; 2.53, s, 3H; 2.56, s, 3H; 3.23, m, 2H; 4.03, m, 1H; 4.28, m, 3H; 4.51, m, 1H; 4.96, ABq, J = 12.2 Hz, 1H; 5.02, ABq, J = 12.2 Hz, 1H; 6.42, br s, NH; 7.19, m, 6H; 7.31, dist t, 2H; 7.49, dist d, 2H; 7.54, d, J = 7.8 Hz, NH; 7.68, ABq, J = 7.8 Hz, 2H. MS (ES +ve) *m/z* 900 (100%) $[M+H]^+$.

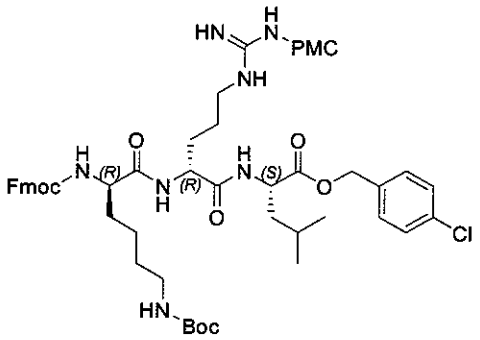
4(iv)



This compound was prepared *via* Protocol 2, using **4(iii)** (798 mg, 0.887 mmol) to yield the desired product **4(iv)** as an off white solid (532 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76, d, J = 6.1 Hz, 3H; 0.88, d, J = 6.1 Hz, 3H; 1.28, s, 6H; 1.57, m, 5H/NH_2; 1.77, m, 3H; 2.02, m, 1H; 2.08, s, 3H; 2.53, s, 3H; 2.55, s, 3H; 2.59, m, 2H; 3.15, m, 2H; 3.41, m, 1H; 4.49, m, 1H; 5.01, ABq, J = 12.2 Hz, 1H; 5.07, ABq, J = 12.2 Hz, 1H; 6.45, br s, NH; 7.22, ABq, J = 8.5 Hz, 2H; 7.26, ABq, J = 8.5 Hz, 2H; 7.83, d, J = 7.9 Hz, NH. MS (ES +ve) *m/z* 678 (100%) $[M+H]^+$.

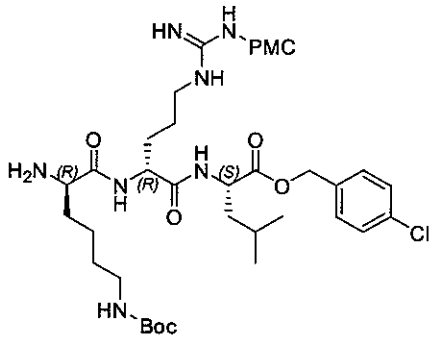
4(v)



This compound was prepared *via* Protocol 1, using **4(iv)** (519 mg, 0.765 mmol) and Fmoc-(*D*)-lys(BOC)-OH (359 mg, 0.766 mmol) to yield the desired product **4(v)** as an off white solid (785 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82, d, J = 5.5 Hz, 3H; 0.84, d, J = 5.9 Hz, 3H; 1.19, br s, 6H; 1.39, s, 9H; 1.63, m, 14H; 2.02, s, 3H; 2.05, m, 1H; 2.51, m, 2H; 2.52, s, 3H; 2.55, s, 3H; 3.02, m, 2H; 3.19, m, 2H; 3.94, m, 1H; 4.14, m, 3H; 4.53, m, 2H; 4.95, m, 2H/NH; 6.47, br m, NH; 7.19, m, 4H; 7.32, m, 2H; 7.54, m, 4H; 7.69, m, 2H. MS (ES +ve) *m/z* 1128 (100%) $[M+H]^+$.

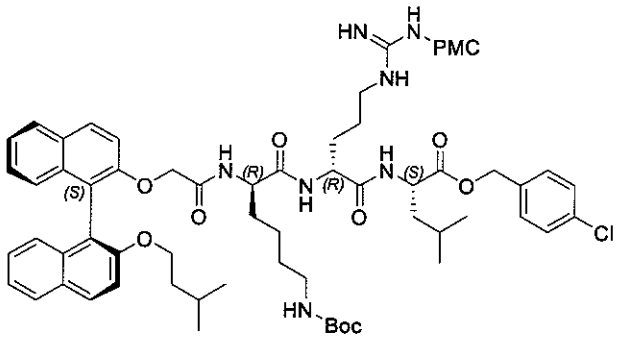
4(vi)



This compound was prepared *via* Protocol 2, using **4(v)** (330 mg, 0.292 mmol) to yield the desired product **4(vi)** as an off white solid (236 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85, d, J = 5.9 Hz, 3H; 0.87, d, J = 5.9 Hz, 3H; 1.29, s, 6H; 1.48, s, 9H; 1.57, m, 14H/NH_2; 2.09, s, 3H; 2.13, m, 1H; 2.54, s, 3H; 2.56, s, 3H; 2.60, m, 2H; 3.04, m, 2H; 3.22, m, 2H; 3.35, m, 1H; 4.52, m, 1H; 4.59, m, 1H; 4.98, m, NH; 5.02, ABq, J = 12.2 Hz, 1H; 5.07, ABq, J = 12.2 Hz, 1H; 6.45, br s, NH; 7.23, ABq, J = 8.5 Hz, 2H; 7.28, ABq, J = 8.5 Hz, 2H; 7.71, m, NH; 8.00, m, NH. MS (ES +ve) *m/z* 906 (100%) $[M+H]^+$.

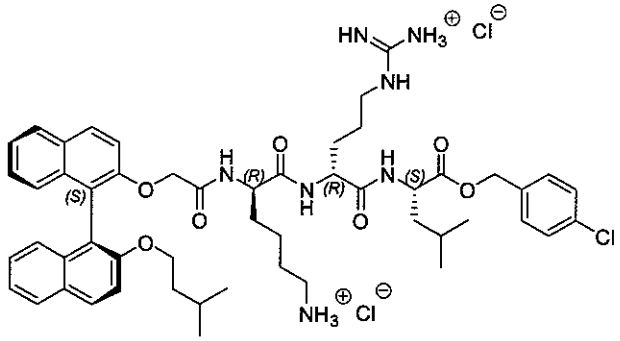
4(vii)



This compound was prepared *via* Protocol 1, using **1(ii)** (105 mg, 0.254 mmol) and **4(vi)** (230 mg, 0.254 mmol) to yield the product **4(vii)** as a white solid (144 mg, 44%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.46, d, J = 5.3 Hz, 3H; 0.52, d, J = 5.3 Hz, 3H; 0.79, m, 2H; 0.87, d, J = 5.9 Hz, 3H; 0.89, d, J = 5.9 Hz, 3H; 0.94, m, 1H; 1.19, m, 6H; 1.28, s, 6H; 1.29, m, 2H; 1.41, s, 9H; 1.64, m, 4H; 1.76, m, 2H; 1.84, m, 1H; 2.09, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.58, m, 2H; 2.90, m, 2H; 3.15, m, 2H; 3.87, m, 1H; 4.04, m, 2H; 4.41, m, 2H; 4.45, m, 3H; 4.82, m, NH; 5.04, ABq, J = 12.2 Hz, 1H; 5.11, ABq, J = 12.2 Hz, 1H; 6.19, d, J = 6.8 Hz, NH; 6.29, br s, NH; 7.26, m, 11H; 7.44, d, J = 9.1 Hz, 1H; 7.83, d, J = 8.3 Hz, 1H; 7.85, d, J = 8.3 Hz, 1H; 7.93, d, J = 9.0 Hz, 1H; 7.94, d, J = 8.9 Hz, 1H. MS (ES +ve) *m/z* 1302 (60%) $[M+H]^+$; 602 (100) $[M+2H\text{-BOC}]^{2+}$.

Compound 4

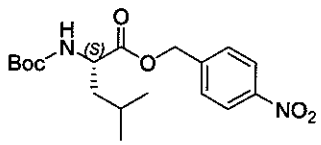


This compound was prepared *via* Protocol 3, using **4(vii)** (140 mg, 0.107 mmol) to yield the desired product **4** as a white solid (101 mg, 93%).

^{1}H NMR (500 MHz, CD_3OD) δ 0.40, d, J = 6.3 Hz, 3H; 0.45, d, J = 6.3 Hz, 3H; 0.78, d, J = 4.8 Hz, 3H; 0.83, d, J = 4.8 Hz, 3H; 0.84, m, 2H; 1.05, m, 2H; 1.13, m, 2H; 1.53, m, 9H; 1.72, m, 1H; 2.70, m, 2H; 3.06, m, 2H; 3.84, m, 1H; 4.03, m, 2H; 4.36, m, 4H; 5.02, s, 2H; 7.06, dist t, 2H; 7.18, m, 2H; 7.33, m, 6H; 7.45, d, J = 9.3 Hz, 1H; 7.54, d, J = 8.8 Hz, 1H; 7.88, d, J = 7.8 Hz, 1H; 7.91, d, J = 8.3 Hz, 1H; 8.00, dist t, 2H. MS (ES +ve) *m/z* 936 (15%) $[M+H]^+$; 469 (100) $[M+2H]^{2+}$.

Synthesis of Compound 5

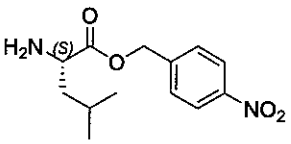
5(i)



To BOC(*L*)-Leu-OH (250 mg, 1.08 mmol) and potassium carbonate (747 mg, 5.40 mmol) in acetone (50 ml) was added 4-nitrobenzyl bromide (350 mg, 1.62 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 1:4 hexane/DCM to first remove 4-nitrobenzyl bromide, then with DCM to yield the product **5(i)** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95, d, *J* = 6.8 Hz, 6H; 1.44, s, 9H; 1.53, m, 1H; 1.63, m, 1H; 1.71, m, 1H; 4.38, m, 1H; 4.99, d, *J* = 8.3 Hz, NH; 5.27, s, 2H; 7.53, ABq, *J* = 8.3 Hz, 2H; 8.22, ABq, *J* = 8.3 Hz, 2H. MS (EI) *m/z* 265 (100%) $[M\text{-}BOC]^+$.

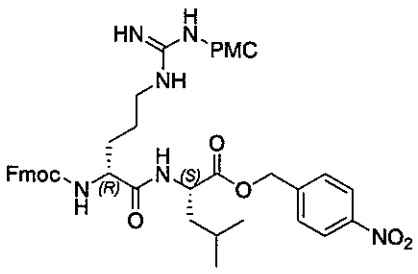
5(ii)



To **5(i)** (215 mg, 0.59 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 3 hrs. The solution was then diluted with DCM (5 ml) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **5(ii)** as a white solid (131 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93, d, *J* = 8.8 Hz, 3H; 0.95, d, *J* = 8.8 Hz, 3H; 1.50, m, 1H; 1.62, m, 1H; 1.54, m, 1H; 1.79, m, 1H; 2.37, br s, NH_2; 3.61, m, 1H; 5.26, s, 2H; 7.54, ABq, *J* = 8.8 Hz, 2H; 8.22, ABq, *J* = 8.8 Hz, 2H. MS (ES +ve) *m/z* 267 (100%) $[M+H]^+$.

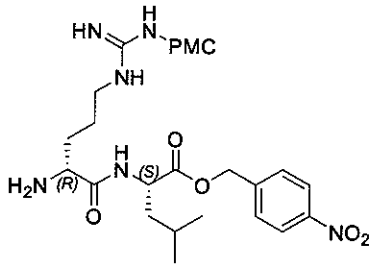
5(iii)



This compound was prepared *via* Protocol 1 using **5(ii)** (130 mg, 0.488 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (323 mg, 0.488 mmol) to yield the desired product **5(iii)** as a white solid (414 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83, br s, 6H; 1.21, s, 6H; 1.61, m, 4H; 1.66, m, 3H; 1.75, m, 2H; 2.03, s, 3H; 2.49, m, 2H; 2.53, s, 3H; 2.57, s, 3H; 3.23, m, 2H; 4.01, m, 1H; 4.23, m,2H; 4.36, m, 1H; 4.56, m, 1H; 5.09, s, 2H; 6.45, br s, NH; 7.17, m, 2H; 7.29, m, 5H (inc NH); 7.48, ABq, J = 8.8 Hz, 2H; 7.66, m, 2H; 7.70, m, NH; 8.04, ABq, J = 8.8 Hz, 2H. MS (ES +ve) *m/z* 911 (100%) $[M+H]^+$.

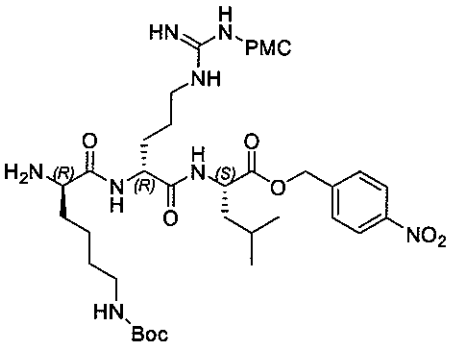
5(iv)



This compound was prepared *via* Protocol 2, using **5(iii)** (400 mg, 0.439 mmol) to yield the desired product **5(iv)** as an off white solid (210 mg, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90, dist d, 6H; 1.28, s, 6H; 1.57, m, 4H; 1.65, m, 2H; 1.78, m, 3H; 2.07, s, 3H; 2.52, s, 3H; 2.54, s, 3H; 2.59, m, 2H; 3.17, m, 2H; 3.49, m, 1H; 4.53, m, 1H; 5.20, s, 2H; 6.45, br s, NH; 7.47, ABq, J = 8.3 Hz, 2H; 7.90, d, J = 5.4 Hz, NH. 8.22, ABq, J = 8.3 Hz, 2H. ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 17.3, 18.4, 21.2, 21.5, 22.6, 22.9, 24.8, 25.2, 26.6, 31.6, 32.6, 40.2, 50.7, 54.0, 65.2, 73.5, 117.9, 123.6, 123.9, 128.2, 133.1, 134.6, 135.2, 142.7, 147.5, 153.5, 156.3, 172.4, 175.3. MS (ES +ve) *m/z* 689 (100%) $[M+H]^+$.

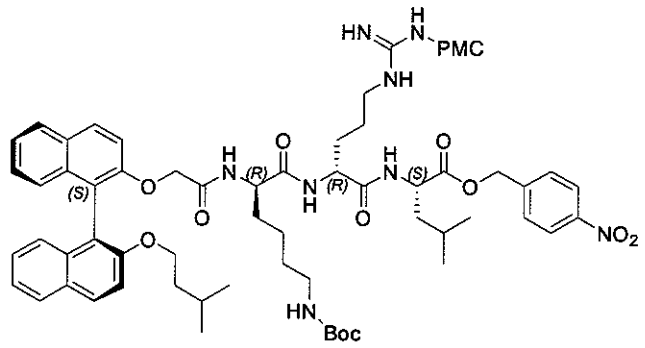
5(vi)



The Fmoc-protected precursor to this compound was prepared *via* Protocol 4, using **5(iv)** (200 mg, 0.290 mmol) and Fmoc-(*D*)-lys(BOC)-OH (136 mg, 0.290 mmol) to yield the Fmoc-protected derivative **5(v)** as an off white solid. The desired deprotected compound was prepared *via* Protocol 2, to yield the product **5(vi)** as an off white solid (201 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87, d, J = 5.8 Hz, 3H; 0.90, d, J = 5.8 Hz, 3H; 1.29, s, 6H; 1.40, s, 9H; 1.60, m, 15H; 2.08, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.60, m, 2H; 3.04, m, 2H; 3.23, m, 2H; 3.51, m, 1H; 4.58, m, 2H; 4.93, m, NH; 5.19, s, 2H; 6.44, br s, NH; 7.48, ABq, J = 8.8 Hz, 2H; 7.77, m, NH; 8.01, m, NH; 8.16, ABq, J = 8.8 Hz, 2H. MS (ES +ve) *m/z* 917 (10%) $[M+H]^+$; 431.5 (100) $[M+H-C_4H_8]^+$.

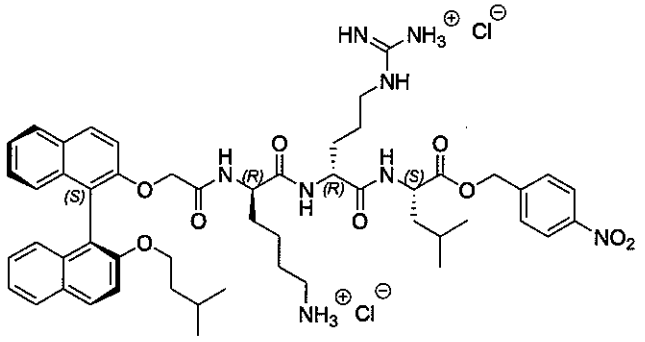
5(vii)



This compound was prepared *via* Protocol 1, using **1(ii)** (91 mg, 0.022 mmol) and **5(vi)** (190 mg, 0.021 mmol) to yield the product **5(vii)** as a white solid (194 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.46, d, J = 6.3 Hz, 3H; 0.51, d, J = 6.3 Hz, 3H; 0.89, d, J = 5.8 Hz, 3H; 0.90, m, 2H; 0.92, d, J = 5.8 Hz, 3H; 1.25, m, 4H; 1.26, s, 6H; 1.40, s, 9H; 1.56, m, 10H; 1.83, m, 1H; 2.07, s, 3H; 2.53, s, 3H; 2.56, s, 3H; 2.58, m, 2H; 2.90, m, 2H; 3.15, m, 2H; 3.93, m, 3H; 4.51, m, 4H; 5.22, s, 2H; 6.20, d, J = 7.0 Hz, NH; 6.29, br s, NH; 7.04, d, J = 7.3 Hz, 1H; 7.06, d, J = 8.3 Hz, 1H; 7.17, m, 2H; 7.31, t, J = 7.3 Hz, 2H; 7.45, d, J = 9.3 Hz, 1H; 7.53, d, J = 9.3 Hz, 1H; 7.58, ABq, J = 8.8 Hz, 2H; 7.87, d, J = 8.3 Hz, 1H; 7.89, d, J = 8.3 Hz, 1H; 7.99, d, J = 8.8 Hz, 1H; 8.00, d, J = 9.3 Hz, 1H; 8.19, ABq, J = 8.8Hz, 2H. MS (ES +ve) *m/z* 1313 (100%) $[M+H]^+$.

Compound 5

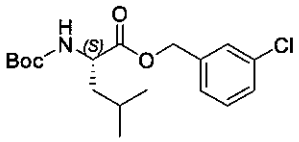


This compound was prepared *via* Protocol 3, using **5(vii)** (194 mg, 0.015 mmol) to yield an impure product. Protocol 3 was repeated on 130 mg of this product to yield the desired product **5** as an off white solid (110 mg, 84%).

^{1}H NMR (500 MHz, CD_3OD) δ 0.38, d, J = 6.4 Hz, 3H; 0.44, d, J = 6.4 Hz, 3H; 0.80, d, J = 5.5 Hz, 3H; 0.85, d, J = 5.5 Hz, 3H; 0.90, m, 2H; 1.10, m, 4H; 1.56, m, 9H; 1.74, m, 1H; 2.70, m, 2H; 3.06, m, 2H; 3.83, m, 1H; 4.02, m, 2H; 4.27, m, 1H; 4.36, ABq, J = 14.5 Hz, 1H; 4.40, m, 1H; 4.46, ABq, J = 14.5 Hz, 1H; 5.26, s, 2H; 7.04, d, J = 7.3 Hz, 1H; 7.06, d, J = 8.3 Hz, 1H; 7.17, m, 2H; 7.31, t, J = 7.3 Hz, 2H; 7.45, d, J = 9.3 Hz, 1H; 7.53, d, J = 9.3 Hz, 1H; 7.58, ABq, J = 8.8Hz, 2H; 7.87, d, J = 8.3 Hz, 1H; 7.89, d, J = 8.3 Hz, 1H; 7.99, d, J = 8.8 Hz, 1H; 8.00, d, J = 9.3 Hz, 1H; 8.19, ABq, J = 8.8 Hz, 2H. MS (ES +ve) *m/z* 947 (10%) $[M+H]^+$; 474.5 (100) $[M+2H]^{2+}$.

Synthesis of Compound 6

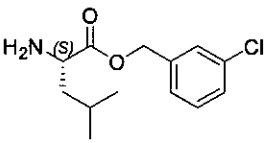
6(i)



To BOC-(*L*)-leu-OH (250 mg, 1.08 mmol) and potassium carbonate (1.00 g, 7.24 mmol) in acetone (25 ml) was added 2-chlorobenzyl bromide (0.16 ml, 1.22 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 5% ethyl acetate/hexane to first remove 2-chlorobenzyl bromide, then with DCM to yield the product **6(i)** as a white solid (370 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92, d, J = 6.3 Hz, 3H; 0.93, d, J = 6.3 Hz, 3H; 1.43, s, 9H; 1.54, m, 1H; 1.68, m, 2H; 4.36, m, 1H; 5.08, m, NH; 5.13, m, 2H; 7.22, m, 1H; 7.27, m, 2H; 7.34, s, 1H. MS (ES +ve) *m/z* 357 (100%) $[M+H]^+$; 257 (70) $[M+H\text{-}BOC]^+$.

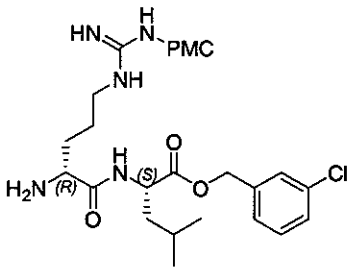
6(ii)



To **6(i)** (360 mg, 1.01 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 3 hrs. The solution was then diluted with DCM (5 ml) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **6(ii)** as a pale yellow oil (179 mg, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85, d, *J* = 6.8 Hz, 3H; 0.87, d, *J* = 6.8 Hz, 3H; 1.41, m, 1H; 1.52, m, 1H; 1.71, m, 1H; 2.41, br s NH_2; 3.50, m, 1H; 5.05, s, 2H; 7.18, m, 1H; 7.23, m, 2H; 7.28, s, 1H. MS (ES +ve) *m/z* 256.0 (100%) $[M+H]^+$.

6(iv)

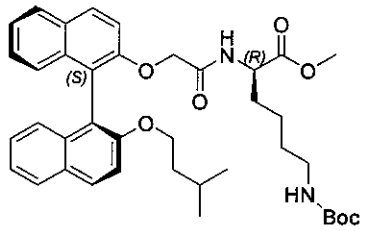


This compound was prepared in two steps. The first step *via* Protocol 1, using **6(ii)** (170 mg, 0.67 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (398 mg, 0.60 mmol) to yield the Fmoc protected precursor **6(iii)** as an off white foamy solid (529

mg, MS (ES +ve) *m/z* 900.0 (100%) $[M+H]^+$). The desired product was then prepared *via* Protocol 2, using precursor **6(iii)** (230 mg, 0.26 mmol) to afford the product **6(iv)** as a colourless oil (150mg, 85% two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80, d, *J* = 6.4 Hz, 3H; 0.82, d, *J* = 6.4 Hz, 3H; 1.21, s, 6H; 1.51, m, 5H; 1.70, m, 3H; 2.01, s, 3H; 2.03, m, 1H; 2.46, s, 3H; 2.48, s, 3H; 2.52, m, 2H; 3.08, m, 2H; 3.36, m, 1H; 4.42, m, 1H; 4.95, ABq, *J* = 12.3 Hz, 1H; 5.01, ABq, *J* = 12.3 Hz, 1H; 6.32, br s, NH; 7.15, m, 4H; 7.76, d, *J* = 6.8 Hz, NH. MS (ES +ve) *m/z* 678.0 (100%) $[M+H]^+$. HRMS for $C_{33}H_{48}ClN_5O_6S$, calculated 678.3092, found 678.3094.

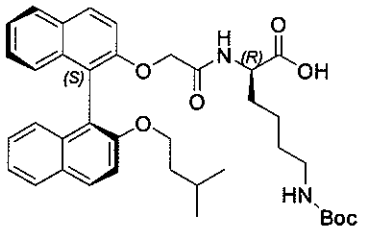
6(v)



This compound was prepared *via* Protocol 1, using **1(ii)** (642 mg, 1.55 mmol) and (*D*)-lys(BOC)-OMe (400 mg, 1.54 mmol) to yield the desired compound **6(v)** as a off white sticky solid (898 mg, 89%). R_f = 0.53 (5% MeOH/DCM).

^{1}H NMR (500MHz, $CDCl_3$) δ 0.54, d, *J* = 6.4 Hz, 3H; 0.58, d, *J* = 6.4 Hz, 3H; 0.78, m, 2H; 1.00, m, 1H; 1.22, m, 6H; 1.42, s, 9H; 2.91, m, 2H; 3.59, s, 3H; 3.95, m, 1H; 4.06, m, 1H; 4.29, m, 1H; 4.45, ABq, *J* = 14.3 Hz, 1H; 4.51, ABq, *J* = 14.3 Hz, 1H; 4.64, br s, NH; 6.15, d, *J* = 8.5 Hz, NH; 7.17, m, 4H; 7.30, m, 3H; 7.46, d, *J* = 8.9 Hz, 1H; 7.83, d, *J* = 7.5 Hz, 1H; 7.84, d, *J* = 7.8 Hz, 1H; 7.92, d, *J* = 10.2 Hz, 1H; 7.94, d, *J* = 10.2 Hz, 1H. MS (ES) *m/z* 657.1 (100%) $[M+H]^+$; 557.1 (90) $[M+H\text{-}BOC]^+$.

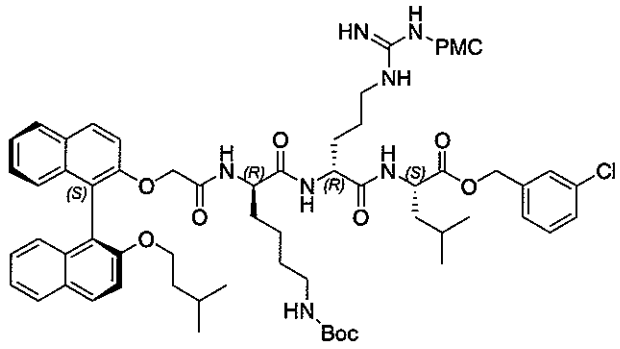
6(vi)



To a solution of **6(v)** (898 mg, 1.37 mmol) in THF (20 ml) was added a solution of $LiOH.H_2O$ (1260 mg, 30.1 mmol) in water (10 ml). The resultant solution was stirred at RT for 1 hr before diethyl ether (20 ml) was added and the layer separated. The aqueous layer was extracted with sat. sodium bicarbonate solution and the aqueous extracts combined then acidified to pH ~2-3 using 1M potassium bisulphate. The aqueous layer was then extracted with DCM (3 x 20 ml). A TLC of the initial and final organic layers was completed and showed the product was in both layers. As a result, all of the organic fractions were combined, dried ($MgSO_4$) and evaporated to dryness to yield the product **6(vi)** as an off white foamy solid (854, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53, d, J = 6.3 Hz, 3H; 0.57, d, J = 6.3 Hz, 3H; 0.82, m, 2H; 1.24, m, 5H; 1.40, m, 2H (obscured by BOC-CH_3); 1.44, s, 9H; 2.92, m, 2H; 3.95, m, 1H; 4.05, m, 1H; 4.31, m, 1H; 4.49, ABq, J = 14.6 Hz, 1H; 4.57, ABq, J = 14.6 Hz, 1H; 4.60, br s, NH (obscured by ABq); 6.15, m, NH; 7.19, m, 4H; 7.32, m, 3H; 7.44, d, J = 9.1 Hz, 1H; 7.85, d, J = 8.0 Hz, 1H; 7.86, d, J = 8.1 Hz, 1H; 7.94, d, J = 9.0 Hz, 1H; 7.96, d, J = 9.1 Hz, 1H. MS (ES+ve) 643.1 (100%) $[M+H]^+$; 543.1 (30) $[M+H\text{-}BOC]^+$.

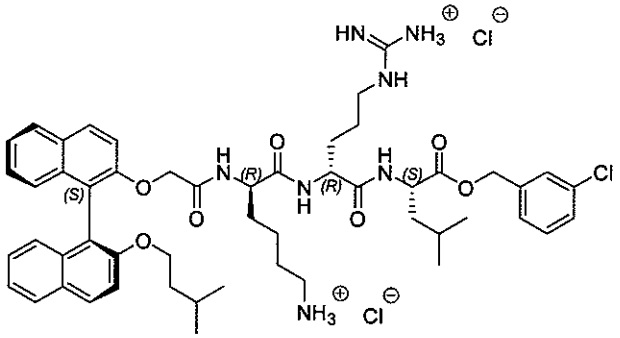
6(vii)



This compound was prepared *via* Protocol 1, using **6(vi)** (122 mg, 0.186 mmol) and **6(iv)** (145 mg, 0.199 mmol) to yield **6(vii)** as a white solid (198 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.39, d, J = 6.5 Hz, 3H; 0.44, d, J = 6.5 Hz, 3H; 0.70, m, 2H; 0.80, d, J = 5.6 Hz, 3H; 0.82, d, J = 5.6 Hz, 3H; 0.89, m, 1H; 1.12, m, 6H; 1.19, s, 6H; 1.29, m, 2H; 1.33, s, 9H; 1.55, m, 4H; 1.68, m, 2H; 1.71, m, 1H; 2.00, s, 3H; 2.48, s, 3H; 2.48, s, 3H; 2.50, m, 2H; 2.82, m, 2H; 3.07, m, 2H; 3.79, m, 1H; 3.96, m, 2H; 4.33, m, 2H; 4.44, m, 3H; 4.73, m, NH; 4.97, ABq, J = 12.7 Hz, 1H; 5.03, ABq, J = 12.7 Hz, 1H; 6.12, d, J = 6.9 Hz, NH; 6.22, br s, NH; 7.26, m, 11H; 7.36, d, J = 9.1 Hz, 1H; 7.75, d, J = 10.1 Hz, 1H; 7.77, d, J = 8.7 Hz, 1H; 7.84, d, J = 8.7 Hz, 1H; 7.86, d, J = 7.6 Hz, 1H. MS (ES +ve) *m/z* 1301.9 (100%) $[M+H]^+$; 602.6 (30) $[M+2H\text{-}BOC]^{2+}$.

Compound 6

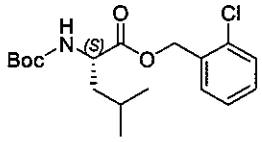


This compound was prepared *via* Protocol 3, using **6(vii)** (180 mg, 0.138 mmol) to yield **6** as an off white solid (130 mg, 93%).

^{1}H NMR (500 MHz, CD_3OD) δ 0.50, d, J = 6.3 Hz, 3H; 0.55, d, J = 6.3 Hz, 3H; 0.90, d, J = 4.8 Hz, 3H; 0.94, d, J = 4.8 Hz, 3H; 0.95, m, 2H; 1.14, m, 2H; 1.23, m, 2H; 1.67, m, 10H; 2.83, m, 2H; 3.18, m, 2H; 3.96, m, 1H; 4.14, m, 2H; 4.36, m, 1H; 4.48, m, 3H; 5.12, s, 2H; 7.05, d, J = 3.7 Hz, 1H; 7.08, d, J = 3.5 Hz, 1H; 7.17, dist t, 2H; 7.30, m, 5H; 7.38, s, 1H; 7.45, d, J = 9.0 Hz, 1H; 7.54, d, J = 9.0 Hz, 1H; 7.88, d, J = 8.5 Hz, 1H; 7.91, d, J = 8.5 Hz, 1H; 7.99, d, J = 8.7 Hz, 1H; 8.02, d, J = 8.5 Hz, 1H. MS (ES +ve) *m/z* 935.7 (5%) $[M+H]^+$; 468.7 (100) $[M+2H]^{2+}$.

Synthesis of Compound 7

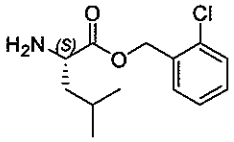
7(i)



To BOC-(*L*)-leu-OH (250 mg, 1.08 mmol) and potassium carbonate (1.00 g, 7.24 mmol) in acetone (25 ml) was added 2-chlorobenzyl bromide (0.16 ml, 1.23 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 5% ethyl acetate/hexane to first remove 2-chlorobenzyl bromide, then with DCM to yield the product **7(i)** as a white solid (353 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92, d, J = 6.4 Hz, 3H; 0.93, d, J = 6.4 Hz, 3H; 1.43, s, 9H; 1.56, m, 1H; 1.68, m, 2H; 4.40, m, 1H; 5.16, d, J = 8.4 Hz, NH; 5.22, ABq, J = 13.1 Hz, 1H; 5.27, ABq, J = 13.1 Hz, 1H; 7.25, m, 2H; 7.35, m, 1H; 7.42, m, 1H. MS (ES +ve) *m/z* 356.1 (100%) $[M+H]^+$; 256.0 (70) $[M+H\text{-}BOC]^+$.

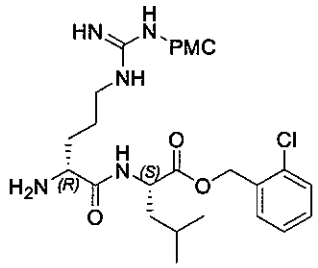
7(ii)



To **7(i)** (350 mg, 0.984 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 3 hrs. The solution was then diluted with DCM (5 ml) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **7(ii)** as a white solid (236 mg, 94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86, d, J = 6.8 Hz, 3H; 0.88, d, J = 6.8 Hz, 3H; 1.45, m, 1H; 1.57, m, 1H; 1.74, m, 1H; 2.64, s, NH_2; 3.54, m, 1H; 5.20, s, 2H; 7.22, m, 2H; 7.35, m, 2H. MS (ES +ve) *m/z* 256.1 (100%) $[M+H]^+$.

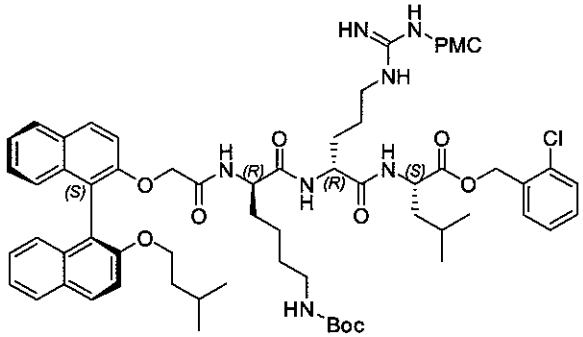
7(iv)



This compound was prepared in two steps. The first step *via* Protocol 1, using **7(ii)** (230 mg, 0.900 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (563 mg, 0.850 mmol) to yield the Fmoc protected precursor **7(iii)** as a white foamy solid (662 mg, MS (ES +ve) *m/z* 900 (100%) $[M+H]^+$). The desired product was then prepared *via* Protocol 2, using the precursor **7(iii)** (200 mg, 0.22 mmol) to affordthe product **7(iv)** as a white solid (135 mg, 66% two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81, d, *J* = 5.9 Hz, 3H; 0.83, d, *J* = 5.9 Hz, 3H; 1.21, s, 6H; 1.51, m, 5H; 1.71, m, 3H; 2.01, s, 3H; 2.01, m, 1H; 2.47, s, 3H; 2.49, s, 3H; 2.53, m, 2H; 3.08, m, 2H; 3.33, m, 1H; 4.46, m, 1H; 5.10, ABq, *J* = 12.9 Hz, 1H; 5.15, ABq, *J* = 12.9 Hz, 1H; 6.34, br s, NH; 7.16, m, 2H; 7.30, m, 2H; 7.75, d, *J* = 7.8 Hz, NH. MS (ES +ve) *m/z* 678.0 (100%) $[M+H]^+$.

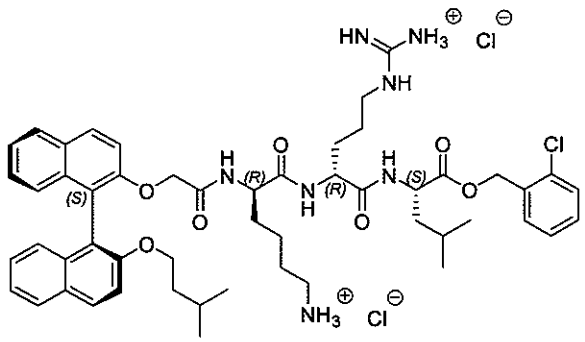
7(v)



This compound was prepared *via* Protocol 1, using **6(vi)** (111 mg, 0.169 mmol) and **7(iv)** (130 mg, 0.179 mmol) to yield **7(v)** as a white solid (172 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.38, d, *J* = 6.2 Hz, 3H; 0.43, d, *J* = 6.6 Hz, 3H; 0.70, m, 2H; 0.81, d, *J* = 5.5 Hz, 3H; 0.82, d, *J* = 5.5 Hz, 3H; 0.89, m, 1H; 1.12, m, 6H; 1.19, s, 6H; 1.29, m, 2H; 1.33, s, 9H; 1.58, m, 4H; 1.68, m, 2H; 1.71, m, 1H; 2.00, s, 3H; 2.46, s, 3H; 2.48, s, 3H; 2.50, m, 2H; 2.81, m, 2H; 3.07, m, 2H; 3.78, m, 1H; 3.96, m, 2H; 4.33, m, 2H; 4.46, m, 3H; 4.73, m, NH; 5.11, ABq, *J* = 12.7 Hz, 1H; 5.19, ABq, *J* = 12.7 Hz, 1H; 6.12, d, *J* = 7.3 Hz, NH; 6.23, br s, NH; 7.26, m, 11H; 7.36, d, *J* = 10.0 Hz, 1H; 7.75, d, *J* = 8.0 Hz, 1H; 7.77, d, *J* = 8.3 Hz, 1H; 7.84, d, *J* = 9.0 Hz, 1H; 7.85, d, *J* = 9.0 Hz, 1H. MS (ES +ve) *m/z* 1301.9 (100%) $[M+H]^+$; 601.7 (60) $[M+2H\text{-}BOC]^{2+}$.

Compound 7

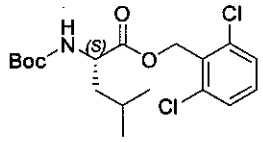


This compound was prepared *via* Protocol 3, using **7(v)** (160 mg, 0.123 mmol) to yield **7** as an off white solid (109 mg, 88%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.51, d, *J* = 6.4 Hz, 3H; 0.56, d, *J* = 6.4 Hz, 3H; 0.90, d, *J* = 5.7 Hz, 3H; 0.95, d, *J* = 5.7 Hz, 3H; 1.15, m, 2H; 1.25, m, 3H; 1.67, m, 11H; 2.82, m, 2H; 3.16, m, 2H; 3.97, m, 1H; 4.15, m, 2H; 4.34, m, 1H; 4.48, m, 3H; 5.21, ABq, *J* = 12.8 Hz, 1H; 5.28, ABq, *J* = 12.8 Hz, 1H; 7.05, d, *J* = 4.5 Hz, 1H; 7.08, d, *J* = 4.5 Hz, 1H; 7.20, m, 2H; 7.32, m, 4H; 7.44, m, 3H; 7.54, d, *J* = 9.0 Hz, 1H; 7.89, d, *J* = 8.1 Hz, 1H; 7.91, d, *J* = 7.7 Hz, 1H; 8.01, d, *J* = 9.0 Hz, 1H; 8.02, d, *J* = 9.0 Hz, 1H. MS (ES +ve) *m/z* 935.7 (5%) $[M+H]^+$; 468.7 (100) $[M+2H]^{2+}$.

Synthesis of Compound 8

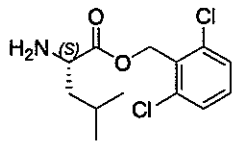
8(i)



To BOC-(*L*)-leu-OH (250 mg, 1.08 mmol) and potassium carbonate (100 mg, 7.24 mmol) in acetone (25 ml) was added 2,6-dichlorobenzyl bromide (266 mg, 1.50 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 5% ethyl acetate/hexane to first remove 2,6-dichlorobenzyl bromide, then with DCM to yield the product **8(i)** as a white solid (383 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85, d, J = 7.8 Hz, 6H; 1.37, s, 9H; 1.46, m, 1H; 1.58, m, 1H; 1.68, m, 1H; 4.40, m, 1H; 5.99, d, J = 7.8 Hz, NH; 5.35, s, 2H; 7.18, dist t, 1H; 7.27, d, J = 8.3 Hz, 2H. MS (ES +ve) *m/z* 333.2 (100%) $[M+H-C4H8]^+$; 289.9 (50) $[M+H-BOC]^+$.

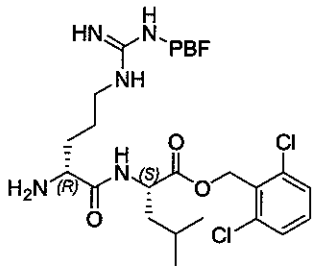
8(ii)



To **8(i)** (380 mg, 0.974 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 1 hr. The solution was then diluted with ethyl acetate (20 ml) and washed with sat. sodium bicarbonate solution added until the washings were basic. The organic layer was then separated and the aqueous layer extracted once more with ethyl acetate (10 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **8(ii)** as a white solid (275 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84, d, J = 7.0 Hz, 3H; 0.86, d, J = 8.0 Hz, 3H; 1.48, m, 1H; 1.57, m, 1H; 1.73, m, 1H; 3.58, m, 1H; 3.76, s, NH_2; 5.35, ABq, J = 11.8 Hz, 1H; 5.38, ABq, J = 11.8 Hz, 1H; 7.19, dist t, 1H; 7.29, d, J = 7.9 Hz, 2H. MS (ES +ve) *m/z* 290 (100%) $[M+H]^+$.

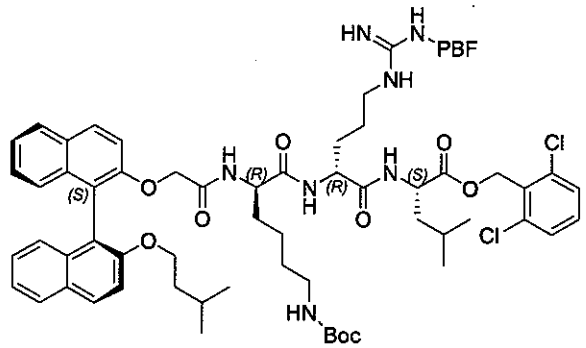
8(iv)



This compound was prepared in two steps. The first step *via* Protocol 1, using **8(ii)** (120 mg, 0.41 mmol) and Fmoc-(*D*)-arg(Pbf)-OH (260 mg, 0.40 mmol) to yield the Fmoc protected precursor **8(iii)** as a white foamy solid (MS (ES +ve) *m/z* 900 (100%) $[M+H]^+$). This was then deprotected *via* Protocol 2 to afford the desired compound **8(iv)** as a white solid (178 mg, 64% two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81, d, J = 5.9 Hz, 3H; 0.83, d, J = 5.9 Hz, 3H; 1.21, s, 6H; 1.51, m, 5H; 1.71, m, 3H; 2.01, s, 3H; 2.02, m, 1H; 2.47, s, 3H; 2.49, s, 3H; 2.53, m, 2H; 3.08, m, 2H; 3.33, m, 1H; 4.46, m, 1H; 5.10, ABq, J = 12.9 Hz, 1H; 5.15, ABq, J = 12.9 Hz, 1H; 6.34, br s, NH; 7.16, m, 2H; 7.30, m, 2H; 7.75, d, J = 7.8 Hz, NH. MS (ES +ve) *m/z* 678 (100%) $[M+H]^+$.

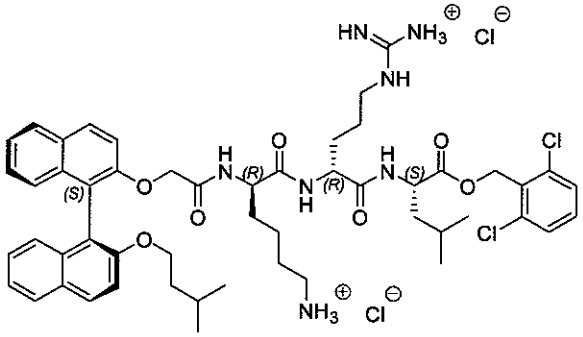
8(v)



This compound was prepared *via* Protocol 1, using **6(vi)** (160 mg, 0.25 mmol) and **8(iv)** (175 mg, 0.25 mmol) to yield **8(v)** as a white solid (231 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.46, d, J = 6.2 Hz, 3H; 0.52, d, J = 6.5 Hz, 3H; 0.79, m, 2H; 0.86, d, J = 6.7 Hz, 3H; 0.88, d, J = 6.7 Hz, 3H; 0.94, m, 1H; 1.19, m, 6H; 1.41, s, 6H; 1.43, s, 9H; 1.64, m, 5H; 1.83, m, 2H; 2.07, s, 3H; 2.51, s, 3H; 2.58, s, 3H; 2.92, s, 2H; 3.08, m, 2H; 3.16, m, 2H; 3.88, m, 1H; 4.05, m, 2H; 4.48, m, 5H; 4.86, m, NH; 5.37, ABq, J = 11.9 Hz, 1H; 5.44, ABq, J = 11.9 Hz, 1H; 6.20, d, J = 7.0 Hz, NH; 6.32, br s, NH; 7.25, m, 10H; 7.47, d, J = 9.1 Hz, 1H; 7.85, d, J = 7.9 Hz, 2H; 7.95, d, J = 9.4 Hz, 1H; 7.98, d, J = 9.7 Hz, 1H. MS (ES +ve) *m/z* 1322.3 (60%) $[M+H]^+$; 612.8 (100) $[M+2H\text{-}BOC]^{2+}$.

Compound 8

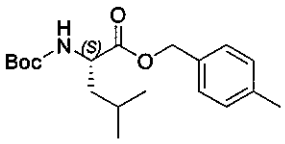


This compound was prepared *via* Protocol 3, using **8(v)** (185 mg, 0.138 mmol) to yield **8** as a white solid (78 mg, 98%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.50, d, J = 6.3 Hz, 3H; 0.56, d, J = 6.4 Hz, 3H; 0.87, d, J = 5.2 Hz, 3H; 0.92, d, J = 5.2 Hz, 3H; 0.99, m, 2H; 1.23, m, 4H; 1.66, m, 10H; 2.86, m, 2H; 3.19, m, 2H; 3.96, m, 1H; 4.16, m, 2H; 4.49, m, 4H; 5.38, ABq, J = 11.7 Hz, 1H; 5.44, ABq, J = 11.7 Hz, 1H; 7.10, m, 2H; 7.17, m, 2H; 7.32, m, 3H; 7.39, m, 2H; 7.46, d, J = 9.0 Hz, 1H; 7.57, d, J = 9.0 Hz, 1H; 7.87, d, J = 8.1 Hz, 1H; 7.93, d, J = 8.1 Hz, 1H; 7.99, d, J = 9.0 Hz, 1H; 8.04, d, J = 9.0 Hz, 1H. MS (ES +ve) *m/z* 969.8 (10%) $[M+H]^+$; 485.7 (100) $[M+2H]^{2+}$.

Synthesis of Compound 9

9(i)

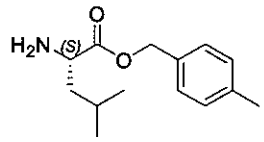


To BOC-(*L*)-Leu-OH (250 mg, 1.08 mmol) and potassium carbonate (747 mg, 5.40 mmol) in acetone (50 mL) was added 4-methylbenzyl bromide (300 mg, 1.62 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 1:4 hexane/DCM to first remove 4-chlorobenzyl bromide, then with DCM to yield the product **9(i)** as a colourless oil (340 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91, d, J = 6.5 Hz, 3H; 0.92, d, J = 6.2 Hz, 3H; 1.43, s, 9H; 1.49, m, 2H; 1.66, m, 1H; 2.35, s, 3H; 4.35, m, 1H; 4.95, d, J = 9.2 Hz, NH; 5.08, ABq, J = 12.3 Hz, 1H; 5.14, ABq, J = 12.3 Hz, 1H;

7.16, ABq, J = 7.9 Hz, 2H; 7.24, ABq, J = 7.9 Hz, 2H. MS (ES +ve) *m/z* 353.3 (100%) $[M+H_2O]^+$; 336.3 (90) $[M+H]^+$.

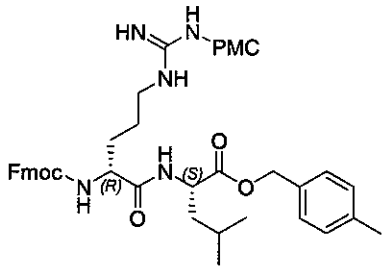
9(ii)



To **9(i)** (340 mg, 1.01 mmol) in DCM (2 mL) was added TFA (2 mL) and the resulting solution stirred at room temperature for 3 hrs. The solution was then diluted with DCM (5 mL) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **9(ii)** as a white solid (215 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90, d, J = 6.5 Hz, 3H; 0.92, d, J = 6.7 Hz, 3H; 1.43, m, 1H; 1.55, m, 1H/NH_2; 1.76, m, 1H; 2.35, s, 3H; 3.49, m, 1H; 5.10, s, 2H; 7.18, ABq, J = 7.9 Hz, 2H; 7.25, ABq, J = 7.9 Hz, 2H. MS (ES +ve) *m/z* 236.0 (100%) $[M+H]^+$.

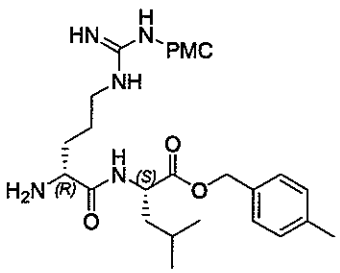
9(iii)



This compound was prepared *via* Protocol 1 using **9(ii)** (215 mg, 0.914 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (606 mg, 0.914 mmol) to yield the desired product **9(iii)** as an off white solid (780 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78, m, 6H; 1.28, s, 6H; 1.61, m, 8H; 1.91, m, 1H; 2.01, s, 3H; 2.26, s, 3H; 2.50, m, 2H; 2.54, s, 3H; 2.57, s, 3H; 3.23, m, 2H; 4.03, m, 1H; 4.25, m, 3H; 4.52, m, 1H; 4.97, ABq, J = 12.2 Hz, 1H; 5.03, ABq, J = 12.2 Hz, 1H; 6.42, br s, NH; 7.06, ABq, J = 7.7, Hz, 2H; 7.13, ABq, J = 7.7, Hz, 2H; 7.17, m, 2H; 7.31, dd, J_1 =7.5 Hz, J_2 = 7.5 Hz, 2H; 7.51, m, 2H; 7.68, d, J = 7.5 Hz, 2H. MS (ES +ve) *m/z* 658.1 (100%) $[M+H\text{-Fmoc}]^+$.

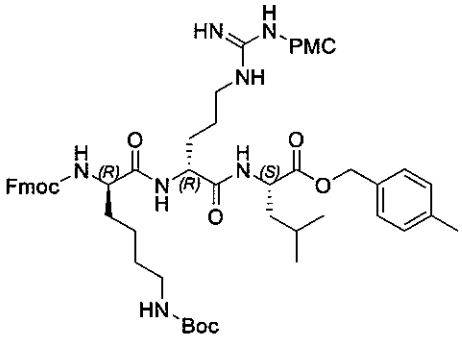
9(iv)



This compound was prepared *via* Protocol 2, using **9(iii)** (650 mg, 0.739 mmol) to yield the desired product **9(iv)** as a colourless oil (409 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86, d, J = 5.9 Hz, 3H; 0.88, d, J = 5.4 Hz, 3H; 1.28, s, 6H; 1.58, m, 5H/NH_2; 1.77, m, 3H; 2.00, m, 1H; 2.09, s, 3H; 2.31, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.59, m, 2H; 3.15, m, 2H; 3.40, m, 1H; 4.49, m, 1H; 5.01, ABq, J = 12.2 Hz, 1H; 5.08, ABq, J = 12.2 Hz, 1H; 6.42, br s, NH; 7.11, ABq, J = 8.0, Hz, 2H; 7.18, ABq, J = 8.0, Hz, 2H; 7.81, d, J = 7.8 Hz, NH. MS (ES +ve) *m/z* 658.1 (100%) $[M+H]^+$.

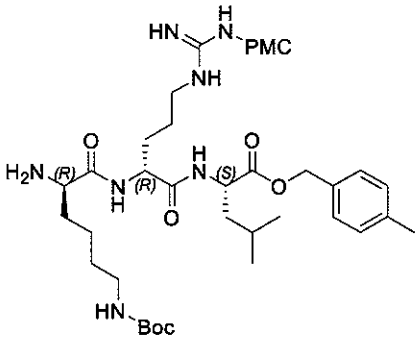
9(v)



This compound was prepared *via* Protocol 1, using **9(iv)** (377 mg, 0.573 mmol) and Fmoc-(*D*)-lys(BOC)-OH (268 mg, 0.573 mmol) to yield the desired product **9(v)** as an off white solid (575 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82, m, 6H; 1.19, s, 6H; 1.39, s, 9H; 1.58, m, 13H; 2.02, s, 3H; 2.28, s, 3H; 2.49, m, 2H; 2.53, s, 3H; 2.55, s, 3H; 3.02, m, 2H; 3.19, m, 2H; 3.93, m, 1H; 4.19, m, 2H; 4.25, m, 1H; 4.53, m, 2H; 4.98, m, 2H; 6.23, m, NH; 6.50, br s, NH; 7.07, m, 2H; 7.11, m, 2H; 7.22, m, 2H; 7.33, m, 2H; 7.53, m, 2H; 7.68, m, 2H. MS (ES +ve) *m/z* 1108.3 (100%) $[M+H]^+$.

9(vi)

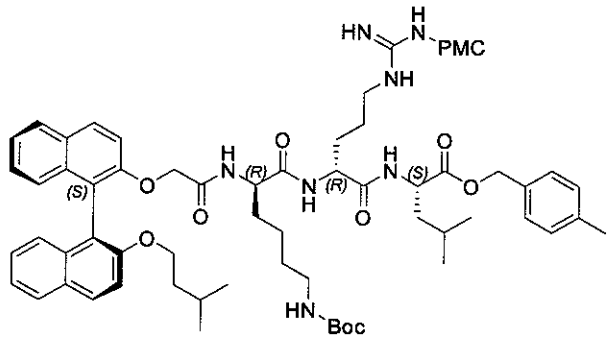


This compound was prepared *via* Protocol 2, using **9(v)** (290 mg, 0.262 mmol) to yield the desired product **9(vi)** as an off white solid (162 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85, d, J = 6.3 Hz, 3H; 0.87, d, J = 6.3 Hz, 3H; 1.29, s, 6H; 1.40, s, 9H; 1.58, m, 10H/NH_2; 1.78, dist t, 2H; 1.89, m, 1H; 2.09, s, 3H; 2.32, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.61, m, 2H; 3.05, m, 2H; 3.22, m, 2H; 3.36, m, 1H; 4.54, m, 2H; 4.95, m, NH; 5.01, ABq, J = 12.2 Hz, 1H; 5.07, ABq, J = 12.2 Hz, 1H; 6.42,

br s, NH; 7.12, ABq, J = 7.8 Hz, 2H; 7.18, ABq, J = 7.8 Hz, 2H; 7.60, d, J = 7.3 Hz, NH; 8.00, d, J = 6.4 Hz, NH. MS (ES +ve) *m/z* 886.3 (100%) $[M+H]^+$.

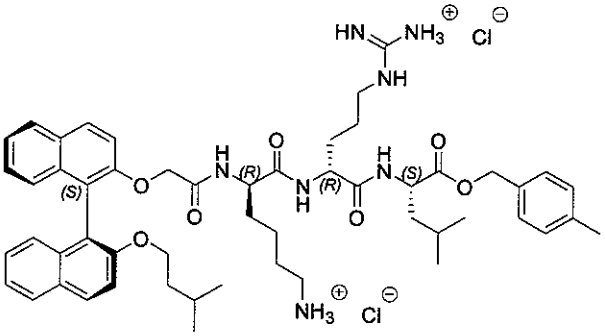
9(vii)



This compound was prepared *via* Protocol 1, using **1(ii)** (75 mg, 0.181 mmol) and **9(vi)** (160 mg, 0.181 mmol) to yield the desired product **9(vii)** as a white solid (193 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.47, d, J = 6.5 Hz, 3H; 0.53, d, J = 6.5 Hz, 3H; 0.78, m, 1H; 0.87, d, J = 5.8 Hz, 3H; 0.89, d, J = 5.8 Hz, 3H; 0.91, m, 1H; 1.22, m, 8H; 1.28, s, 6H; 1.42, s, 9H; 1.62, m, 3H; 1.76, dist t, 2H; 1.82, m, 1H; 2.09, s, 3H; 2.33, s, 3H; 2.55, s, 3H; 2.57, s, 3H; 2.59, m, 2H; 2.91, m, 2H; 3.16, m, 2H; 3.88, m, 1H; 4.05, m, 2H; 4.49, m, 4H; 4.84, m, NH; 5.04, ABq, J = 12.2 Hz, 1H; 5.13, ABq, J = 12.2 Hz, 1H; 6.19, d, J = 6.4 Hz, NH; 6.27, s, NH; 7.22, m, 11H; 7.46, d, J = 9.1 Hz, 1H; 7.85, dist t, 2H; 7.94, dist t, 2H. MS (ES +ve) *m/z* 1282 (100%) $[M+H]^+$.

Compound 9

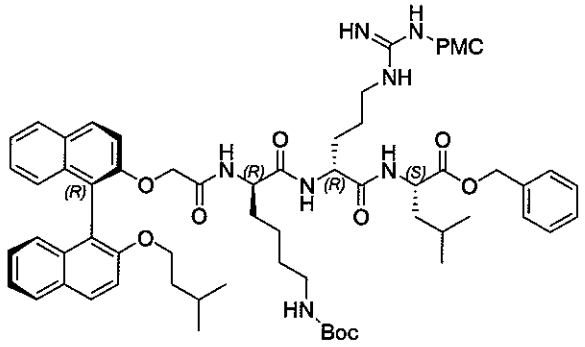


This compound was prepared *via* Protocol 3, using **9(vii)** (107 mg, 0.083 mmol) to yield the product **9** as a white solid (28 mg, 34%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.38, δ, J = 6.2 Hz, 3H; 0.43, d, J = 6.2 Hz, 3H; 0.85, m, 8H; 1.07, m, 2H; 1.18, m, 2H; 1.59, m, 9H; 2.25, s, 3H; 2.74, m, 2H; 3.09, m, 2H; 3.90, m, 1H; 4.06, m, 2H; 4.34, m, 3H; 4.40, ABq, J = 14.7 Hz, 1H; 4.51, ABq, J = 14.7 Hz, 1H; 4.99, ABq, J = 12.1 Hz, 1H; 5.05, ABq, J = 12.1 Hz, 1H; 6.99, d, J = 8.5Hz, 1H; 7.01, d, J = 8.5 Hz, 1H; 7.09, d, J = 7.8 Hz, 1H; 7.15, m, 4H; 7.27, m, 3H; 7.41, d, J = 9.0 Hz, 1H; 7.49, dd, J_1 = 9.1 Hz, J_2 = 11.6 Hz, 1H; 7.84, m, 2H; 7.95, m, 2H. MS (ES +ve) *m/z* 916 (5%) $[M+H]^+$; 812 (10) [M+H-pMeBz]$^+$; 459 (95) $[M+2H]^{2+}$; 407 (100) [M+2H-pMeBz]$^{2+}$.

Synthesis of Compound 10

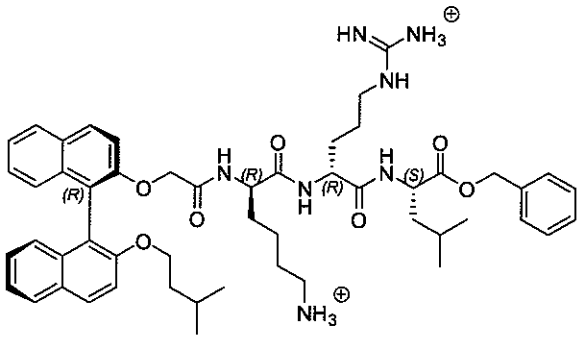
10(i)



This compound was prepared *via* Protocol 1, using **(*R*)-1(ii)** (67 mg, 0.162 mmol) and **1(viii)** (140 mg, 0.161 mmol) to yield the desired product **10(i)** as a white solid (108 mg, 53%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51, d, J = 6.3 Hz, 3H; 0.56, d, J = 6.3 Hz, 3H; 0.84, d, J = 5.4 Hz, 3H; 0.86, m, 3H; 0.88, d, J = 5.4 Hz, 3H; 1.21, m, 6H; 1.25, s, 6H; 1.29, m, 2H; 1.43, s, 9H; 1.64, m, 4H; 1.76, m, 2H; 1.84, m, 1H; 2.09, s, 3H; 2.52, s, 3H; 2.54, s, 3H; 2.58, m, 2H; 2.94, m, 2H; 3.11, m, 2H; 3.89, m, 1H; 3.99, m, 2H; 4.35, m, 1H; 4.37, ABq, J = 14.7 Hz, 1H; 4.90, m, 1H; 4.58, ABq, J = 14.7 Hz, 1H; 4.90, m, NH; 5.04, ABq, J = 12.3 Hz, 1H; 5.13, ABq, J = 12.3 Hz, 1H; 6.10, br s NH; 6.19, br s, NH; 7.45, m, 12H; 7.44, d, J = 9.3 Hz, 1H; 7.82, d, J = 8.3 Hz, 1H; 7.84, d, J = 8.3 Hz, 1H; 7.89, d, J = 8.8 Hz, 1H; 7.94, d, J = 8.8 Hz, 1H. MS (ES +ve) *m/z* 1268 (50%) $[M+H]^+$; 585 (100) $[M+2H\text{-}BOC]^{2+}$.

Compound 10



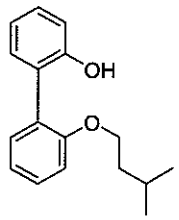
This compound was prepared *via* Protocol 3, using **10(i)** (105 mg, 0.083 mmol) to yield an impure product. Protocol 3 was repeated on 80 mg of this product to yield **10** as an off white solid (58 mg, 82%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.41, d, J = 6.6 Hz, 3H; 0.46, d, J = 6.6 Hz, 3H; 0.78, d, J = 5.7 Hz, 3H; 0.83, d, J = 5.7 Hz, 3H; 1.06, m, 6H; 1.38, m, 1H; 1.53, m, 8H; 1.72, m, 1H; 2.78, m, 2H; 3.05, m, 2H; 3.84, m, 1H; 3.97, m, 1H; 4.02, m, 1H; 4.25, m, 1H; 4.35, m, 2H; 4.51, ABq, J = 15.0 Hz, 1H; 5.00, ABq, J = 12.3 Hz, 1H; 5.05, ABq, J = 12.3 Hz, 1H; 6.96, d, J = 8.7 Hz, 1H; 7.05, d, J = 8.4 Hz, 1H; 7.13, m, 2H; 7.24, m, 7H; 7.38, d, J = 9.0 Hz, 1H;

7.45, d, J = 9.0 Hz, 1H; 7.80, d, J = 8.1 Hz, 1H; 7.84, d, J = 7.8 Hz, 1H; 7.91, d, J = 9.0 Hz, 1H; 7.96, d, J = 8.7 Hz, 1H. MS (ES +ve) *m/z* 902 (10%) $[M+H]^+$; 452.0 (100) $[M+H]^{2+}$.

Synthesis of Compound 11

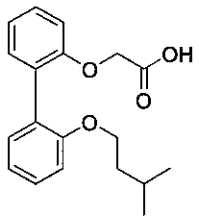
11(i)



To a solution of 1,1'-biphen-2,2'-diol (0.21 g, 1.15 mmol) in dry acetone (25 ml) was added potassium carbonate (1.62 g, 12.0 mmol). To the resulting suspension a solution of 1-bromo-3-methylbutane (0.18 ml, 1.50 mmol) in dry acetone (10 ml) was added portionwise over 90 minutes. The reaction mixture was then heated at reflux for 18 hours. The cooled mixture was filtered and the solid residue was washed with acetone (2 x 20 ml). The combined filtrate and washes were concentrated *in vacuo* to yield the product **11(i)** as a colourless oil (292 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95, d, J = 6.2 Hz, 6H; 1.71, m, 3H; 4.13, t, J = 6.4 Hz, 2H; 7.25, m, 8H. MS (EI) *m/z* 256 (30%) $[M]^+$; 186 (100) $[M-(CH_2CH_2CH(CH_3)_2)]^+$.

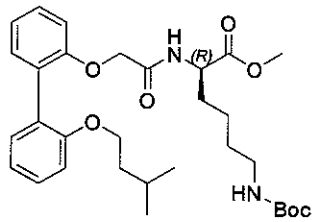
11(ii)



To a solution of **11(i)** (0.29 g, 1.13 mmol) in methanol (20 ml) was added potassium carbonate (1.83 g, 13.2 mmol) and bromoacetic acid (0.56 g, 4.03 mmol) and the resulting suspension was heated at reflux for 16 hours. The cooled reaction mixture was concentrated *in vacuo* and the residue was dissolved in distilled water (100 ml) then washed with ether (3 x 20 ml). The aqueous solution was acidified (10% HCl) and extracted with DCM (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **11(ii)** as a thick colourless oil (111 mg, 30%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77, d, J = 4.4 Hz, 6H; 1.45, m, 3H; 3.99, t, J = 6.5 Hz, 2H; 4.62, s, 2H; 6.87, dd, J = 8.2, 0.9 Hz, 1H; 7.08, m, 3H; 7.31, m, 4H. MS (ES +ve) *m/z* 353 (12%) $[M+K]^+$; 337 (39) $[M+Na]^+$; 332 (96) $[M+NH_4]^+$; 315 (100) $[M+H]^+$; 245 (38).

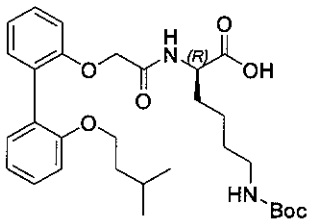
11(iii)



This compound was prepared *via* Protocol 1, using (*R*)-Lysine(Boc)-methyl ester (0.10 g, 0.38 mmol) and **11(ii)** (0.11 g, 0.34 mmol) in anhydrous acetonitrile (10 ml) with EDCI (0.09 g, 0.45 mmol) and HOBt (0.08 g, 0.58 mmol). Purification with 1-2% methanol:DCM gave product **11(iii)** as a pale yellow oil (179 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76, dd, J = 6.4 Hz, 6H; 1.08, m, 2H; 1.43, m, 12H; 1.67, m, 2H; 3.00, m, 3H; 3.66, s, 3H; 3.90, m, 3H; 4.44, m, 4H; 6.74, br d, J = 8.5 Hz, 1H; 8.86, d, J = 7.9 Hz, 1H; 7.03, m, 3H; 7.27, m, 4H. MS (ES +ve) *m/z* 579 (11%) $[M+Na]^+$; 557 (100) $[M+H]^+$; 457 (29) $[M-Boc+H]^+$; 233 (88).

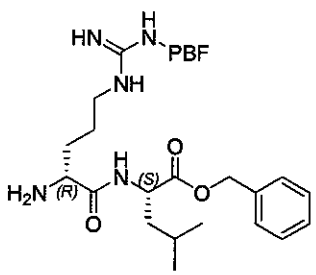
11(iv)



To a solution of **11(iii)** (0.18 g, 0.32 mmol) in THF:water (4:1) (15 ml) was added lithium hydroxide (0.11 g, 2.60 mmol) and the resulting solution was stirred at 20 °C for 16 hours. The reaction mixture was diluted with water (5 ml), acidified with 10% HCl and extracted with DCM (4 x 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the product **11(iv)** as a pale yellow oil (108 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77, dd, J = 6.3, 4.4 Hz, 6H; 1.13, m, 2H; 1.44, m, 14H; 1.75, br s, 1H; 3.12, m, 2H; 3.94, m, 2H; 4.49, ABq, J = 14.6 Hz, 2H; 4.64, m, 1H; 6.87, m, 2H; 6.99, m, 2H; 7.05, t, J = 7.8 Hz, 1H; 7.26, m, 4H. MS (ES +ve) *m/z* 543, (100%) $[M+H]^+$; 487 (46) $[M+H-56]^+$; 443 (46) $[M+H-Boc]^+$.

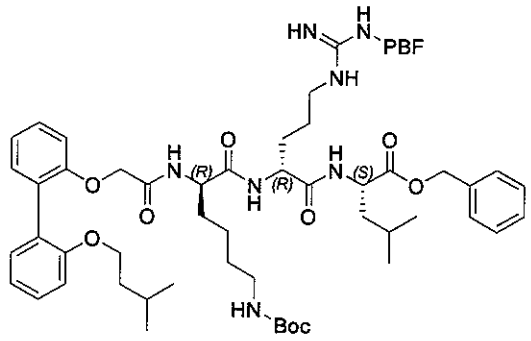
11(vi)



This compound was prepared in two steps. The first step *via* Protocol 1, using **1(iv)** (1.12 g, 5.06 mmol) and Fmoc-(*D*)-arg(Pbf)-OH (3.06 mg, 4.72 mmol) to yield the Fmoc protected precursor **11(v)** as a white foamy solid (MS (ES +ve) *m/z* 852 (100%) $[M+H]^+$). This was then deprotected *via* Protocol 2 to afford the desired compound **11(vi)** as a yellow oil (1.54 g, 52% two steps).

MS (ES +ve) *m/z* 630 (100%) $[M+H]^+$

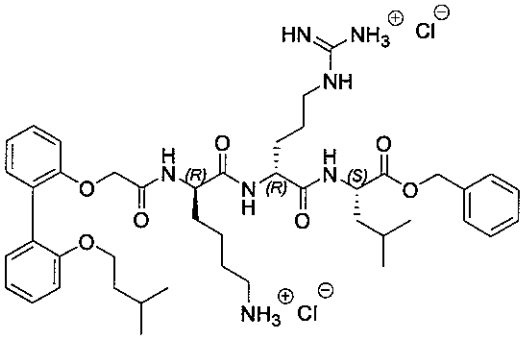
11(vii)



This compound was prepared *via* Protocol 1, using **11(iv)** (70 mg, 0.13 mmol) and **11(vi)** (77 mg, 0.12 mmol) in anhydrous acetonitrile with EDCI (40 mg, 0.21 mmol) and HObt (39 mg, 0.29 mmol). Purification with 1-2% methanol:DCM gave product **11(vii)** as a clear colourless oil (103 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77, dd, *J* = 6.4, 1.8 Hz, 6H; 0.88, dd, *J* = 7.3, 7.3 Hz, 6H; 1.08, m, 2H; 1.43, m, 23H; 1.63, m, 5H; 1.83, m, 1H; 2.05, s, 3H; 2.47, s, 3H; 2.54, s, 3H; 2.91, s, 2H; 3.00, m, 2H; 3.17, m, 2H; 3.93, m, 2H; 4.46, m, 5H; 4.85, m, 1H; 5.14, ABq, *J* = 12.3 Hz, 2H; 6.15, br s, 2H; 6.79, m, 2H; 7.01, m, 3H; 7.28, m, 10H; 7.61, br d, 1H. MS (ES +ve) *m/z* 1153 (100%) $[M+H]^+$; 527 (68); 288 (98).

Compound 11

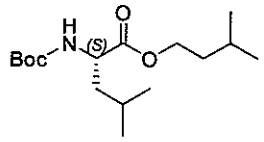


This compound was prepared *via* Protocol 3, using **11(vii)** (95 mg, 82 μmol) and TFA:TIPS:H_2O (95:2.5:2.5) (2 ml). Precipiation from methanol using ether (3 times) gave the product **11** as off-white crystals (67 mg, 93%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.78, dd, *J* = 6.4, 1.2 Hz, 6H; 0.91, dd, *J* = 14.4, 5.6 Hz, 6H; 1.25, m, 2H; 1.55, m, 14H; 2.89, m, 2H; 3.16, m, 2H; 3.96, m, 2H; 4.44, m, 5H; 5.14, ABq, *J* = 10.7 Hz, 2H; 7.02, m, 4H; 7.23, m, 2H; 7.35, m, 7H. MS (ES +ve) *m/z* 802 (4%) $[M+H]^+$; 401 (100) $[M+H]^{2+}$.

Synthesis of Compound 12

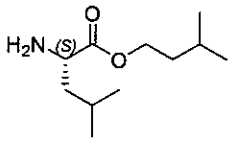
12(i)



To BOC(*L*)-Leu-OH (300 mg, 1.30 mmol) and potassium carbonate (0.4 g, 2.90 mmol) in acetone (25 ml) was added 4-bromo-1-methylbutane (0.2 ml, 1.60 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with DCM to yield the product **12(i)** as a colourless oil (172 mg, 44%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94, m, 12H; 1.44, s, 9H; 1.55, m, 4H; 1.70, m, 2H; 4.14, dt, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H. 4.29, m, 1H; 5.04, d, J = 8.3 Hz, NH. MS (ES +ve) *m/z* 302.1 (100%) $[M+H]^+$; 246.1 (70) $[M+H\text{-}i\text{Bu}]^+$; 202.1 (70) $[M+H\text{-BOC}]^+$.

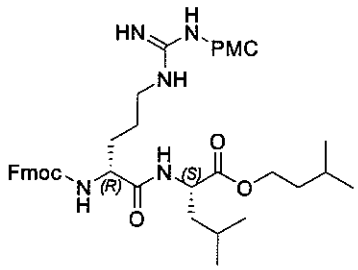
12(ii)



To **12(i)** (170 mg, 0.592 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 1 hr. The solution was then diluted with ethyl acetate (10 ml) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **12(ii)** as a white solid (93 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93, m, 12H; 1.43, m, 1H; 1.55, m, 3H/NH_2; 1.73, m, 2H; 3.45, dd, J_1 = 8.2 Hz, J_2 = 5.9 Hz, 1H; 4.14, t, J = 6.9 Hz, 2H. MS (ES +ve) *m/z* 202.0 (100%) $[M+H]^+$.

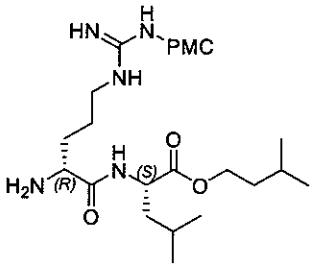
12(iii)



This compound was prepared *via* Protocol 1 using **12(ii)** (90 mg, 0.481 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (160 mg, 0.241 mmol) to yield the desired product **12(iii)** as an off white solid (198 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84, m, 12H; 1.21, s, 3H; 1.22, s, 3H; 1.47, m, 2H; 1.60, m, 9H; 1.90, m, 1H; 2.05, s, 3H; 2.51, m, 2H; 2.55, s, 3H; 2.58, s, 3H; 3.24, m, 2H; 4.05, m, 3H; 4.24, m, 3H; 4.47, m, 1H; 6.26, br s, NH; 6.35, d, J = 8.0 Hz, NH; 6.40, br s, NH; 7.18, t, J = 7.4 Hz, 2H; 7.32, t, J = 7.5 Hz, 2H; 7.37, d, J = 7.7 Hz, NH; 7.51, d, J =7.4 Hz, 2H; 7.69, d, J = 7.5 Hz, 2H. MS (ES +ve) *m/z* 846.0 (100%) $[M+H]^+$.

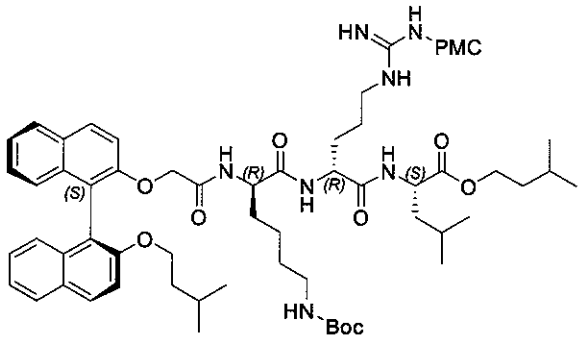
12(iv)



This compound was prepared *via* Protocol 2, using **12(iii)** (150 mg, 0.177mmol) to yield the desired product **12(iv)** as a colourless oil (101 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92, m, 12H; 1.30, s, 6H; 1.52, m, 3H; 1.62, m, 4H/NH_2; 1.80, m, 5H; 2.10, s, 3H; 2.55, s, 3H; 2.57, s, 3H; 2.62, t, J = 6.7 Hz, 2H; 3.19, m, 2H; 3.40, m, 1H; 4.11, m, 2H; 4.46, m, 1H; 6.31, br s, NH; 6.38, br s, NH; 7.76, d, J = 8.0 Hz, NH. MS (ES +ve) *m/z* 624.0 (100%) $[M+H]^+$.

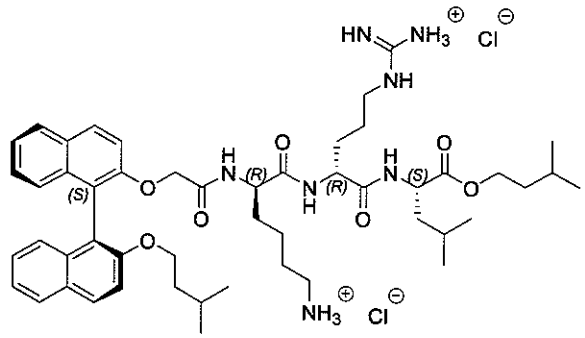
12(v)



This compound was prepared *via* Protocol 1, using **6(vi)** (75 mg, 0.117 mmol) and **12(iv)** (86 mg, 0.138 mmol) to yield **12(v)** as a light brown solid (122 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47, d, J = 6.6 Hz, 3H; 0.52, d, J = 6.6 Hz, 3H; 0.76, m, 2H; 0.91, m, 12H; 1.18, m, 6H; 1.27, s, 6H; 1.41, s, 9H; 1.53, m, 5H; 1.63, m, 5H; 1.77, m, 3H; 2.09, s, 3H; 2.55, s, 3H; 2.57, s, 3H; 2.60, m, 2H; 2.92, m, 2H; 3.19, m, 2H; 3.89, m, 1H; 4.11, m, 4H; 4.43, m, 4H; 4.84, m, NH; 6.19, d, J = 7.7 Hz, NH; 6.28, br s, NH; 7.26, m, 7H; 7.46, d, J = 9.2 Hz, 1H; 7.84, d, J = 8.9 Hz, 1H; 7.86, d, J = 8.8 Hz, 1H; 7.93, d, J = 9.3 Hz, 1H; 7.96, d, J = 9.5 Hz, 1H. MS (ES +ve) *m/z* 1247.9 (40%) $[M+H]^+$; 574.7 (100) $[M+2H\text{-}BOC]^{2+}$.

Compound 12

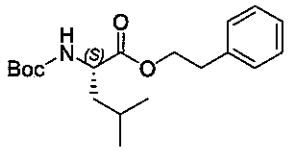


This compound was prepared *via* Protocol 3, using **12(v)** (120 mg, 0.096 mmol) to yield **12** as an off white solid (84 mg, 92%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.52, d, *J* = 6.6 Hz, 3H; 0.57, d, *J* = 6.6 Hz, 3H; 0.91, m, 14H; 1.14, m, 2H; 1.26, m, 2H; 1.54, m, 5H; 1.65, m, 7H; 1.84, m, 1H; 2.82, m, 2H; 3.18, m, 2H; 3.95, m, 1H; 4.14, m, 4H; 4.36, m, 2H; 4.46, ABq, *J* = 14.6 Hz, 1H; 4.58, ABq, *J* = 14.6 Hz, 1H; 7.07, dist t, 2H; 7.21, dist t, 2H; 7.34, dist t, 2H; 7.47, d, *J* = 9.3 Hz, 1H; 7.56, d, *J* = 9.3 Hz, 1H; 7.91, dist t, 2H; 8.03, dist t, 2H. MS (ES +ve) *m/z* 882.0 (5%) $[M+H]^+$; 441.6 (100) $[M+2H]^{2+}$.

Synthesis of Compound 13

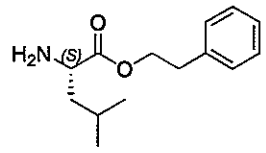
13(i)



To BOC-(*L*)-Leu-OH (200 mg, 0.865 mmol) and potassium carbonate (400 mg, 2.89 mmol) in acetone (40 ml) was added (2-bromoethyl)benzene (0.14 ml, 1 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 5% ethyl acetate/hexane to first remove (2-bromoethyl)benzene, then with DCM to yield the product **13(i)** as a colourless oil (235 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86, d, *J* = 6.6 Hz, 3H; 0.88, d, *J* = 6.6 Hz, 3H; 1.42, s, 9H; 1.47, m, 2H; 1.54, m, 1H; 2.92, t, *J* = 7.0 Hz, 2H; 4.31, m, 3H; 5.04, d, *J* = 8.3 Hz, NH; 7.19, m, 3H; 7.26, m, 2H. MS (ES +ve) *m/z* 374.2 (80%) $[M+K]^+$; 358.3 (100) $[M+Na]^+$; 336.3 (10) $[M+H]^+$; 236.2 (50) $[M+H\text{-}BOC]^+$.

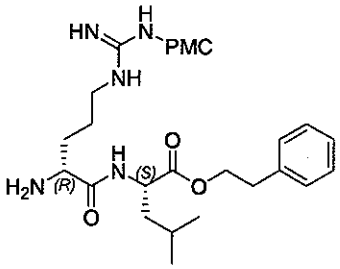
13(ii)



To **13(i)** (230 mg, 0.686 mmol) dissolved in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 2 hrs. Ethyl acetate (15 ml) was then added and the solution washed with sat. sodium bicarbonate solution until the washing were basic. The organic layer was then dried ($MgSO_4$) and evaporated to dryness to yield the desired product **13(ii)** as a yellow oil (140 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87, d, J = 5.7 Hz, 3H; 0.89, d, J = 5.7 Hz, 3H; 1.35, m, 1H; 1.48, m, 1H; 1.69, m, 1H; 1.89, m, NH_2; 2.94, t, J = 7.0 Hz, 2H; 3.42, dd, J_1 = 8.3 Hz, J_2 = 5.9 Hz, 1H; 4.33, m, 2H; 7.21, m, 3H; 7.28, m, 2H. MS (ES +ve) *m/z* 236.2 (100%) $[M+H]^+$.

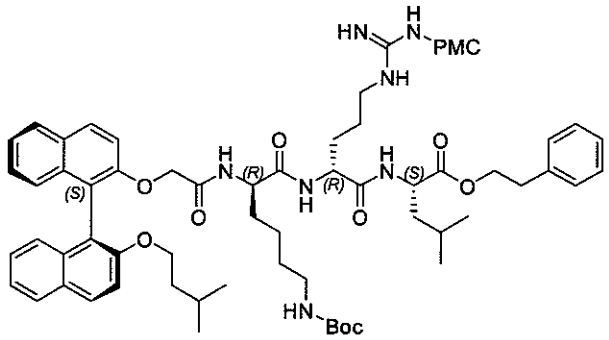
13(iv)



This compound was prepared in two steps. The first *via* Protocol 1, using using **13(ii)** (92 mg, 0.391 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (265 mg, 0.400 mmol) to yield the Fmoc protected precursor **13(iii)** as a colourless oil (308 mg, 90% MS (ES +ve) *m/z* 880.2 (100%) $[M+H]^+$). The desired product was then prepared *via* Protocol 2, using **13(iii)** (280 mg, 0.318 mmol) to afford the product **13(iv)** as a colourless oil (123 mg, 59%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85, d, J = 5.7 Hz, 3H; 0.86, d, J = 5.9 Hz, 3H; 1.29, s, 6H; 1.53, m, 4H/NH_2; 1.78, m, 5H; 2.09, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.60, m, 2H; 2.91, t, J = 7.0 Hz, 2H; 3.17, m, 2H; 3.37, m, 1H; 4.29, m, 2H; 4.43, m, 1H; 6.33, br s, NH; 6.38, br s, NH; 7.22, m, 5H; 7.73, d, J = 8.0 Hz, NH. MS (ES +ve) *m/z* 658.0 (100%) $[M+H]^+$; 554.1 (60) $[M+H\text{-}EtPh]^+$.

13(v)

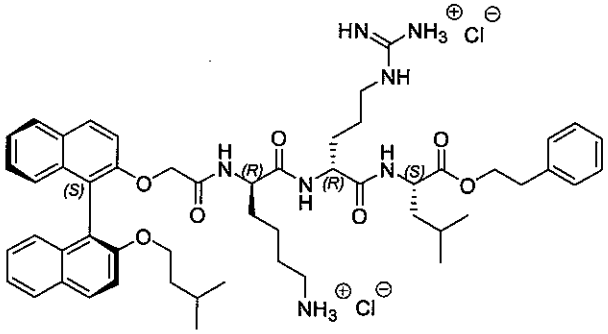


This compound was prepared *via* Protocol 1, using **6(vi)** (107 mg, 0.166 mmol) and **13(iv)** (107 mg, 0.167 mmol) to yield **13(v)** as a white solid (118 mg, 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.46, d, J = 6.3 Hz, 3H; 0.51, d, J = 6.3 Hz, 3H; 0.77, m, 2H; 0.89, m, 6H; 1.19, m, 3H; 1.27, s, 6H; 1.41, s, 9H; 1.54, m, 5H; 1.76, m, 4H; 2.09, s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.61, m, 2H; 2.91, m, 2H;

2.93, t, J = 7.1 Hz; 3.15, m, 2H; 3.87, m, 1H; 4.04, m, 2H; 4.42, m, 4H; 4.82, m, NH; 6.18, d, J = 7.1 Hz, NH; 6.28, br s, NH; 7.21, m, 12H; 7.43, d, J = 9.1 Hz, 1H; 7.83, d, J = 7.8 Hz, 1H; 7.85, d, J = 7.8 Hz, 1H; 7.92, d, J = 9.0 Hz, 1H; 7.93, d, J = 8.9 Hz, 1H. MS (ES +ve) *m/z* 1282.0 (80%) $[M+H]^+$; 591.7 (100) $[M+2H\text{-}BOC]^{2+}$.

Compound 13

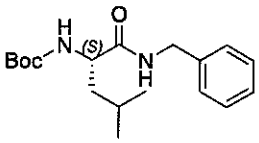


This compound was prepared *via* Protocol 3, using **13(v)** (110 mg, 0.086 mmol) to yield **13** as a white solid (80 mg, 96%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.50, d, J = 6.2 Hz, 3H; 0.55, d, J = 6.2 Hz, 3H; 0.85, d, J = 6.1 Hz, 3H; 0.89, d, J = 6.1 Hz, 3H; 0.96, m, 2H; 1.16, m, 5H; 1.57, m, 10H; 1.81, m, 1H; 2.80, m, 2H; 2.93, t, J = 6.7 Hz, 2H; 3.16, m, 2H; 3.94, m, 1H; 4.14, m, 2H; 4.34, m, 2H; 5.45, ABq, J = 14.8 Hz, 1H; 5.56, ABq, J = 14.8 Hz, 1H; 7.04, d, J = 4.3 Hz, 1H; 7.07, d, J = 4.3 Hz, 1H; 7.22, m, 9H; 7.45, d, J = 9.0 Hz, 1H; 7.53, d, J = 9.0 Hz, 1H; 7.88, d, J = 7.6 Hz, 1H; 7.91, d, J = 7.3 Hz, 1H; 7.99, d, J = 9.0 Hz, 1H; 8.00, d, J = 9.0 Hz, 1H. MS (ES +ve) *m/z* 915.9 (5%) $[M+H]^+$; 458.9 (100) $[M+2H]^{2+}$.

Synthesis of Compound 14

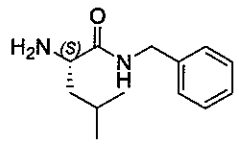
14(i)



This compound was prepared *via* Protocol 1, using BOC-(*L*)-leu-OH (200 mg, 0.865 mmol) and benzylamine (0.1 ml, 0.916 mmol) to yield the desired product **14(i)** as an off white solid (239 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86, d, J = 6.8 Hz, 3H; 0.88, d, J = 6.8 Hz, 3H; 1.34, s, 9H; 1.53, m, 2H; 1.64, m, 1H; 4.30, m, 3H; 5.57, d, J = 7.7 Hz, NH; 7.17, m, 5H, 7.50, m, NH. MS (ES +ve) *m/z* 359.2 (100%) $[M+K]^+$; 343.3 (20) $[M+Na]^+$; 321.3 (20) $[M+H]^+$; 222.3 (40) $[M+H\text{-}BOC]^+$.

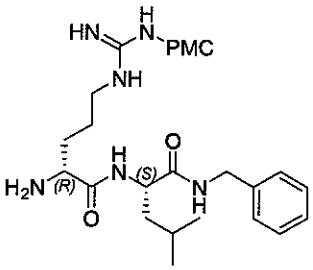
14(ii)



To **14(i)** (230 mg, 0.719 mmol) dissolved in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 2 hrs. Ethyl acetate (15 ml) was then added and the solution washed with sat. sodium bicarbonate solution until the washing were basic. The organic layer was then dried ($MgSO_4$) and evaporated to dryness to yield the desired product **14(ii)** as a colourless oil (65 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93, d, J = 5.6 Hz, 3H; 0.96, d, J = 5.6 Hz, 3H; 1.37, m, 1H; 1.68, br s, NH_2; 1.73, m, 2H; 3.43, m, 1H; 4.42, d, J = 5.8 Hz, 2H; 7.27, m, 2H; 7.32, m, 3H; 7.69, m, NH. MS (ES +ve) *m/z* 221.2 (100%) $[M+H]^+$.

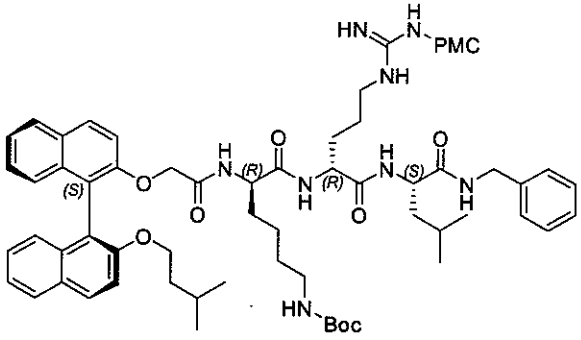
14(iv)



This compound was prepared in two steps. The first step *via* Protocol 1, using **14(ii)** (60 mg, 0.272 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (176 mg, 0.272 mmol) to yield the Fmoc protected precursor **14(iii)** as a white foamy solid (156 mg, 67%. MS (ES +ve) *m/z* 851.2 (100%) $[M+H]^+$). The desired product was then prepared *via* Protocol 2, using **14(iii)** (156 mg, 0.183 mmol) to afford the product **14(iv)** as a white solid (85 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83, m, 6H; 1.44, s, 9H; 1.62, m, 6H/NH_2; 1.80, m, 1H; 2.05, s, 3H; 2.43, s, 3H; 2.51, s, 3H; 2.90, s, 2H; 3.15, m, 2H; 3.62, m, 1H; 4.25, m, 2H; 4.45, m, 1H; 6.54, br s, NH; 7.14, m, 5H; 7.72, dd, J_1= 7.8 Hz, J_2 = 16.0 Hz, NH; 8.25, m, NH. MS (ES +ve) *m/z* 629.0 (100%) $[M+H]^+$.

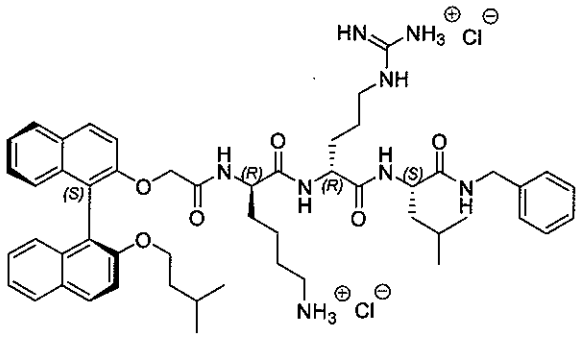
14(v)



This compound was prepared *via* Protocol 1, using **6(vi)** (82 mg, 0.127mmol) and **14(iv)**(80 mg, 0.127 mmol) to yield **14(v)** as a white solid (63 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.44, d, J = 6.5 Hz, 3H; 0.49, d, J = 6.5 Hz, 3H; 0.79, d, J = 6.3 Hz, 3H; 0.83, d, J = 6.3 Hz, 3H; 0.85, m, 2H; 1.11, m, 4H; 1.26, m, 4H; 1.40, s, 6H; 1.43, s, 9H; 1.69, m, 5H; 1.95, m, 1H; 2.04, s, 3H; 2.46, s, 3H; 2.52, s, 3H; 2.90, s, 2H; 2.93, m, 2H; 3.19, m, 2H; 3.80, m, 1H; 4.13, m, 2H; 4.30, m, 5H; 4.49, m, 1H; 5.05, m, NH; 5.04, ABq, J = 12.2 Hz, 1H; 5.11, ABq, J = 12.2 Hz, 1H; 6.19, d, J = 6.8 Hz, NH; 6.15, br s, NH; 6.46, br s, NH; 7.10, m, 6H; 7.31, m, 5H; 7.71, m, 3H; 7.84, dist d, 1H; 7.90, d, J = 9.2 Hz, 2H. MS (ES +ve) *m/z* 1252.9 (80%) $[M+H]^+$; 577.4 (100) $[M+2H\text{-}BOC]^{2+}$.

Compound 14

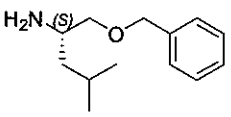


This compound was prepared *via* Protocol 3, using **14(v)** (63mg, 0.050 mmol) to yield **14** as a white solid (40 mg, 82%).

^{1}H NMR (500 MHz, CD_3OD) δ 0.48, d, J = 6.5 Hz, 3H; 0.53, d, J = 6.5 Hz, 3H; 0.90, m, 8H; 1.17, m, 5H; 1.36, m, 1H; 1.53, m, 3H; 1.68, m, 6H; 1.81, m, 1H; 2.77, m, 2H; 3.19, m, 2H; 3.87, m, 1H; 4.00, m, 1H; 4.10, m, 1H; 4.21, m, 1H; 4.37, m, 3H; 4.44, ABq, J = 15.0 Hz, 1H; 4.52, ABq, J = 15.0 Hz, 1H; 7.06, dist t, 2H; 7.25, m, 7H; 7.34, m, 2H; 7.46, d, J = 9.5 Hz, 2H; 7.90, d, J = 9.0 Hz, 2H; 7.99, d, J = 8.8 Hz, 1H; 8.02, d, J = 8.7 Hz, 1H. MS (ES +ve) *m/z* 901.0 (5%) $[M+H]^+$; 451.1 (100) $[M+2H]^{2+}$.

Synthesis of Compound 15

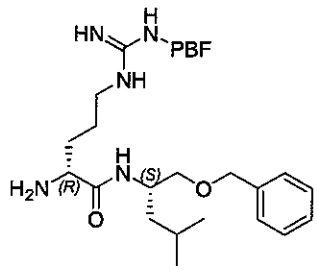
15(i)



To a stirring suspension of NaH (60% dispersion, 73 mg, 1.86 mmol) in dry THF (10 ml) was added dropwise (*L*)-leucinol (0.2 ml, 1.55 mmol). The solution was then heated at reflux overnight before being cooled and water (1 ml) added. After evaporation to near dryness the residue was taken up in DCM (20 ml) and extracted with 1M HCl (3 x 20 ml). The combined acid extracts were then basified with 2M KOH and back extracted with DCM (5 x 15 ml). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **15(i)** as a white solid (172 mg, 54%) of sufficient purity to use in the next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87, d, J = 5.4 Hz, 3H; 0.89, d, J = 5.4 Hz, 3H; 1.23, m, 1H; 1.41, m, 1H; 1.56, m, 1H; 2.42, br s, NH_2; 2.74, m, 1H; 3.31, dABq, J_1 = 10.7 Hz, J_2 = 6.2 Hz, 1H; 3.55, dABq, J_1 = 10.7 Hz, J_2 = 3.9 Hz, 1H; 3.76, ABq, J = 12.9, Hz, 1H; 3.82, ABq, J = 12.9, Hz, 1H; 7.32, m, 5H. MS (ES +ve) *m/z* 208 (100%) $[M+H]^+$,

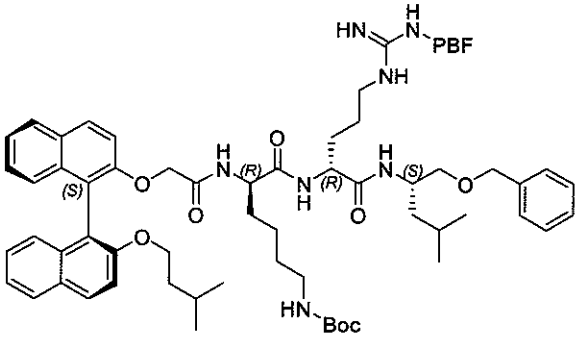
15(iii)



This compound was prepared in two steps. The initial coupling reaction *via* Protocol 1, using **15(i)** (140 mg, 0.675 mmol) and Fmoc-(*D*)-arg(Pbf)-OH (438 mg, 0.675 mmol) to yield the Fmoc protected precursor **15(ii)** as an off white foamy solid (MS (ES +ve) *m/z* 837.9 (25% $[M+H]^+$; 419.8 (100) $[M+2H]^{2+}$). This compound was then deprotected *via* Protocol 2, **15(ii)** (200 mg, 0.238 mmol) to afford a colourless oil **15(iii)** (27mg, 18% two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, d, J = 6.5 Hz, 3H; 0.89, d, J = 6.5 Hz, 3H; 1.25, m, 2H; 1.44, s, 6H; 1.56, m, 3H; 1.70, m, 2H; 2.02, br s, NH_2; 2.08, s, 3H; 2.50, s, 3H; 2.57, s, 3H; 2.93, s, 2H; 3.15, m, 2H; 3.40, m, 2H; 3.63, m, 1H; 4.13, m, 1H; 4.45, ABq, J = 12.1 Hz, 1H; 4.50, ABq, J = 12.1 Hz, 1H; 6.34, br s, NH; 7.29, m, 5H; 7.39, d, J = 9.0 Hz, NH. MS (ES +ve) *m/z* 616.3 (100%) $[M+H]^+$.

15(iv)

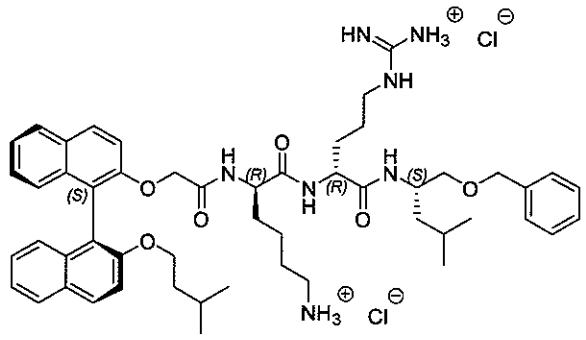


This compound was prepared *via* Protocol 1, using **6(vi)** (58 mg, 0.090 mmol) and **15(iii)** (53 mg, 0.086 mmol) to yield **15(iv)** as a white solid (53 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.49, d, J = 6.5 Hz, 3H; 0.53, d, J = 6.6 Hz, 3H; 0.79, m, 2H; 0.88, d, J = 6.6 Hz, 3H; 0.90, d, J = 6.7 Hz, 3H; 0.95, m, 2H; 1.21, m, 6H; 1.42, s, 6H; 1.44, s, 9H; 1.56, m, 5H; 1.83, m, 1H; 2.07, s, 3H; 2.49, s, 3H; 2.56, s, 3H; 2.91, s, 2H; 2.93, m, 2H; 3.17, m, 2H; 3.41, dABq, J_1 = 9.6 Hz, J_2 = 5.2 Hz, 1H; 3.45, dABq, J_1 = 9.6 Hz, J_2 = 4.6 Hz, 1H; 3.89, m, 1H; 4.01, m, 2H; 4.17, m, 1H; 4.46, m, 5H; 4.76, m, NH; 6.13, d, J = 6.8 Hz, NH; 6.17, br s, NH; 6.66, d, J = 8.4 Hz, NH; 7.14, m, 2H; 7.24, m, 4H; 7.30, m, 6H; 7.42, d, J = 9.0 Hz, 1H;

7.84, d, J = 8.4 Hz, 1H; 7.86, d, J = 8.4 Hz, 1H; 7.92, d, J = 8.8 Hz, 1H; 7.93, d, J = 8.8 Hz, 1H. MS (ES +ve) *m/z* 1240 (100%) $[M+H]^+$; 832.4 (100) $[M+H\text{-BOC-pbf-}ibu]^+$.

Compound 15

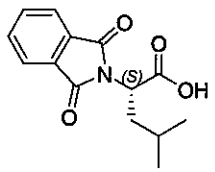


This compound was prepared *via* Protocol 3, using **15(iv)** (50 mg, 0.040 mmol) to yield **15** as a white solid (32 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.51, d, J = 6.6 Hz, 3H; 0.56, d, J = 6.6 Hz, 3H; 0.90, d, J = 6.7 Hz, 3H; 0.92, m, 2H; 0.93, d, J = 6.7 Hz, 3H; 1.24, m, 4H; 1.64, m, 9H; 1.84, m, 1H; 2.75, m, 2H; 3.17, m, 2H; 3.43, d, J = 7.4 Hz, 2H; 3.92, m, 1H; 4.12, m, 2H; 4.29, m, 1H; 4.49, m, 4H; 7.06, dist t, 2H; 7.21, m, 2H; 7.34, m, 7H; 7.47, d, J = 9.1 Hz, 1H; 7.54, d, J = 9.1 Hz, 1H; 7.91, d, J = 8.8 Hz, 1H; 7.92, d, J = 8.8 Hz, 1H; 8.02, d, J = 9.3 Hz, 2H. MS (ES +ve) *m/z* 888.3 (10%) $[M+H]^+$; 444.9 (100) $[M+2H]^{2+}$.

Synthesis of Compound 16 & Compound 17

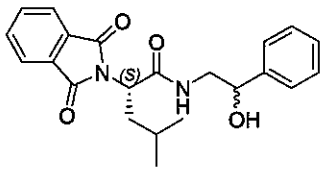
16(i)



To a suspension of L-leucine (1.17 g, 8.92 mmol) and phthalic anhydride (1.26 g, 8.51 mmol) in toluene (25 ml) was added triethylamine (0.11 ml, 0.79 mmol). The flask was fitted with a Dean-Stark water separator and a condenser and heated at vigorous reflux for 3 hours. The cooled solution was concentrated *in vacuo*, suspended in 2.5% HCl (50 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic layers were extracted with sat. aqueous sodium bicarbonate (3 x 25 ml), acidified with 10% HCl and back-extracted with ethyl acetate (3 x 25 ml). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the product **16(i)** as a white solid (2.12 g, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87, dd, J = 10.7, 6.6 Hz, 6H; 1.44, m, 1H; 1.89, m, 1H; 2.30, m, 1H; 4.93, dd. J = 11.3, 4.4 Hz, 1H; 7.67, dd, J = 5.3, 2.8 Hz, 2H; 7.79, dd, J = 5.3, 2.8 Hz, 2H; 11.23, br s, 1H. MS (ES -ve) *m/z* 260 (100%) $[M-H]^+$; 216 (46) $[M\text{-COOH}]^+$.

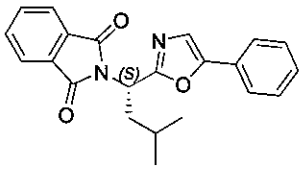
16(ii)



To a solution of **16(i)** (0.70, 2.69 mmol) in THF (15 ml) under a N_2 atmosphere at 0 °C was added dicyclohexylcarboddimide (0.76 g, 3.69 mmol). The resultant solution was stirred at 0 °C for 1 hour. To this was added 2-amino-1-phenylethanol (0.45 g, 3.28 mmol) and the solution was stirred at 0 °C for 30 minutes then at room temperature (~15 °C) for a further 16 hours. The reaction mixture was filtered to remove the byproduct DCU, then concentrated *in vacuo*. The crude residue was subjected to flash silica column chromatography and elution with 50% ethyl acetate:petroleum spirit gave the title compound **16(ii)** as a pale yellow oil (783 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90, d, J = 6.8 Hz, 6H; 1.43, m, 1H; 1.83, m, 1H; 2.30, m, 1H; 3.28, m, 1H; 3.66, m, 1H; 4.82, m, 1H; 4.87, m, 1H; 6.73, br s, 1H; 7.26, m, 5H; 7.73, m, 2H; 7.83, m, 2H. MS (ES +ve) *m/z* 381.0 (100%) $[M+H]^+$; 363.0 (39); 225 (45).

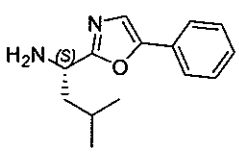
16(iii)



To a solution of chromium trioxide (0.45 g, 4.5 mmol) in water (10 ml) was slowly added concentrated H_2SO_4 (10 ml, 95%). The cooled solution was then added portionwise to a solution of **16(ii)** (0.72 g, 1.9 mmol) in acetone (7.5 ml) (CAUTION: exothermic reaction). The resulting solution was stirred at room temperature for 16 hours. The reaction mixture was rendered basic by addition of sat. aqueous sodium carbonate and the alkaline solution was extracted with DCM (3 x 25 ml), brine was added to facilitate complete separation. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was subjected to flash silica column chromatography, eluting with 20% ethyl acetate:petroleum spirit to yield the title compound **16(iii)** as a pale yellow oil (231 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02, dd, J = 18.0, 6.6 Hz, 6H; 1.66, m, 1H; 2.25, m, 1H; 2.60, m, 1H; 5.64, dd, J = 10.9, 5.0 Hz, 1H, 7.27, m, 1H; 7.28, t, J = 7.8 Hz, 1H; 7.36, t, J = 7.9 Hz, 2H; 7.56, d, J = 7.4 Hz, 2H; 7.74, dd, J = 5.3, 2.9 Hz, 2H; 7.87, dd, J = 5.3, 2.9 Hz, 2H. MS (ES +ve) *m/z* 361.0 (100%) $[M+H]^+$.

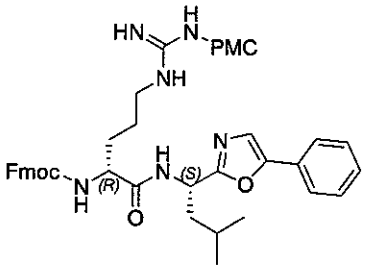
16(iv)



To a solution of **16(iii)** (0.19 g, 0.53 mmol) in ethanol (10 ml) was added ethylenediamine (0.14 ml, 2.25 mmol) and the resulting solution was heated at reflux for 5 hours. The cooled reaction mixture was diluted with ethyl acetate (50 ml) then extracted with 1M HCl (3 x 25 ml). The combined aqueous extracts were rendered alkaline with addition of 1 M NaOH then extracted with DCM (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the product **16(iv)** as pale yellow crystals (100 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96, dd, J = 6.2, 9.0 Hz, 6H; 1.73, m, 5H; 4.13, t, J = 7.2 Hz, 1H; 7.24, s, 1H; 7.31, t, J = 7.7, Hz, 1H; 7.42, t, J = 7.8 Hz, 2H; 7.62, d, J = 7.8 Hz, 2H. MS (ES +ve) *m/z* 231 (100%) $[M+H]^+$.

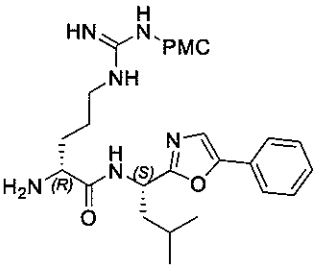
16(v)



This compound was prepared *via* Protocol 1, using **16(iv)** (0.10 g, 0.43 mmol) and (*R*)-Fmoc-arginine(PMC)-OH (0.28 g, 0.42 mmol) in anhydrous acetonitrile (5 ml) with EDCI (0.11 g, 0.57 mmol) and HObt (0.07 g, 0.52 mmol). Purification with 2% methanol:DCM gave the product **16(v)** as a thick off-white oil (292 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88, m, 6H; 1.23, d, J = 3.2 Hz, 6H; 1.66, m, 6H; 1.77, m, 2H; 2.03, m, 4H; 2.53, m, 8H; 3.23, m, 2H; 4.02, br s, 1H; 4.23, m, 4H; 5.24, m, 2H; 6.37, m, 4H; 7.10, s, 1H; 7.26, m, 6H; 7.69, m, 3H; 7.67, m, 2H. MS (ES +ve) *m/z* 874.9 (48%) $[M+H]^+$; 438 (74); 143 (100).

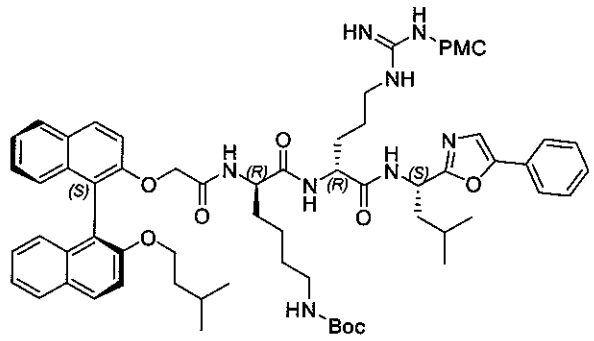
16(vi)



This compound was prepared *via* Protocol 2, using **16(v)** (0.26 g, 0.30 mmol) and piperidine (0.1 ml, 1.01 mmol) in anhydrous acetonitrile (8 ml). Purification with 2-10% methanol:DCM gave the product **16(vi)** as a pale yellow solid (189 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ ; 0.94, dd, J = 12.3, 6.6 Hz, 6H; 1.28, s, 6H; 1.61, m, 4H; 1.79, m, 5H; 2.07, s, 3H; 2.13, br s, 2H; 2.52, s, 3H; 2.54, s, 3H; 2.58, m, 2H; 3.17, m, 2H; 3.48, m, 1H; 5.23, ABquart, J = 6.6 Hz, 1H; 6.42, br s, 3H; 7.18, s, 1H; 7.27, m, 1H; 7.35, t, J = 7.6 Hz, 2H; 7.55, d, J = 7.3 Hz, 2H; 8.08, br d, 1H. MS (ES +ve) *m/z*; 653 (100%) $[M+H]^+$; 327 (41) $[M+H]^{2+}$.

16(vii)



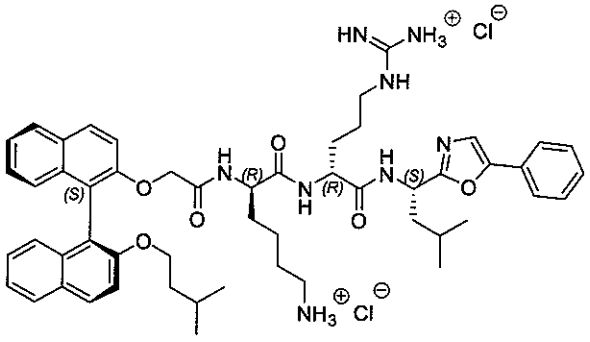
This compound was prepared *via* Protocol 1, **16(vi)** (0.19 g, 0.29 mmol) and **6(vi)** (0.19 0.29 mmol) in anhydrous acetonitrile (7 ml) with EDCI (0.08 g, 0.42 mmol) and HObt (0.06 g, 0.41 mmol). Purification with 2% methanol:DCM gave product **16(vii)** as an off-white solid (343 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48, dd, J = 16.1, 6.4 Hz, 6H; 0.88, m, 2H; 0.95, m, 7H; 1.17, m, 6H; 1.27, m, 7H; 1.41, s, 9H; 1.74, m, 8H; 2.06, s, 3H; 2.52, m, 8H; 2.81, m, 3H; 3.18, m, 1H; 3.85, m, 1H; 4.03, m, 2H; 4.41, m, 3H; 4.79, m, 1H; 5.25, m, 1H; 6.15, m, 1H; 6.29, br s, 2H; 7.32, m, 17H; 7.90, m, 4H. MS (ES +ve) *m/z* 1278 (47%) $[M+H]^+$; 1277 (56) $[M]^+$; 639 (100) $[M+H]^+$.

Compound 16 & Compound 17

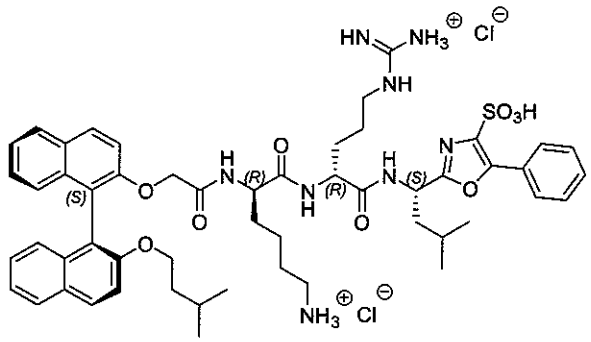
These compounds were prepared *via* Protocol 3, **16(vii)** (0.34 g, 0.27 mmol) and TFA (2 ml, 27.0 mmol) in DCM (2 ml). Precipiation from methanol using ether (3 times) gave a mixture of two compounds that were separated by preparative reverse-phase HPLC to give **16** as a white solid (73 mg, 25%) and **17** as an off-white solid (62 mg, 21%).

Compound 16



^{1}H NMR (300 MHz, CD_3OD) δ 0.50, dd, J = 16.9, 6.6 Hz, 6H; 0.98, m, 9H; 1.21, m, 5H; 1.38, m, 4H; 1.69, m, 4H; 1.88, m, 2H; 2.73, m, 2H; 3.19, m, 1H; 3.96, m, 1H; 4.10, m, 2H; 4.45, ABquart, J = 14.6 Hz, 2H; 5.22, m, 1H; 7.05, t, J = 6.6 Hz, 2H; 7.21, m, 2H; 7.43, m, 8H; 7.71, m, 2H; 8.00, m, 4H. MS (ES +ve) *m/z* 911 (16%) $[M+H]^+$; 456 (100) $[M+H]^{2+}$.

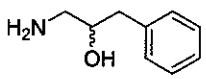
Compound 17



^{1}H NMR (300 MHz, CD_3OD) δ 0.50, dd, J = 12.4, 12.4 Hz, 6H; 0.96, m, 6H; 1.24, m, 20H; 2.10, m, 2H; 3.15, m, 1H; 3.98, m, 1H; 4.15, m, 2H; 4.46, m, 2H; 5.06, m, 1H; 7.09, m, 3H; 7.40, m, 4H; 7.66, m, 4H; 7.92, m, 4H; 8.33, m, 2H. MS (ES +ve) *m/z* 992 (38%) $[M+H]^+$; 496 (100) $[M+H]^{2+}$.

Synthesis of Compound 18

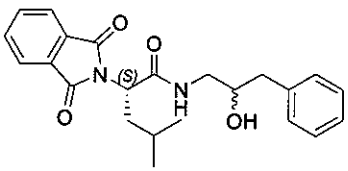
18(i)



A suspension of (2,3-epoxypropyl)benzene (0.5 ml, 3.80 mmol) in concentrated ammonia solution (10 ml, 28%) was placed in a Teflon tube with a 100 bar pressure cap, then heated in a microwave reactor at 110 °C for 30 minutes. After cooling the mixture was extracted with DCM (3 x 15 ml), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the product **18(i)** as colourless prisms (490 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01, br s, 3H; 2.59, m, 1H, 2.73, d, J = 6.4 Hz, 2H; 2.78, m, 1H; 3.72, m, 1H; 7.22, m, 5H. MS (ES +ve) *m/z* 152 (100%) $[M+H]^+$; 134 (21); 117 (12).

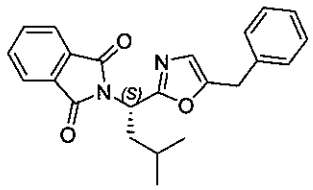
18(ii)



This compound was prepared *via* Protocol 1, using **18(i)** (0.84, 3.23 mmol) and **16(i)** in acetonitrile (10 ml), with EDCI (0.75 g, 3.94 mmol) and HObt (0.53 g, 3.97 mmol). Purification with 50% ethyl acetate:petroleum spirit gave the product **18(ii)** as a colourless oil (1.02 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, dd, J = 6.4, 2.1 Hz, 6H; 1.43, m, 1H; 1.81, m, 1H; 2.30, m, 1H; 2.67, m, 2H; 3.01, br s, 1H; 3.07, m, 1H; 3.44, m, 1H; 3.86, m, 1H; 4.84, dd, J = 11.4, 4.7 Hz, 1H; ; 6.74, br s, 1H; 7.20, m, 5H; 7.69, m, 2H; 7.80, m, 2H. MS (ES +ve) *m/z* 433 (20%) $[M+K]^+$; 417 (51) $[M+Na]^+$; 395 (100) $[M+H]^+$.

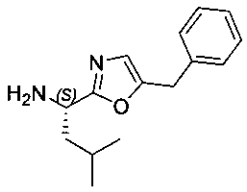
18(iii)



To a solution of chromium trioxide (0.51 g, 5.1 mmol) in water (10 ml) was slowly added concentrated H_2SO_4 (10 ml, 95%). The cooled solution was then added portionwise to a solution of **18(ii)** (0.82 g, 2.1 mmol) in acetone (7.5 ml) (CAUTION: exothermic reaction). The resulting solution was stirred at room temperature for 16 hours. The reaction mixture was rendered basic by addition of sat. aqueous sodium carbonate and the alkaline solution was extracted with DCM (3 x 25 ml), brine was added to facilitate complete separation. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was subjected to flash silica column chromatography, elution with 25% ethyl acetate:petroleum spirit gave the product **18(iii)** as a dark yellow oil (200 mg, 25%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98, dd, J = 9.1, 6.4 Hz, 6H; 1.60, m, 1H; 2.14, m, 1H; 2.51, m, 1H; 3.92, s, 2H; 5.52, dd, J = 5.0, 11.1 Hz, 1H; 6.65, s, 1H; 7.22, m, 5H; 7.72, dd, J = 5.3, 3.2 Hz, 2H; 7.85, dd, J = 5.6, 2.9 Hz, 2H. MS (ES +ve) *m/z* 375 (100%) $[M+H]^+$.

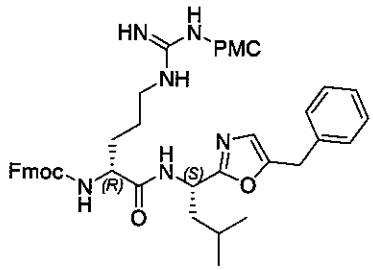
18 (iv)



A solution of **18(iii)** (0.20 g, 0.53 mmol) and ethylenediamine (0.20 ml, mmol) in ethanol (10 ml) was placed in a Teflon tube with a 100 bar pressure cap, then heated in a microwave reactor at 100 °C for 20 minutes The cooled reaction mixture was diluted with ethyl acetate (50 ml) then extracted with 5% HCl (4 x 25 ml). The combined aqueous extracts were rendered alkaline with addition of 1 M NaOH then extracted with DCM (4 x 25 ml). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the product **18(iv)** as a thick colourless oil (111 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89, m, 6H; 1.64, m, 5H; 3.95, s, 2H; 4.0, m, 1H; 6.62, s, 1H; 7.26, m, 5H. MS (ES +ve) *m/z* 245 (83%) $[M+H]^+$; 228 (100) $[M-NH_2]^+$.

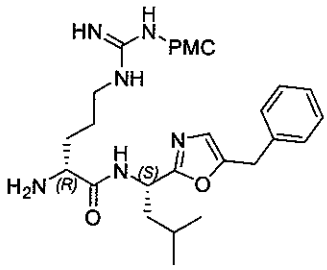
18(v)



This compound was prepared *via* Protocol 1, using **18(iv)** (88 mg, 36 μmol) and (*R*)-Fmoc-arginine(PMC)-OH (240 mg, 37 μmol) in anhydrous acetonitrile (6 ml) with EDCI (95 mg, 50 μmol) and HObt (64 mg, 47 μmol). Purification with 2% methanol:DCM gave the product **18(v)** as a pale yellow oil (302 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82, d, J = 6.4 Hz, 6H; 1.24, s, 6H; 1.72, m, 9H; 2.01, s, 3H; 2.54, m, 8H; 3.23, m, 2H; 3.81, s, 2H; 4.03, m, 1H; 4.24, m, 3H; 5.14, q, J = 7.3 Hz, 1H; 6.47, m, 5H; 7.21, m, 8H; 7.37, m, 2H; 7.49, d, J = 7.3 Hz, 2H; 7.69, J = 7.3 Hz, 2H. MS (ES +ve) *m/z* 888.9, (78%) $[M+H]^+$; 445.3 (100) $[M+H]^{2+}$.

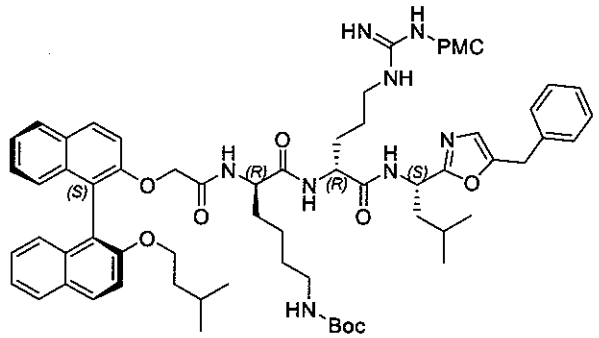
18(vi)



This compound was prepared *via* Protocol 2, using **18(v)** (0.30 g, 0.34 mmol) and piperidine (0.15 ml, 1.51 mmol) in anhydrous acetonitrile (7 ml). Purification with 2-10% methanol:DCM gave the product **18(vi)** as a thick pale yellow oil (222 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, dd, J = 6.4, 5.3 Hz, 6H; 1.28, s, 6H; 1.62, m, 9H; 2.08, s, 3H; 2.19, m, 2H; 2.53, s, 3H; 2.55, s, 3H; 2.57, m, 2H; 3.14, m, 2H; 3.42, m, 1H; 3.90, s, 2H; 5.09, q, J = 7.0 Hz, 1H; 6.38, m, 3H; 6.59, s, 1H; 7.23, m, 5H; 8.00, br d, J = 8.5 Hz, 1H.

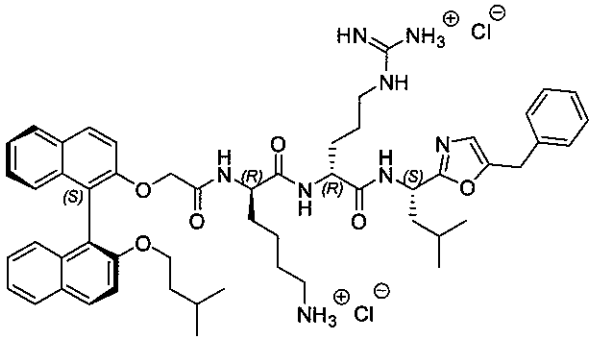
18(vii)



This compound was prepared *via* Protocol 1, using **18(vi)** (0.11 g, 0.16 mmol) and **6(vi)** (0.10 g, 0.16 mmol) in anhydrous acetonitrile (5 ml) with EDCI (0.04 g, 0.21 mmol) and HObt (0.03 g, 0.24 mmol). Purification with 2-5% methanol:DCM gave the product **18(vii)** as an off-white solid (131 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.46, dd, J = 18.25, 6.4 Hz, 6H; 0.78, m, 2H; 0.89, m, 8H; 1.18, m, 14H; 1.42, s, 9H; 1.64, m, 8H; 2.08, s, 3H; 2.58, m, 10H; 2.79, br s, 1H; 2.91, m, 2H; 3.19, m, 1H; 3.92, m, 5H; 4.43, m, 3H; 4.79, m, 1H; 5.10, m, 1H; 6.25, m, 3H; 7.27, m, 12H; 7.91, m, 5H. MS (ES +ve) *m/z* 1291 (28%) $[M+H]^+$; 646 (67) $[M+H]^{2+}$; 83 (100). HRMS (ES +ve) for $C_{73}H_{95}N_8O_{11}S$, calculated 1291.6841, found 1291.6835.

Compound 18

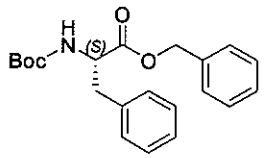


This compound was prepared *via* Protocol 3, using **18(vii)** (132 mg, 0.10 mmol) and TFA:TIPS:H_2O (95:2.5:2.5) (2 ml). Precipiation from methanol using ether (3 times) gave the product **18** as an off-white powder (57 mg, 62%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.52, dd, J = 16.1, 6.4 Hz, 6H; 0.91, m, 8H; 1.19, m, 5H; 1.57, m, 10H; 2.78, m, 2H; 3.17, m, 2H; 3.30, m, 2H; 3.49, q, J = 7.0 Hz, 2H; 4.04, m, 4H; 4.53, ABquart, J = 14.1 Hz, 1H; 5.17, m, 1H; 7.08, m, 2H; 7.25, m, 9H; 7.49, dd, J = 17.3, 9.0 Hz, 2H; 7.89, m, 2H; 8.01, dd, J = 9.1, 2.6 Hz, 2H. MS (ES +ve) *m/z* 925 (4%) $[M+H]^+$; 463.5 (100) $[M+H]^{2+}$.

Synthesis of Compound 19

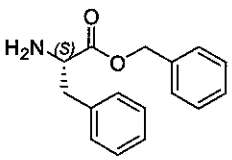
19(i)



To Boc-(*L*)-Phe-OH (265 mg, 1.00 mmol) and potassium carbonate (691 mg, 5.0 mmol) in acetone (30 ml) was added benzyl bromide (0.24 ml, 2.0 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 5% ethyl acetate/hexane to first remove benzyl bromide, then with DCM to yield the product **19(i)** as a white solid (351 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46, s, 9H; 3.12, m, 2H; 4.68, m, 1H; 5.15, ABq, J = 12.3 Hz, 1H; 5.16, m, NH; 5.19, ABq, J = 12.3 Hz, 1H; 7.09, m, 2H; 7.25, m, 3H; 7.32, m, 2H; 7.36, m, 2H. MS (ES +ve) *m/z* 401.1 (40%) $[M+HCOOH]^+$; 378.1 (20) $[M+Na]^+$; 356.1 (25) $[M+H]^+$; 300.0 (60) $[M+H-C_4H_8]^+$; 256.0 (100) $[M+H-BOC]^+$.

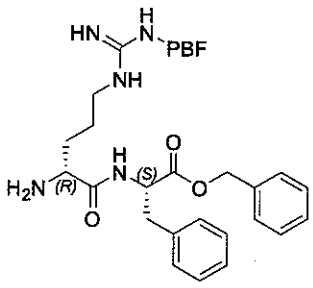
19(ii)



To **19(i)** (346 mg, 0.973 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 3 hrs. The solution was then diluted with DCM (5 ml) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **19(ii)** as a colourless oil (203 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54, s, NH_2; 2.78, dABq, J_1 = 13.5 Hz, J_2 = 5.5 Hz, 1H; 2.96, dABq, J_1 = 13.5 Hz, J_2 = 7.5 Hz, 1H; 3.65, m, 1H; 5.00, ABq, J = 12.3 Hz, 1H; 1.56, m, NH; 5.03, ABq, J = 12.3 Hz, 1H; 7.02, d, J = 6.9 Hz, 2H; 7.15, m, 8H. MS (ES +ve) *m/z* 256.1 (100%) $[M+H]^+$.

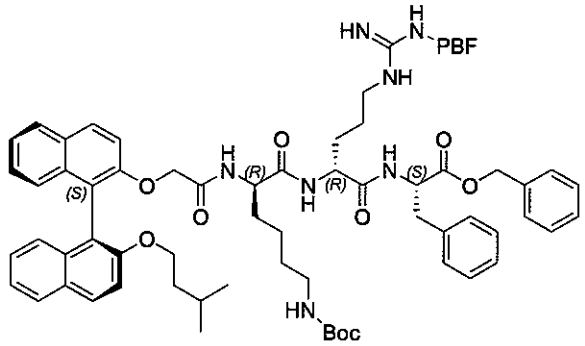
19(iv)



This compound was prepared in two steps. The first step *via* Protocol 1, using **19(ii)** (200 mg, 0.78 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (464 mg, 0.70 mmol) to yield the Fmoc protected precursor **19(iii)** as a white foamy solid (573 mg, MS (ES +ve) *m/z* 899.8 (100%) $[M+H]^+$). This precursor (200 mg) was then deprotected *via* Protocol 2 to afford the desired compound **19(iv)** as a white solid (148 mg, 89% two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32, s, 6H; 1.44, m, 2H/NH_2; 1.66, m, 2H; 1.80, dist t, 2H; 2.12, s, 3H; 2.58, s, 3H; 2.60, s, 3H; 2.61, m, 2H; 3.12, m, 4H; 3.36, m, 1H; 4.81, m, 1H; 5.07, ABq, J = 12.2 Hz, 1H; 5.15, ABq, J = 12.2 Hz, 1H; 6.41, m, NH; 7.09, d, J = 6.6 Hz, 2H; 7.25, m, 5H; 7.32, m, 3H; 7.88, d, J = 6.8 Hz, NH. MS (ES +ve) *m/z* 677.9 (100%) $[M+H]^+$.

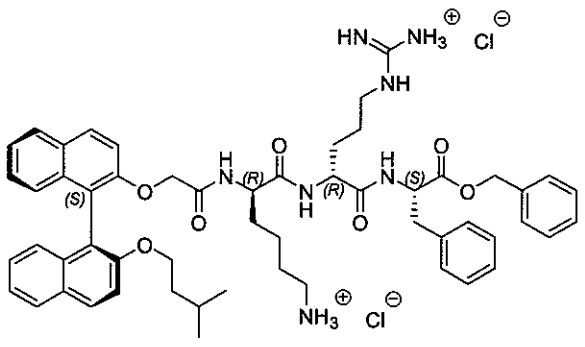
19(v)



This compound was prepared *via* Protocol 1, using **6(vi)** (122 mg, 0.190 mmol) and **19(iv)** (140 mg, 0.207 mmol) to yield **19(v)** as a white solid (197 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48, d, J = 6.2 Hz, 3H; 0.54, d, J = 6.2 Hz, 3H; 0.78, m, 2H; 0.89, m, 2H; 1.20, m, 8H; 1.43, s, 9H; 1.58, m, 1H; 1.78, dist t, 2H; 2.12, s, 3H; 2.60, s, 3H; 2.61, s, 3H; 2.62, m, 2H; 2.90, m, 3H; 3.06, m, 2H; 3.19, m, 1H; 3.88, m, 1H; 4.06, m, 2H; 4.37, m, 1H; 4.39, ABq, J = 6.6 Hz, 1H; 4.52, ABq, J = 6.6 Hz, 1H; 4.86, m, 1H/NH; 5.10, ABq, J = 12.3 Hz, 1H; 5.18, ABq, J = 12.3 Hz, 1H; 6.19, d, J = 7.3 Hz, NH; 6.35, br s, NH; 7.22, m, 8H; 7.33, m, 9H; 7.45, d, J = 9.1 Hz, 1H; 7.85, d, J = 8.2 Hz, 1H; 7.88, d, J = 7.9 Hz, 1H; 7.96, d, J = 8.7 Hz, 2H. MS (ES +ve) *m/z* 1301.8 (100%) $[M+H]^+$.

Compound 19

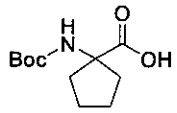


This compound was prepared *via* Protocol 3, using **19(v)** (195 mg, 0.148 mmol) yield **19** as an off white solid (128 mg, 85%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.46, d, J = 6.6 Hz, 3H; 0.52, d, J = 6.6 Hz, 3H; 0.92, m, 2H; 1.08, m, 2H; 1.20, m, 2H; 1.50, m, 5H; 2.76, m, 2H; 3.03, m, 3H; 3.15, m, 1H; 3.88, m, 1H; 4.06, m, 2H; 4.28, m, 1H; 4.46, m, 2H; 4.69, m, 1H; 5.11, s, 2H; 7.13, m, 8H; 7.27, m, 8H; 7.41, d, J = 9.0 Hz, 1H; 7.51, d, J = 9.1 Hz, 1H; 7.85, m, 2H; 7.98, dist t, 2H. MS (ES +ve) *m/z* 936 (10%) $[M+H]^+$; 468.9 (100) $[M+2H]^{2+}$.

Synthesis of Compound 20

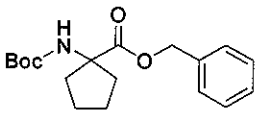
20(i)



To 1-amino-1-cyclopentane carboxylic acid (100 mg, 0.774 mmol) in dry acetonitrile (10 ml) was added tetramethylammonium hydroxide pentahydrate (190 mg, 1.04 mmol) and the mixture stirred at room temperature until the acid had dissolved. Boc anhydride (300 mg, 1.37 mmol) was then added and the resultant solution stirred for four days. The solvent was then removed and the resultant residue partitioned between water and ether. The aqueous layer was washed with an additional portion of ether and then acidified with solid citric acid to pH 3-4. The aqueous layer was then back-extracted with ethyl acetate (3 x 15 ml), before being combined, dried ($MgSO_4$), and evaporated to dryness to yield **20(i)** as a pale yellow oil (101 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44, s, 9H; 1.78, m, 4H; 1.96, m, 2H; 2.29, m, 2H; 5.06, br s, NH; 10.19, br s, COOH.

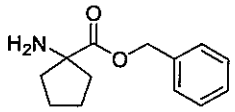
20(ii)



To **20(i)** (120 mg, 0.523 mmol) and potassium carbonate (178 mg, 1.29 mmol) in acetone (25 ml) was added benzyl bromide (0.1 ml, 0.920 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 5% ethyl acetate/hexane to first remove benzyl bromide, then with DCM to yield the product **20(ii)** as a colourless oil that solidified to a white solid upon standing (173 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37, s, 9H; 1.74, m, 4H; 1.91, m, 2H; 1.20, m, 2H; 5.08, br s, NH; 5.13, s, 2H; 7.30, m, 5H. MS (ES +ve) *m/z* 320 (50%) $[M+H]^+$; 220 (100) $[M+H\text{-}BOC]^+$.

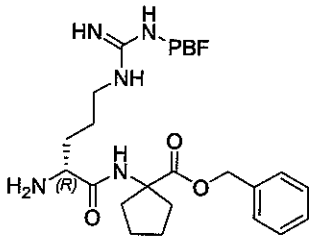
20(iii)



To **20(ii)** (170 mg, 0.532 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 90 mins. The solution was then diluted with ethyl acetate (5 ml) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **20(iii)** as a pale yellow oil (102 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58, m, 2H; 1.67, s, NH_2; 1.73, m, 2H; 1.84, m, 2H; 2.08, m, 2H; 5.12, s, 2H; 7.32, m, 5H. MS (ES +ve) *m/z* 219.9 (100%) $[M+H]^+$.

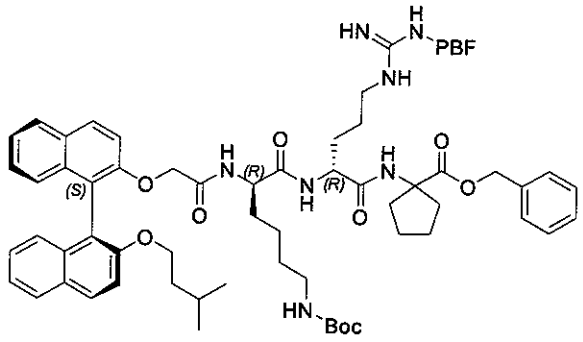
20(v)



This compound was prepared in two steps. The initial coupling *via* Protocol 1, using **20(iii)** (100 mg, 0.456 mmol) and Fmoc-(*D*)-arg(Pbf)-OH (296 mg, 0.456 mmol) to yield the Fmoc protected precursor **20(iv)** as a white foamy solid (MS (ES +ve) *m/z* 850 (100%) $[M+H]^+$). This precursor was then deprotected *via* Protocol 2 to afford the desired compound **20(v)** as a white solid (152 mg, 53% two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44, s, 6H; 1.46, m, 2H; 1.63, m, 2H; 1.76, 4H/NH_2; 1.93, m, 2H; 2.07, s, 3H; 2.24, m, 2H; 2.50, s, 3H; 2.58, s, 3H; 2.93, s, 2H; 3.20, m, 2H; 3.87, m, 1H; 5.08, s, 2H; 6.37, br s, NH; 6.42, br s, NH; 7.28, m, 5H; 7.52, s, NH; 7.75, m, NH. MS (ES +ve) *m/z* 628 (100%) $[M+H]^+$.

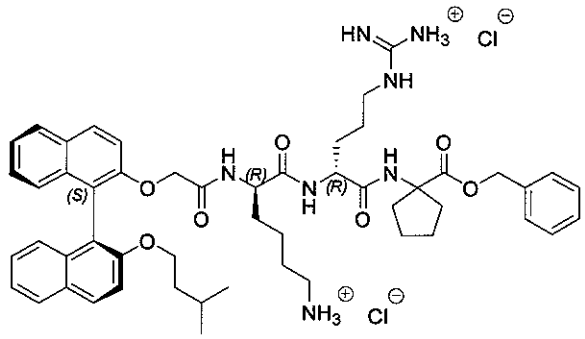
20(vi)



This compound was prepared *via* Protocol 1, using **6(vi)** (100 mg, 0.155 mmol) and **20(v)** (141 mg, 0.224 mmol) to yield **20(vi)** as a white solid (123 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.47, d, J = 6.4 Hz, 3H; 0.52, d, J = 6.4 Hz, 3H; 0.78, m, 2H; 0.94, m, 1H; 1.23, m, 7H; 1.42, s, 9H; 1.43, s, 3H; 1.44, s, 3H; 1.70, m, 4H; 1.96, m, 2H; 2.07, s, 3H; 2.11, m, 1H; 2.25, m, 1H; 2.50, s, 3H; 2.57, s, 3H; 2.91, s, 2H; 2.93, m, 2H; 3.07, m, 2H; 3.87, m, 1H; 4.00, m, 2H; 4.37, m, 2H; 4.59, m, 1H; 4.79, m, NH; 5.07, s, 2H; 6.15, d, J = 6.9 Hz, NH; 6.25, br s, NH; 7.11, d, J = 8.5 Hz, 1H; 7.15, d, J = 8.5 Hz, 1H; 7.26, m, 10H; 7.43, d, J = 9.1 Hz, 1H; 7.84, d, J = 8.4 Hz, 1H; 7.85, d, J = 8.4 Hz, 1H; 7.93, d, J = 6.9 Hz, 1H; 7.94, d, J = 9.0 Hz, 1H. MS (ES +ve) *m/z* 1252 (100%) $[M+H]^+$.

Compound 20

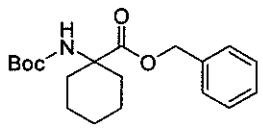


This compound was prepared *via* Protocol 3, using **20(vi)** (110 mg, 0.088 mmol) to yield **20** as an off white solid (83 mg, 97%).

^{1}H NMR (500 MHz, CD_3OD) δ 0.51, d, J = 6.5 Hz, 3H; 0.57, d, J = 6.5 Hz, 3H; 0.95, m, 2H; 1.14, m, 2H; 1.24, m, 2H; 1.42, m, 1H; 1.57, m, 5H; 1.77, m, 4H; 1.98, m, 2H; 2.12, m, 1H; 2.30, m, 1H; 2.79, m, 2H; 3.08, m, 2H; 3.95, m, 1H; 4.14, m, 2H; 4.27, m, 1H; 4.45, ABq, J = 14.7 Hz, 1H; 4.55, ABq, J = 14.7 Hz, 1H; 5.07, ABq, J = 12.3 Hz, 1H; 5.12, ABq, J = 12.3 Hz, 1H; 7.06, t, J = 9.3 Hz, 2H; 7.20, m, 2H; 7.34, m, 7H; 7.47, d, J = 8.9 Hz, 1H; 7.55, d, J = 9.0 Hz, 1H; 7.89, d, J = 8.3 Hz, 1H; 7.92, d, J = 8.3 Hz, 1H; 8.01, d, J = 8.9 Hz, 1H; 8.02, d, J = 8.9 Hz, 1H. MS (ES +ve) *m/z* 900 (5%) $[M+H]^+$; 450.7 (100) $[M+2H]^{2+}$.

Synthesis of Compound 21

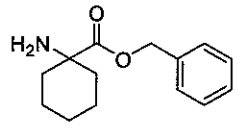
21(i)



To Boc-1-amino-1-cyclohexane carboxylic acid (168 mg, 0.69 mmol) and potassium carbonate (691 mg, 5.00 mmol) in acetone (30 ml) was added benzyl bromide (0.17 ml, 1.40 mmol). The resulting solution was heated at reflux overnight before being cooled, filtered and evaporated to dryness. The resultant residue was subjected to flash column chromatography over silica, eluting with 5% ethyl acetate/hexane to first remove benzyl bromide, then with DCM to yield the product **21(i)** as a colourless oil (226 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28, m, 1H; 1.38, s, 9H; 1.42, m, 2H; 1.58, m, 3H; 1.82, m, 2H; 1.98, m, 2H; 4.86, s, NH; 5.12, s, 2H; 7.32, m, 5H. MS (ES +ve) *m/z* 379 (70%) $[M+HCOOH]^+$; 356.1 (20) $[M+Na]^+$; 334.1 (40) $[M+H]^+$; 278.1 (100) $[M+H-C_4H_8]^+$; 234.0 (95) $[M+H\text{-}BOC]^+$.

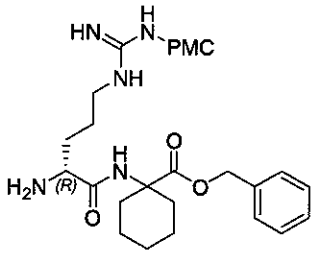
21(ii)



To **21(i)** (218 mg, 0.654 mmol) in DCM (2 ml) was added TFA (2 ml) and the resulting solution stirred at room temperature for 3 hrs. The solution was then diluted with DCM (5 ml) and washed with sat. sodium bicarbonate solution until the washings were basic. The organic layer was then dried ($MgSO_4$), filtered and evaporated to dryness to yield the desired product **21(ii)** as a pale yellow oil (121 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39, m, 6H; 1.56, m, 2H; 1.72, s, NH_2; 1.87, m, 2H; 5.06, s, 2H; 7.26, m, 5H. MS (ES +ve) *m/z* 234.0 (100%) $[M+H]^+$.

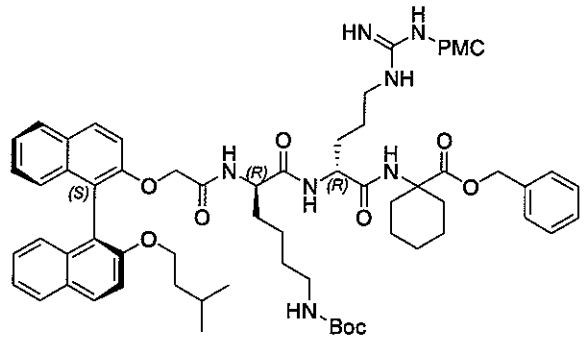
21(iv)



This compound was prepared in two steps. The first step *via* Protocol 1, using **21(ii)** (115 mg, 0.49 mmol) and Fmoc-(*D*)-arg(Pmc)-OH (318 mg, 0.48 mmol) to yield the Fmoc protected precursor **21(iii)** as a white foamy solid (402 mg, MS (ES +ve) *m/z* 877.9 (100%) $[M+H]^+$). This precursor **21(iii)** (200 mg) was then deprotected *via* Protocol 2 to afford the desired compound **21(iv)** as a white solid (141 mg, 87% two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30, s, 6H; 1.58, m, 10H/NH_2; 1.79, dist t, 2H; 1.90, m, 2H; 2.10, s, 3H; 2.57, s, 3H; 2.58, s, 3H; 2.62, m, 2H; 3.14, m, 4H; 3.44, m, 1H; 5.06, ABq, J = 12.6 Hz, 1H; 5.09, ABq, J = 12.6 Hz, 1H; 6.41, m, NH; 7.29, m, 5H; 7.80, s, NH. MS (ES +ve) *m/z* 656.3 (100%) $[M+H]^+$.

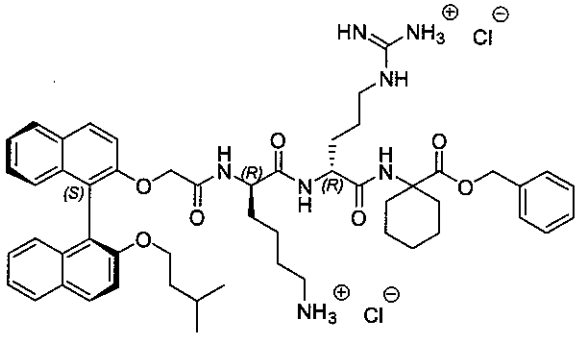
21(v)



This compound was prepared *via* Protocol 1, using **6(vi)** (122 mg, 0.190 mmol) and **21(iv)** (140 mg, 0.213 mmol) to yield **21(v)** as a white solid (163 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.49, d, J = 6.4 Hz, 3H; 0.54, d, J = 6.4 Hz, 3H; 0.78, m, 2H; 0.92, m, 2H; 1.20, m, 6H; 1.29, s, 6H; 1.44, s, 9H; 1.53, m, 2H; 1.77, m, 3H; 1.89, m, 1H; 2.09, s, 3H; 2.55, s, 3H; 2.57, s, 3H; 2.59, m, 2H; 2.89, m, 2H; 3.09, m, 2H; 3.89, m, 1H; 4.04, m, 2H; 4.36, ABq, J = 14.6 Hz, 1H; 4.42, m, 1H; 4.54, ABq, J = 14.6 Hz, 1H; 4.80, m, NH; 5.06, s, 2H; 6.14, br s NH; 6.36, br s, NH; 7.26, m, 12H; 7.44, d, J = 9.1 Hz, 1H; 7.84, d, J = 8.9 Hz, 1H; 7.86, d, J = 7.9 Hz, 1H; 7.92, d, J = 8.8 Hz, 1H; 7.95, d, J = 7.6 Hz, 1H. MS (ES +ve) *m/z* 1280.3 (100%) $[M+H]^+$.

Compound 21

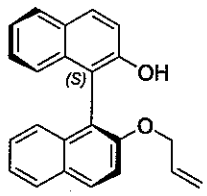


This compound was prepared *via* Protocol 3, using **21(v)** (106 mg, 0.083 mmol) to yield **21** as an off white solid (35 mg, 43%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.50, d, J = 6.4 Hz, 3H; 0.56, d, J = 6.4 Hz, 3H; 0.94, m, 2H; 1.18, m, 3H; 1.57, m, 13H; 1.94, m, 5H; 2.78, m, 2H; 3.08, m, 2H; 3.93, m, 1H; 4.12, m, 2H; 4.30, m, 1H; 4.42, ABq, J = 14.6 Hz, 1H; 4.54, ABq, J = 14.6 Hz, 1H; 5.02, ABq, J = 12.3 Hz, 1H; 5.09, ABq, J = 12.3 Hz, 1H; 7.06, dist t, 2H; 7.20, dist t, 2H; 7.32, m, 7H; 7.44, d, J = 8.8 Hz, 1H; 7.53, d, J = 9.1 Hz, 1H; 7.90, dist t, 2H; 8.00, d, J = 9.1 Hz, 1H; 8.01, d, J = 9.1 Hz, 1H; 8.09, s, NH. MS (ES +ve) *m/z* 915.0 (10%) $[M+H]^+$; 457.9 (100) $[M+2H]^{2+}$.

Synthesis of Compound 22

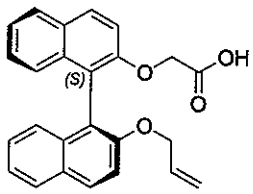
22(i)



To a solution of 1,1'-binaphth-2,2'-diol (4.89 g, 17.1 mmol) in dry acetone (40 ml) was added anhydrous potassium carbonate (3g) under an N_2 atmosphere. After stirring for an hour a solution of allyl bromide (1.55 ml, 17.9 mmol) in acetone (20 ml) was added dropwise over a 2 hr period. The mixture was then heated at reflux overnight before being cooled and filtered. The solid residue was then washed twice more with acetone (10 ml) before the combined organic extracts were evaporated to dryness to yield a honey coloured oil. Subsequent flash column chromatography with 1:3 DCM/Hexane as the eluant affords the desired product **22(i)** as a yellow solid (1.905 g, 53%). $R_f = 0.06$ (1:1 hexane/DCM). The disubstituted product (4%) and starting material (7%) were also recovered.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48, m, 2H, 5.00, m, 2H; 5.51, m, 1H; 7.13, dist d, J = 8.3 Hz, 1H; 7.28, m, 7H; 7.83, m, 3H; 7.92, d, J = 9.1 Hz, 1H.

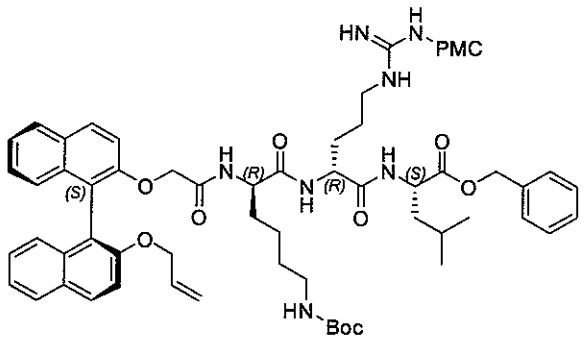
22(ii)



To **22(i)** (1.91 g, 5.84 mmol) in dry MeOH (50 ml) was added potassium carbonate (8.1 g, 58.6 mmol) and bromoacetic acid (4.05 g, 29.3 mmol). The colour of the solution changed from yellow to almost clear upon addition of the bromoacetic acid. The solution was then heated at reflux for three hours over which time a white ppte had fallen out of solution. The reaction mixture was then evaporated to dryness and the residue dissolved in water (50 ml). This was then washed with three 30 ml portions of ether before the aqueous layer was acidified with 3M HCl. This acidified solution was then extracted with three 30 ml portions of DCM to yield a yellow solution. This yellow solution was then dried over $MgSO_4$ before being evaporated to dryness to yield the product **22(ii)** as a yellow foamy solid (1.87 g, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48, m, 2H; 4.55, ABq, J = 16.7 Hz, 1H; 4.67, ABq, J = 16.7 Hz, 1H; 4.95, m, 2H; 5.65, m, 1H; 7.13, app t, 2H; 7.24, m, 2H; 7.34, m, 3H; 7.42, d, J = 9.1 Hz, 1H; 7.87, d, J = 8.2 Hz, 1H; 7.87, d, J = 8.2 Hz, 1H; 7.96, d, J = 8.8 Hz, 1H; 7.97, d, J = 8.8 Hz, 1H. MS (ES +ve) *m/z* 385.0 (90%) $[M+H]^+$; 402.0 (100) $[M+NH_4]^+$.

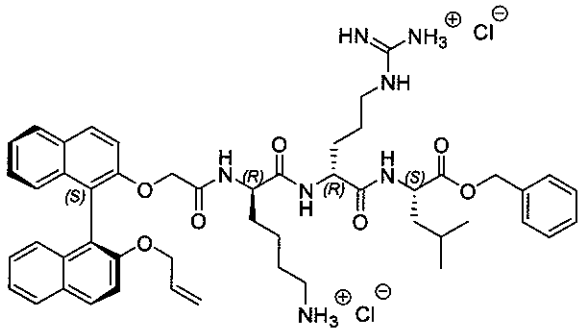
22(iii)



This compound was prepared *via* Protocol 1, using **22(ii)** (46 mg, 0.12 mmol) and **1(viii)** (110 mg, 0.12 mmol) to yield the desired product **22(iii)** as a white solid (124 mg, 84%). R_f = 0.16 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78, m, 2H; 0.87, d, *J* = 5.6 Hz, 3H; 0.89, d, *J* = 5.6 Hz, 3H; 0.97, m, 1H; 1.20, m, 4H; 1.27, s, 6H; 1.39, m, 2H; 1.41, s, 9H; 1.63, m, 3H; 1.75, m, 3H; 2.08, s, 3H; 2.53, s, 3H; 2.56, s, 3H; 2.57, m, 2H; 2.88, m, 2H; 3.13, m, 2H; 4.09, m, 1H; 4.47, m, 6H; 4.79, m, NH; 4.86, m, 2H; 5.08, ABq, *J* = 12.3 Hz, 1H; 5.16, ABq, *J* = 12.3 Hz, 1H; 5.63, m, 1H; 6.24, m, NH; 7.10, dist d, 1H; 7.16, dist d, 1H; 7.32, m, 10H; 7.42, d, *J* = 9.3 Hz, 1H; 7.85, dist t, 2H; 7.92, d, *J* = 8.8 Hz, 2H. MS (ES +ve) *m/z* 1260 (100%) $[M+Na]^+$; 1238 (80) $[M+H]^+$.

Compound 22

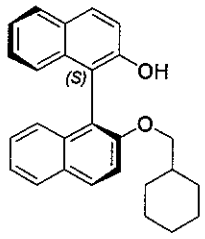


This compound was prepared *via* Protocol 3, using **22(iii)** (94 mg, 0.076 mmol) to yield the desired product **22** as a white solid (62 mg, 86%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.88, d, *J* = 5.6 Hz, 3H; 0.93, d, *J* = 5.6 Hz, 3H; 0.97, m, 2H; 1.15, m, 1H; 1.66, m, 10H; 2.79, m, 2H; 3.14, m, 2H; 4.14, m, 1H; 4.35, m, 1H; 4.46, m, 2H; 4.56, m, 3H; 4.93, m, 2H; 5.11, ABq, *J* = 12.3 Hz, 1H; 5.17, ABq, *J* = 12.3 Hz, 1H; 5.71, m, 1H; 7.05, m, 2H; 7.20, dist t, 2H; 7.33, m, 7H; 7.46, d, *J* = 9.1 Hz, 1H; 7.53, d, *J* = 9.1 Hz, 1H; 7.90, dist t, 2H; 8.01, d, *J* = 9.1 Hz, 2H. MS (ES +ve) *m/z* 437 (100%) $[M+2H]^{2+}$.

Synthesis of Compound 23

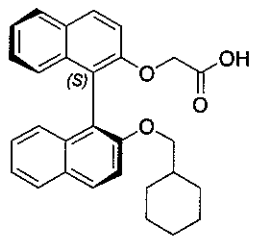
23(i)



Bromomethylcyclohexane (240 µl, 1.75 mmol) was added to a mixture of 1,1'-binaphth-2,2'-diol (500 mg, 1.75 mmol), potassium carbonate (1.00g, 7.27 mmol) and acetone (10 ml). The mixture was stirred at reflux for 3 days, and then cooled and concentrated *in vacuo*. The crude product was purified by flash chromatography with 1-10 % ethyl acetate-petrol as eluent to give the product **23(i)** as a viscous oil (400 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51, m, 10H; 2.44, m, 1H; 3.92, m, 2H; 7.06, d, J = 8.5 Hz, 1H; 7.26, m, 8H; 7.44, d, J = 9.2 Hz, 1H; 7.84, d, J=8.1 Hz, 1H; 7.89, dd, J=6.2, 6.2 Hz, 2H; 8.02, d, J = 9.2 Hz, 1H.

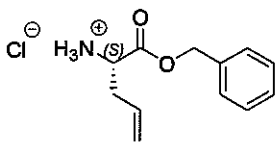
23(ii)



To **23(i)** (400 mg, 1.05 mmol) in methanol (10 ml) was added potassium carbonate (1.50 g, 10.9 mmol) and bromoacetic acid (900 mg, 6.48 mmol) and the mixture stirred at reflux for 2 days. The reaction mixture was cooled down, methanol removed *in vacuo*, and the crude residue redissolved in water and acidified with 1M HCl. Extraction with ether, drying (Na_2SO_4) and concentration gave the crude product that was purified by flash chromatography. Elution with chloroform gave unreacted **23(i)** (25 %). Further elution with 2 % methanol-chloroform gave **23(ii)** as a viscous oil (240 mg, 51.9 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.51, m, 2H; 0.83, m, 3H; 1.17, br t, 2H; 1.36, m, 4H; 3.71, m, 1H; 3.79, m; 4.49, ABq, J = 16.6, 1H; 4.61, ABq, J = 16.6 Hz, 1H; 7.18, m, 4H; 7..30, m, 3H; 7.40, d, J = 9.3 Hz, 1H; 7.82, d, J = 7.8 Hz, 1H; 7.83, d, J = 7.8 Hz, 1H; 7.91, d, J = 9.3 Hz, 1H; 7.92, d, J = 9.3 Hz, 1H, 9.25, br s, 1H.

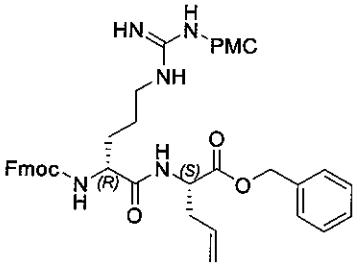
23(iii)



To a solution of (*S*)-allylglycine (225 mg, 1.96 mmol) in benzyl alcohol (5 mL) was added thionyl chloride (2 mL) and the resulting mixture was allowed to stir for 16 h before addition of diethyl ether (30 mL) and extraction with water (3 x 30 mL). The aqueous layer was concentrated, diluted with 2M sodium bicarbonate (20 mL), and extracted with DCM (3 x 30 mL). The combined organic fractions were dried and acidified with 1M HCl/diethyl ether (2 mL) and evaporated. The crude product dissolved in a minimal volume of MeOH and precipitated with diethyl ether to yield the title compound **23(iii)** as a white solid (322 mg, 1.34 mmol, 68%) Mp 186-191°C.

^{1}H NMR (300 MHz, D_2O) δ 2.55, m, 2H; 4.08, t, *J* = 5.4 Hz, 1H; 5.11, m, 4H; 5.51, m, 1H; 7.28, m, 5H. MS (CI +ve) *m/z* 205 (25%) $[M+H]^+$.

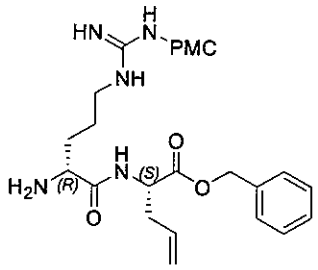
23(iv)



This compound was prepared *via* Protocol 1, using **23(iii)** (155 mg, 0.65 mmol) and (*R*)-Fmoc-Arg(PMC)-OH (431 mg, 0.65 mmol) to afford **23(iv)** (280 mg, 0.33 mmol, 51%) as a white solid. Mp 78-74°C.

^{1}H NMR (300 MHz $CDCl_3$) δ 1.22, s, 6H; 1.58, m, 2H; 1.69, t, *J* = 6.3 Hz; 1.85, m, 2H; 2.05, s, 3H; 2.52, m, 4H; 2.54, s, 3H; 2.57, s, 3H; 3.20, m, 2H; 4.05, t, *J* = 7.2 Hz, 1H; 4.24, m, 3H; 4.58, m, 1H; 4.99, m, 4H; 5.61, m, 1H; 5.68, m, 1H; 6.33, m, 3H; 7.28, m, 9H; 7.51, d, *J* = 7.5 Hz, 2H; 7.69, d, *J* = 7.5 Hz, 2H. MS (ES +ve) *m/z* 850 (100%) $[M+H]^+$.

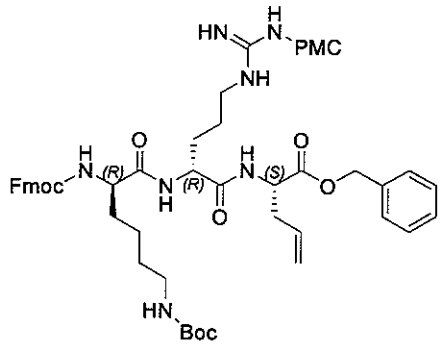
23(v)



This compound was prepared *via* Protocol 2, using **23(iv)** (278 mg, 0.33 mmol) to yield **32(v)** as a cream semi-solid (144 mg, 0.23 mmole, 70%). Mp 66-68°C.

^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.29, s, 6H; 1.54, m, 2H; 1.68, m, 4H; 1.78, t, *J* = 7.2 Hz, 2H; 2.09, s, 3H; 2.55, s, 3H; 2.56, s, 3H; 2.61, t, *J* = 6.9 Hz, 2H; 3.09, m, 2H; 3.16, m, 2H; 3.40, m, 1H; 4.56, m, 1H; 5.14, m, 4H; 5.63, s, 1H; 6.33, m, 2H; 7.32, m, 5H; 7.60, d, *J* = 7.8 Hz, 1H; 7.85, d, *J* = 7.8 Hz, 1H. MS (ES +ve) *m/z* 628 (100%) $[M+H]^+$.

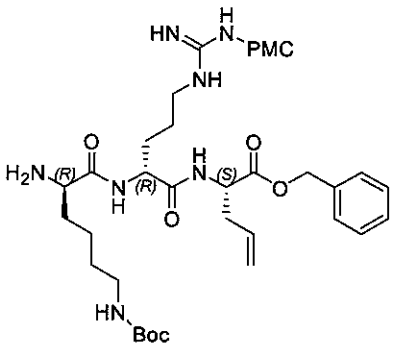
23(vi)



This compound was prepared *via* Protocol 1, using **23(v)** (200 mg, 0.32 mmol) and (*R*)-Fmoc-Lys(Boc)-OH (151 mg, 0.32 mmol) to afford **23(vi)** as a white solid (202 mg, 0.19 mmol, 59%). Mp 116°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41, s, 6H; 1.59, m, 2H; 1.67, m, 4H; 1.74, m, 2H; 1.95, m, 4H; 2.03, s, 3H; 2.50, m, 4H; 2.52, s, 3H; 2.55, s, 3H; 3.05, m, 2H; 3.18, m, 2H; 3.98, m, 1H; 4.20, m, 2H; 4.29, m, 1H; 4.51, m, 1H; 4.59, m, 1H; 5.03, m, 4H; 5.64, m, 1H; 6.25, m, 3H; 7.29, m, 11H; 7.45, m, 1H; 7.55, d, J = 7.8 Hz, 2H; 7.72, d, J = 7.8 Hz, 2H. MS (ES +ve) *m/z* 1078 (10%) $[M+H]^+$; 288 (100).

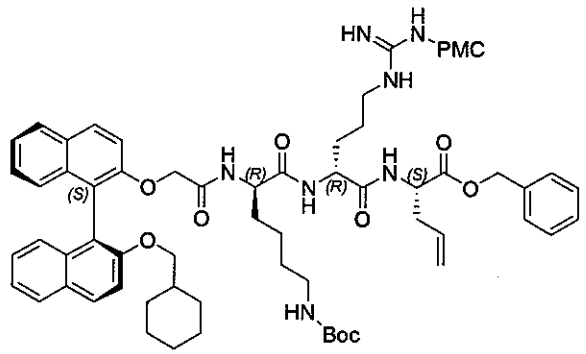
23(vii)



This compound was prepared *via* Protocol 2, using **23(vi)** (202 mg, 0.19 mmol) to yield **23(vii)** as a cream oil (157 mg, 0.18 mmole, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31, s, 6H; 1.42, s, 9H; 1.58, m, 4H; 1.72, m, 4H; 1.80, t, J = 6.3 Hz; 1.89, m, 2H; 2.10, s, 3H; 2.15, m, 2H; 2.47, m, 2H; 2.56, s, 3H; 2.58, s, 3H; 2.62, m, 2H; 3.05, m, 2H; 3.22, m, 2H; 3.36, m, 1H; 4.61, m, 2H; 5.09, m, 4H; 5.63, m, 1H; 6.44, m, 3H; ; 7.32, m, 5H; 7.58, d, J = 7.2 Hz, 1H; 8.00, d, J = 7.2 Hz, 1H. MS (ES +ve) *m/z* 856 (100%) $[M+H]^+$.

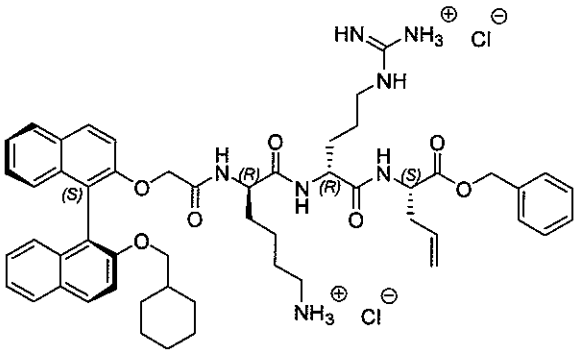
23(viii)



This compound was prepared *via* Protocol 1, from acid **23(ii)** with the **23(vii)** (80 mg, 94 μmol). Purification by radial chromatography (1-2% methanol-chloroform) gave the product **23(viii)** (94 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.48, m, 2H; 0.85, m, 6H; 1.28, s, 6H; 1.41, s, 9H; 1.32, m, 12H; 1.76, br t, 3H; 2.09, s, 3H; 2.55, s, 3H; 2.57, s, 3H; 2.56, m, 4H; 2.91, br s, 2H; 3.09, m, 2H; 3.67, m, 1H; 3.81, m, 1H; 4.12, m, 1H; 4.43, ABq, J = 14.4 Hz, 1H; 4.51, ABq, J = 14.4 Hz, 1H; 4.41, m, 1H; 4.60, m, 1H; 4.84, b s, 1H; 5.06, m, 2H; 5.09, ABq, 1H, *J* = 12.5; 5.18, ABq, 1H, *J* = 12.5; 5.68, m, 1H; 6.19, br d, *J* = 7.0 Hz, 1H; 6.26, br s, 2H; 7.25, m, 7H; 7.43, 1H, d, *J* = 9.0 Hz; 7.85, m, 2H; 7.95, d, *J* = 9.0 Hz, 2H. MS (ES +ve) *m/z* 1278 (100%) $[M+H]^+$.

Compound 23

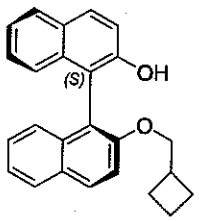


This compound was prepared *via* Protocol 3, using **23(viii)** (80 mg, 62.6 μmol). Standard work-up gave the product **23** as a cream crystalline solid (40 mg, 65%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 0.57, m, 2H; 0.90, m, 3H; 1.33, m, 11H; 2.39, br s, 3H; 2.49, br s, 3H; 2.65, m, 2H; 2.40, m, 4H; 3.76, m, 1H; 3.87, m, 1H; 4.20, m, 3H, 4.51, br s, 2H; 5.05, m, 4H; 5.70, m, 1H; 6.92, d, *J* = 8.5 Hz, 1H; 7.00, d, *J* = 8.0 Hz, 1H; 7.27, m, 10H; 7.54, m, 1H; 7.91, m, 2H; 8.02, m, 2H. MS (ES +ve) *m/z* 912 (45%) $[M+H]^+$; 457 (100) $[M+2H]^{2+}$.

Synthesis of Compound 24

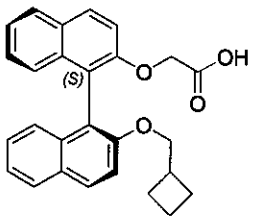
24(i)



Bromomethylcyclobutane (200 µl, 1.75 mmol) was added to a mixture of 1,1'-binaphth-2,2'-diol (500 mg, 1.75 mmol), potassium carbonate (1.00g, 7.27 mmol) and acetone (10 ml). The mixture was stirred at reflux for 18 h, and then cooled down and concentrated *in vacuo*. The crude product was purified by flash chromatography with 1-4% ethyl acetate-petrol as eluent to give the product **24(i)** as a viscous oil (300 mg, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52, m, 6H; 2.43, m, 1H; 3.92, m, 2H; 4.95, s, 1H; 7.06, d, J = 8.3 Hz, 1H; 7.28, m, 6H; 7.43, d, J = 8.8 Hz, 1H; 7.84, d, J = 7.8 Hz, 1H; 7.88, d, J = 9.3 Hz, 1H; 7.89, d, 1H, J = 8.3 Hz; 8.00, d, J = 9.3 Hz, 1H.

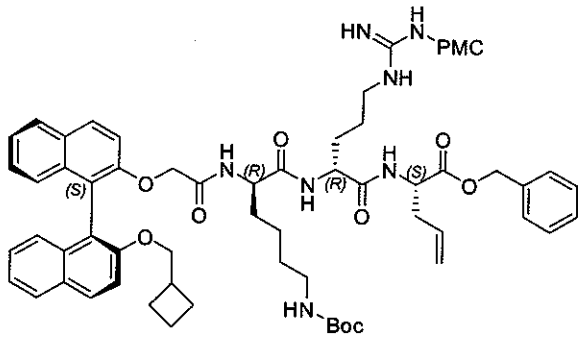
24(ii)



To **24(i)** (300 mg, 0.85 mmol) in methanol (10 ml) was added potassium carbonate (1.00 g, 7.27 mmol) and bromoacetic acid (560 mg, 4.03 mmol) and the mixture stirred at reflux for 2 days. The reaction mixture was cooled down, methanol removed *in vacuo*, and the crude residue redissolved in water and acidified with 1M HCl. Extraction with ether, drying (Na_2SO_4) and concentration gave the crude product that was purified by flash chromatography. Elution with 10% methanol:DCM gave the product **24(ii)** as a viscous oil (200 mg, 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43, m, 6H; 2.33, m, 1H; 3.80, m, 1H; 3.99, m, 1H; 4.52, ABq, 1H, J = 16.5 Hz; 4.69, ABq, 1H, J = 16.5 Hz; 7.15, d, J = 8.5 Hz, 2H; 7.29, m, 5H; 7.43, d, J = 8.8 Hz, 1H; 7.87, d, J = 7.0 Hz, 2H; 7.94, d, J = 8.5 Hz, 1H; 7.96, d, J = 8.8 Hz, 1H.

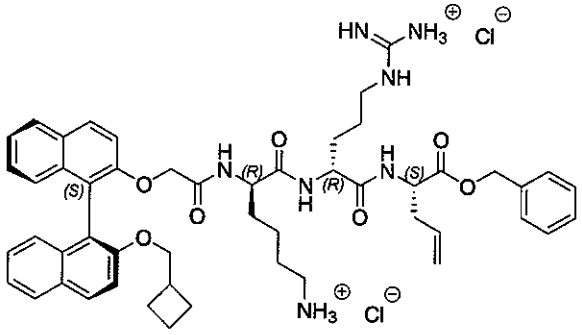
24(iii)



This compound was prepared *via* Protocol 1, using **24(ii)** and **23(viii)** (110 mg, 117 μmol). Purification by radial chromatography (1-3% methanol-DCM) gave the product **24(iii)** (80 mg, 55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79, m, 2H; 0.94, m, 1H; 1.28, s, 6H; 1.41, s, 9H; 1.38, m, 12H; 1.76, br t, 3H; 2.09, s, 3H; 2.29, m, 1H; 2.55, s, 3H; 2.57, s, 3H; 2.54, m, 4H; 2.90, m, 2H; 3.08, m, 2H; 3.80, m, 1H; 3.97, m, 1H; 4.09, br s, 1H; 4.41, ABq, J = 14.5 Hz, 1H; 4.51, ABq, J = 14.5 Hz, 1H; 4.42, m, 1H; 4.59, m, 1H; 4.84, br s, 1H; 5.06, m, 2H; 5.12, ABq, J = 12.5 Hz, 1H; 5.18, ABq, J = 12.5 Hz, 1H; 5.66, m, 1H; 6.22, m, 3H; 7.25, m, 7H; 7.43, d, J = 8.8 Hz, 1H; 7.84, d, J = 8.3 Hz, 1H; 7.86, d, J = 8.8 Hz, 1H; 7.93, d, J = 9.3 Hz, 1H; 7.94, d, J = 8.8 Hz, 1H. MS (ES +ve) *m/z* 1250 (100%) $[M+H]^+$.

Compound 24

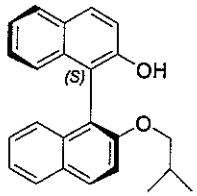


This compound was prepared *via* Protocol 3, using **24(iii)** (70 mg, 55.98 μmol). Standard work-up gave the product **24** as a cream crystalline solid (35 mg, 65%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97, br s, 1H; 1.15, br s, 1H; 1.45, m, 10H; 2.10, s, 1H; 2.45, m, 5H; 2.66, br s, 1H; 3.07, br s, 3H; 3.99, m, 3H; 4.34, m, 4H; 5.09, m, 4H; 5.73, br s, 1H; 6.03, m, 3H; 7.29, m, 8H; 7.57, m, 2H; 8.01, m, 4H, 8.19, br s, 1H; 8.41, br s, 2H. MS (ES +ve) *m/z* 884 (95%) $[M+H]^+$; 443 (100) $[M+2H]^{2+}$.

Synthesis of Compound 25

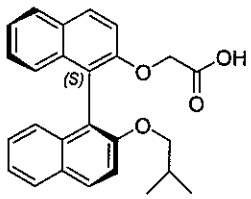
25(i)



1-Bromo-2-methylpropane (190 µl, 1.75 mmol) was added to a mixture of 1,1'-binaphth-2,2'-diol (500 mg, 1.75 mmol), potassium carbonate (1.00g, 7.27 mmol) and acetone (10 ml). The mixture was stirred at reflux for 42 h, and then cooled down and concentrated *in vacuo*. The crude product was purified by flash chromatography with 1-4% ethyl acetate-petrol as eluent to give the product **25(i)** as a viscous oil (280 mg, 47%). Further elution with 10% ethyl acetate-petrol gave unreacted diol (200 mg, 40%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63, d, J = 6.6 Hz, 3H; 0.66, d, J = 6.6Hz, 3H; 1.77, m, 1H; 3.75, m, 2H; 4.98, br s, 1H; 7.09, d, J = 8.4 Hz; 7.30, m, 6H; 7.44, d, J = 9.3 Hz, 1H; 7.87, d, J = 8.1 Hz, 1H; 7.91, d, J = 8.4 Hz, 2H; 8.01, d, J = 9.0Hz, 1H.

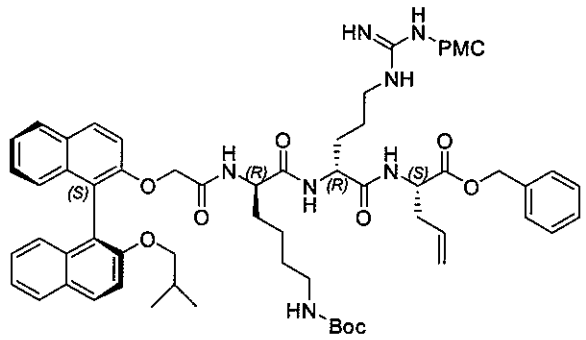
25(ii)



To **25(i)** (280 mg, 0.82 mmol) in methanol (10 ml) was added potassium carbonate (500 mg, 3.63 mmol) and bromoacetic acid (454 mg, 3.27 mmol) and the mixture stirred at reflux for 4 days. The reaction mixture was cooled down, methanol removed *in vacuo*, and the crude residue redissolved in water and acidified with 1M HCl. Extraction with ether, drying (Na_2SO_4) and concentration gave the crude product which was purified by flash chromatography. Elution with 4% ethyl acetate:petrol gave unreacted **25(i)** (150 mg, 54%). Further elution with 10% methanol:DCM gave the product **25(ii)** (100 mg, 31%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.44, d, J = 6.5 Hz, 3H; 0.51, d, J = 7.0 Hz, 3H; 1.68, m, 1H; 3.63, ABq, J = 7.0, 9.5 Hz, 1H; 3.83, ABq, J = 6.5, 9.5 Hz, 1H; 4.56, ABq, J = 17 Hz, 1H; 4.71, ABq, J = 16 Hz, 1H; 7.14, d, J = 8.0 Hz; 7.25, m, 2H, 7.35, m, 4H; 7.45, d, J = 9.5 Hz, 1H; 7.89, d, J = 8.5 Hz, 2H; 7.99, d, J = 8.5 Hz, 2H.

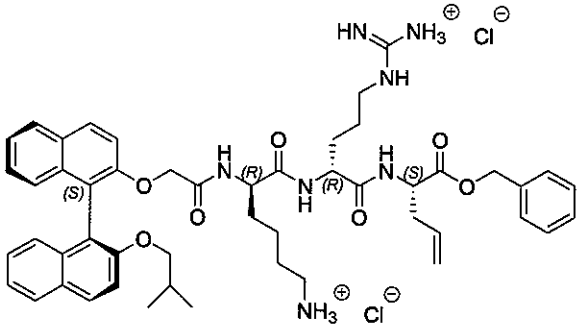
25(iii)



This compound was prepared *via* Protocol 1, using **25(ii)** with **23(viii)**. Purification by radial chromatography (1-4% methanol:DCM) gave the product **25(iii)** (90 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.43, d, J = 7.0 Hz, 3H; 0.49, d, J = 6.0 Hz, 3H, 0.77, m, 2H; 0.93, m, 1H; 1.28, s, 6H; 1.41, s, 9H; 1.45, m, 7H; 1.76, br t, 3H; 2.08, b s, 2H; 2.54, s, 3H; 2.56, s, 3H; 2.56, m, 4H; 2.95, m, 2H; 3.13, m, 1H; 3.60, m, 1H; 3.81, m, 1H; 4.07, br s, 1H; 4.40, ABq, J = 14.5 Hz, 1H; 4.50, ABq, J = 14.5 Hz, 1H; 4.40, m, 1H; 4.57, m, 1H; 4.83, b s, 1H; 5.03, m, 2H; 5.09, ABq, J = 12.5 Hz; 5.18, ABq, J = 12.5 Hz; 5.63, m, 1; 6.20, m, 3H; 7.26, m, 7H; 7.43, d, J = 9.5 Hz, 1H; 7.85, m, 2H; 7.94, d, J = 9.0 Hz, 2H. MS (ES +ve) 1260 (35%) $[M+Na]^+$; 1238 (15) $[M+H]^+$.

Compound 25

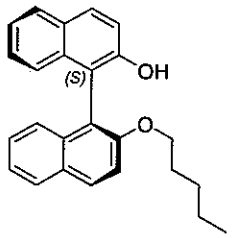


This compound was prepared *via* Protocol 3, using **25(iii)** (70 mg, 56.5 μmol) to give the product **25** as a cream crystalline solid (30 mg, 56%).

^{1}H NMR (500 MHz, CD_3OD) δ 0.52, d, J = 6.2 Hz, 3H; 0.57, d, J = 6.6 Hz, 3H; 0.87, m, 2H; 0.96, br s, 1H; 1.13, m, 1H; 1.62, m, 4H; 1.28, m, 2H; 2.57, m, 2H; 2.79, br s, 2H; 3.15, br s, 2H; 3.70, m, 1H; 3.91, m, 1H; 4.14, b s, 1H; 4.48, m, 4H; 4.89, br s, 1H; 5.11, m, 2H; 5.15, ABq, 1H, J = 12.5 Hz; 5.19, ABq, 1H, J = 12.5 Hz; 5.74, m, 1H; 7.09, m, 2H; 7.22, m, 2H; 7.37, m, 7H; 7.47, d, J = 8.5 Hz, 1H; 7.54, d, J = 8.5 Hz, 1H; 7.91, d, J = 7.7 Hz, 2H; 8.03, d, J=8.5 Hz, 2H. MS (ES +ve) 872 (25%) $[M+H]^+$; 437 (100) $[M+2H]^{2+}$.

Synthesis of Compound 26

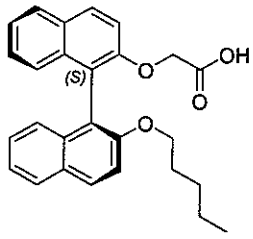
26(i)



Bromopentane (216 µl, 1.75 mmol) was added to a mixture of 1,1'-binaphth-2,2'-diol (500 mg, 1.75 mmol), potassium carbonate (1.00g, 7.27 mmol) and acetone (10 ml). The mixture was stirred at reflux for 18 h, and then cooled and concentrated *in vacuo*. The crude product was purified by flash chromatography with 1-4% ethyl acetate:petrol as eluent to give the product **26(i)** as a viscous oil (380 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66, t, J = 7 Hz, 3H; 0.96, m, 2H; 1.03, m, 2H; 1.43, m, 2H; 3.95, m, 2H; 4.94, s, 1H; 7.05, d, J = 8.5 Hz, 1H; 7.28, m, 6H; 7.42, d, J = 9.0 Hz, 1H; 7.83, d, J = 8.5 Hz; 7.87, d, J = 9.0 Hz, 2H; 7.98, d, J = 9.0 Hz, 1H.

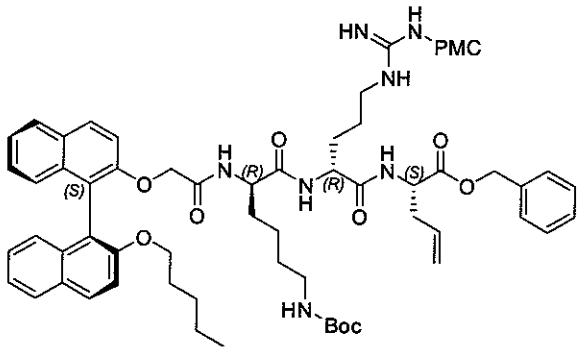
26(ii)



To **26(i)** (280 mg, 0.82 mmol) in methanol (10 ml) was added potassium carbonate (500 mg, 3.63 mmol) and bromoacetic acid (454 mg, 3.27 mmol) and the mixture stirred at reflux for 4 days. The reaction mixture was cooled down, methanol removed *in vacuo*, and the crude residue redissolved in water and acidified with 1M HCl. Extraction with ether, drying (Na_2SO_4) and concentration gave the crude product that was purified by flash chromatography. Elution with 4% ethyl acetate:petrol gave unreacted **26(i)** (150 mg, 54%). Further elution with 10% methanol:DCM gave the desired compound **26(ii)** as a viscous oil (100 mg, 31%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.53, t, J=7.5 Hz, 3H; 0.79, m, 4H; 1.35, m, 2H; 3.88, m, 1H; 4.05, m, 1H; 4.55, ABq, J = 16.5 Hz, 1H; 4.74, ABq, J = 16.5 Hz, 1H; 7.14, dd, J = 8.5, 2.5 Hz, 1H; 7.25, dd, J = 5.5, 5.5 Hz, 1H; 7.33, d, J = 9.5 Hz, 1H; 7.36, m, 3H; 7.46, d, J = 7.46 Hz, 1H; 7.89, d, J = 8.0 Hz, 1H; 7.98, d, J = 8.5 Hz, 1H.

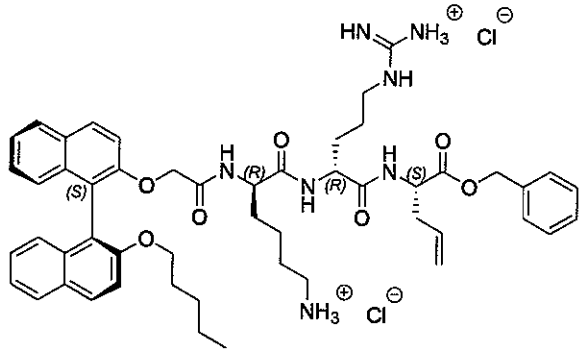
26(iii)



This compound was prepared *via* Protocol 1, using **26(ii)** with **23(viii)** (80 mg, 94 μmol). Purification by radial chromatography (1-4% methanol:DCM) gave the desired product **26(iii)** (110 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.54, d, J = 7.2 Hz, 3H; 0.83, m, 7H; 1.27, s, 6H; 1.41, s, 9H; 1.33, m, 8H; 1.76, br t, 3H; 2.08, br s, 3H; 2.54, s, 3H; 2.56, s, 3H; 2.53, m, 4H; 2.90, m, 2H; 3.06, m, 4H; 3.85, m, 1H; 4.00, m, 1H; 4.08, br s, 1H; 4.40, ABq, J = 14.5 Hz, 1H; 4.52, ABq, J = 14.5 Hz, 1H; 4.54, m, 2H; 4.85, br s, 1H; 5.05, m, 2H; 5.15, ABq, J = 12.0 Hz, 1H; 5.17, ABq, J = 12.0 Hz, 1H; 5.65, m, 1H; 6.23, m, 3H; 7.11, d, J = 8.3 Hz, 1H; 7.15, d, J = 8.3 Hz, 1H; 7.26, m, 10H; 7.44, d, J = 9.05 Hz; 7.85, m, 2H; 7.93, m, 2H. MS (ES +ve) *m/z* 1252 (100%) $[M+H]^+$.

Compound 26

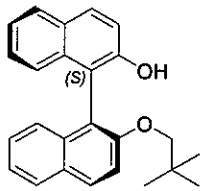


This compound was prepared *via* Protocol 3, using **26(iii)** (90 mg, 71.9 μmol). Standard work-up gave the product **26** as a white crystalline solid (45 mg, 65%).

MS (ES +ve) *m/z* 886 (70%) $[M+H]^+$; 444 (100) $[M+2H]^{2+}$

Synthesis of Compound 27

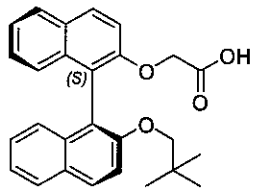
27(i)



1-Bromo-2,2-dimethylpropane (220 µl, 1.75 mmol) was added to a mixture of 1,1'-binaphth-2,2'-diol (500 mg, 1.75 mmol), potassium carbonate (1.00g, 7.27 mmol) and dimethylformamide (10 ml). The mixture was stirred at 80°C for 7 days, and then cooled down and acidified with diluted hydrochloric acid. The mixture was diluted with water and extracted with ether. The crude product was purified by flash chromatography with 1-4% ethyl acetate:petrol as eluent to give the product **27(i)** as a viscous oil (80 mg, 13%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.57, s, 9H; 3.57, m, 2H; 4.94, s, 1H; 7.05, d, 1H, J = 8.5 Hz; 7.17, m, 1H; 7.26, m, 2H; 7.35, m, 4H; 7.81, d, J = 8 Hz, 1H; 7.85, d, J = 9 Hz, 2H; 7.95, d, J = 9.5 Hz, 1H.

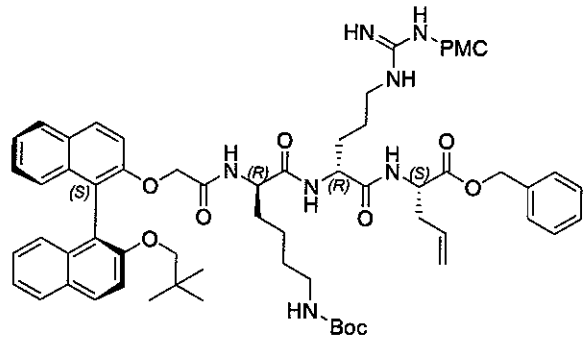
27(ii)



To **27(i)** (80 mg, 0.22 mmol) in methanol (10 ml) was added potassium carbonate (1.00 g, 7.27 mmol) and bromoacetic acid (560 mg, 4.03 mmol) and the mixture stirred at reflux for 18h. The reaction mixture was cooled down, methanol removed *in vacuo*, and the crude residue redissolved in water and acidified with 1M HCl. Extraction with ether, drying (Na_2SO_4) and concentration gave the crude product that was purified by flash chromatography. Elution with 10% methanol:DCM gave the acid **27(ii)** as a viscous oil (85 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.50, s, 9H; 3.51, ABq, J = 8.0 Hz, 1H; 3.66, ABq, J = 8.0 Hz, 1H; 4.52, s, 2H; 7.20, m, 4H; 7.32, m, 3H; 7.38, d, J = 9.0 Hz, 1H; 7.85, d, J = 8.5 Hz, 2H; 7.93, m, 2H.

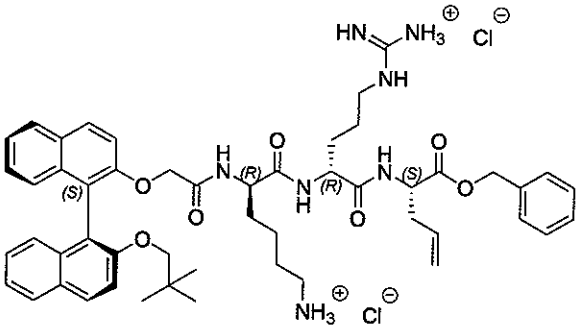
27(iii)



This compound was prepared *via* Protocol 1, using **27(ii)** and **23(viii)** (82 mg, 96 μmol). Purification by radial chromatography (1-3% methanol:DCM) gave the product **27(iii)** (73 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47, s, 9H; 0.80, m, 2H; 0.91, m, 1H; 1.28, s, 6H; 1.41, s, 9H; 1.40, m, 6H; 1.77, br t, 3H; 2.08, s, 3H; 2.54, 4H; 3.11, m, 4H; 3.48, ABq, J = 8.1Hz, 1H; 3.72, ABq, J = 8.4 Hz, 1H; 4.08, br s, 1H; 4.49, m, 4H; 4.84, br s, 1H; 5.03, m, 2H; 5.09, ABq, J = 12.3 Hz, 1H; 5.18, ABq, J = 12.3 Hz, 1H; 5.66, m, 1H; 6.13, d, J = 7.2 Hz, 1H; 6.30, br s, 2H; 7.27, m, 7H; 7.42, d, J = 9.0 Hz, 1H; 7.85, m, 2H; 7.94, d, J = 8.7 Hz, 2H. MS (ES +ve) *m/z* 1252 (20%) $[M+H]^+$.

Compound 27

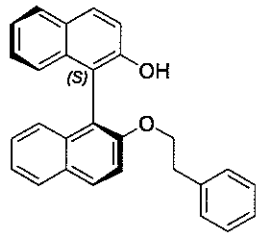


This compound was prepared *via* Protocol 3, using **27(iii)** (60 mg, 47.9 μmol). Standard work-up gave the product **27** as a cream crystalline solid (30 mg, 65%).

^{1}H NMR (300 MHz, CD_3OD) δ 0.52, br s, 9H; 1.05, m, 3H; 1.66, m, 6H; 2.52, m, 2H; 2.79, br s, 2H, 3.34, br s, 2H; 3.55, ABq, J = 8.1 Hz, 1H; 3.79, ABq, J = 8.1 Hz, 1H; 4.14, br s, 1H; 4.42, m, 4H; 4.86, br s, 1H; 5.11, m, 4H; 5.73, m, 1H; 7.31, 13H; 7.90, d, J = 8.1 Hz, 2H; 8.02, d, J = 8.4 Hz, 2H. MS (ES +ve) *m/z* 887 (20%) $[M+H]^+$; 444 (100) $[M+2H]^{2+}$.

Synthesis of Compound 28

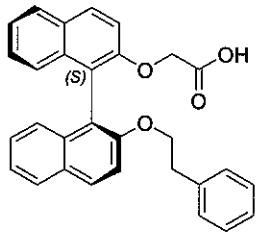
28(i)



2-Bromoethylbenzene (240 µl, 1.75 mmol) was added to a mixture of 1,1'-binaphth-2,2'-diol (500 mg, 1.75 mmol), potassium carbonate (1.00g, 7.27 mmol) and acetone (10 ml). The mixture was stirred at reflux for 18 h, and then cooled down and filtered. The crude product was purified by flash chromatography with 1-4% ethyl acetate:petrol as eluent to give the product **28(i)** as viscous oil (250 mg, 37%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69, m, 2H; 4.12, m, 2H; 4.90, s, 1H; 6.76, m, 2H; 7.02, m, 4H; 7.26, m, 7H; 7.89, m, 4H.

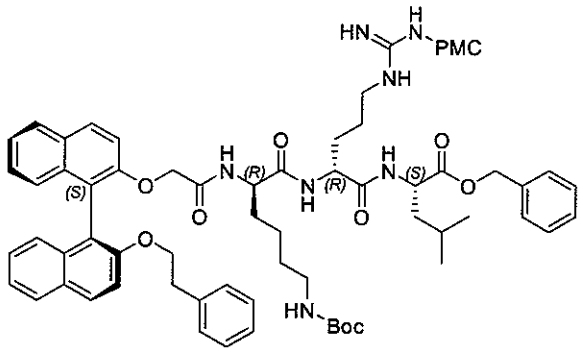
28(ii)



To **28(i)** (250 mg, 0.64 mmol) in methanol (10 ml) was added potassium carbonate (1.00 g, 7.27 mmol) and bromoacetic acid (560 mg, 4.03 mmol) and the mixture stirred at reflux for 18h. The reaction mixture was cooled down, methanol removed *in vacuo*, and the crude residue redissolved in water and acidified with 1M HCl. Extraction with ether, drying (Na_2SO_4) and concentration gave the crude product that was purified by flash chromatography. Elution with 10% methanol-DCM gave the acid **28(ii)** as a viscous oil (257 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62, m, 2H; 4.06, m, 2H; 4.15, m, 2H; 6.67, d, J = 7.5 Hz, 2H; 6.98, m, 3H; 7.15, m, 3H; 7.27, m, 2H; 7.34, m, 3H; 7.80, d, J = 8.5 Hz, 1H; 7.89, m, 3H; 10.30, br s, 1H.

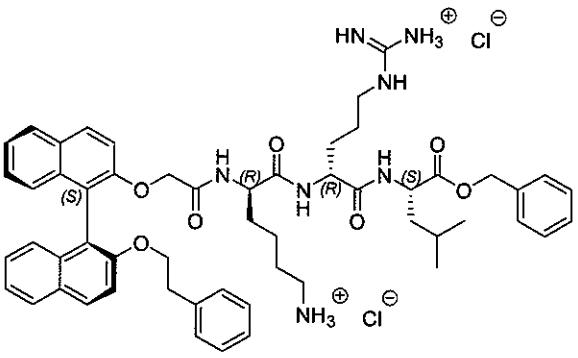
28(iii)



This compound was prepared *via* Protocol 1, using **28(ii)** and **1(viii)** (100 mg, 115 μmol). Purification by radial chromatography (1-3% methanol:DCM) gave the product **28(iii)** (83 mg, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, m, 2H; 0.89, m, 6H; 1.26, s, 6H; 1.40, s, 9H; 1.60, m, 6H; 1.76, br t, 3H; 2.08, s, 3H; 2.62, m, 4H; 3.00, m, 4H; 4.05, m, 2H; 4.31, m, 4H; 4.54, m, 1H; 4.80, m, 1H; 5.09, ABq, J = 12.6 Hz, 1H; 5.17, ABq, J = 12.6 Hz, 1H; 6.10, br d, J = 7.2 Hz, 1H; 6.31, br s, 2H; 6.59, d, J = 6.9 Hz, 2H; 6.99, m, 1H; 7.22, m, 9H; 7.82, d, J = 8.1 Hz, 1H; 7.90, m, 2H. MS (ES +ve) *m/z* 1302 (100%) $[M]^+$.

Compound 28

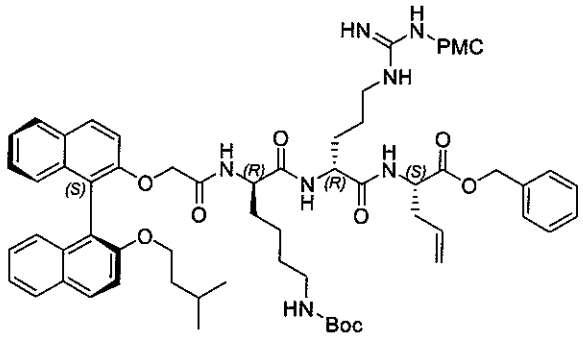


This compound was prepared *via* Protocol 3, using **28(iii)** (80 mg, 61.4 μmol). Standard work-up gave the product **28** as a cream crystalline solid (40 mg, 65%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.47, m, 6H; 1.12, m, 3H; 1.47, m, 4H; 2.07, s, 1H; 2.41, m, 1H; 2.49, br s, 3H; 2.66, m, 1H; 2.66, m, 1H; 3.04, m, 1H; 3.55, m, 8H; 4.26, m, 4H; 5.03, m, 2H; 5.74, m, 1H; 6.94, br d, J = 8.4 Hz, 1H; 7.02, br d, J = 8.4 Hz, 1H; 7.30, m, 15H; 7.51, m, 1H; 7.92, m, 2H; 8.02, m, 2H. MS (ES +ve) *m/z* 936 (100%) $[M]^+$.

Synthesis of Compound 29

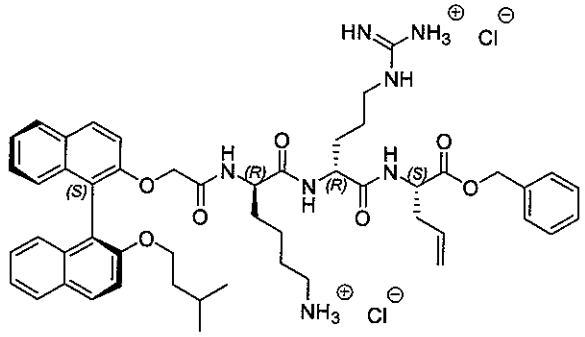
29(i)



This compound was prepared *via* Protocol 1, using **23(vii)** (121 mg, 0.14 mmol) and **1(ii)** (58 mg, 0.14 mmol) to afford **29(i)** as a white solid (114 mg, 65%) Mp 90-94 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.46, d, J = 6.3 Hz, 3H; 0.52, d, J = 6.3 Hz, 3H; 0.79, m, 4H; 0.92, m, 2H; 1.12, m, 2H; 1.26, s, 6H; 1.41, s, 9H; 1.52, m, 4H; 1.76, t, J = 5.7 Hz, 1H; 2.09, s, 3H; 2.49, m, 2H; 2.55, s, 3H; 2.56, s, 3H; 2.64, m, 2H; 2.92, m, 2H; 3.14, m, 2H; 3.95, m, 2H; 4.80, m, 5H; 5.05, m, 2H; 5.13, ABq, J = 12.3 Hz, 2H; 5.65, m, 1H; 6.18, d, J = 6.9 Hz, 1H; 6.29, br s, 2H; 6.47, m, 1H; 7.30, m, 13H; 7.90, m, 4H. MS (ES +ve) *m/z* 1274 (100%) $[M+NH_4]^+$.

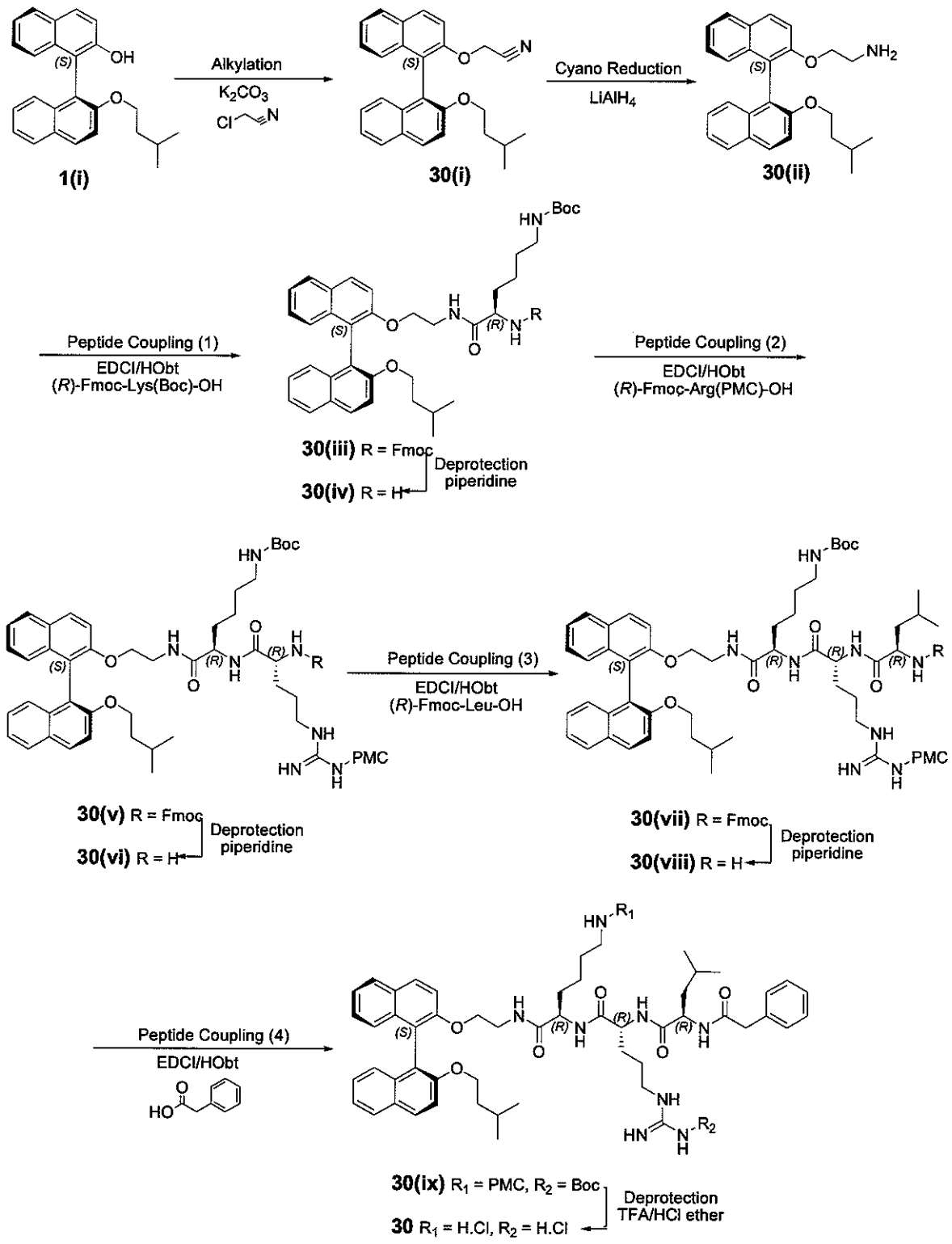
Compound 29



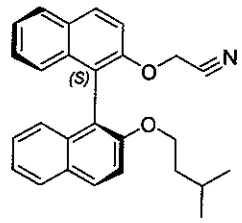
This compound was prepared *via* Protocol 3, using **29(i)** (114 mg, 0.091 mmol) to yield **29** as a highly hydroscopic cream solid (48 mg, 55%).

^{1}H NMR (500 MHz, CD_3OD) δ 0.47, d, J = 6.3 Hz, 3H; 0.53, d, J = 6.3 Hz, 3H; 0.96, m, 2H; 1.17, m, 2H; 1.24, m, 2H; 1.55, m, 4H; 1.71, m, 2H; 1.79, m, 2H; 2.55, m, 2H; 2.79, m, 2H; 3.14, m, 2H; 3.95, m, 1H; 4.14, m, 2H; 4.35, m, 1H; 4.49, m, 3H; 5.11, m, 4H; 5.74, m, 1H; 5.32, m, 13H; 7.96, m, 4H. MS (ES +ve) *m/z* 886 (5%) $[M]^{2+}$; 444 (100%).

General Synthetic Scheme for Reverse-Peptide Compounds (Example – Compound 30)



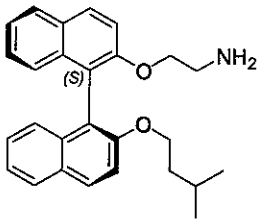
30(i)



To **1(i)** (10.0 g, 28 mmol) in dry acetone (200 ml) was added potassium carbonate (20.0 g, 145 mmol), chloroacetonitrile (3.0 ml, 47 mmol) and potassium iodide (2.50 g, 15 mmol). The resultant solution was heated at reflux for 18 hrs and then cooled down and filtered. Acetone was removed and the residue redissolved in ethyl acetate and water, and neutralized with 1M HCl. Organic extract was separated and water phase extracted with more ethyl acetate. Organic extracts were combined, dried ($MgSO_4$) and concentrated. Purification by column chromatography with 1-20% ethyl acetate/petrol gave the product **30(i)** as a colourless viscous oil (10.0 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.54, d, J = 6.0 Hz, 3H; 0.60, d, J = 5.7 Hz, 3H; 1.25, m, 2H; 3.89, m, 1H; 4.05, m, 1H; 7.22, m, 6H; 7.38, d, J = 9.0 Hz, 1H; 7.40, d, J = 9.3 Hz, 1H; 7.80, d, J = 7.5 Hz, 7.81, d, J = 8.1 Hz, 1H, 7.90, d, J = 9.0 Hz, 1H; 7.91, d, J = 9.3 Hz, 1H.

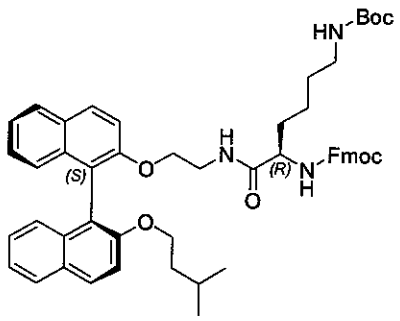
30(ii)



A solution of **30(i)** (10.00 g, 25 mmol) in dry ether (50 ml) was added dropwise to a suspension of lithium aluminium hydride (3.00g, 79 mmol) in ether (30 ml) during 2 hrs with ice bath cooling, and then stirred for 18 hrs at room temperature. Ether (100 ml) was added to the reaction mixture and then a potassium hydroxide solution in water (20%) was added until a white precipitate separated on the bottom of the flask. Ether solution was filtered to give the crude product that was purified by column chromatography to give the product **30(ii)** (8.05 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.55, d, J = 6.3 Hz, 3H; 0.60, d, J = 6.3 Hz, 3H; 0.87 m, 1H; 1.22, m, 4H; 2.64, br s, 2H; 3.95, m, 4H; 7.20, m, 4H; 7.31, m, 2H; 7.38, d, J = 8.7 Hz, 1H; 7.41, d, J = 8.7 Hz, 1H; 7.84, d, J = 8.1 Hz, 2H; 7.91, d, J = 8.7 Hz, 2H.

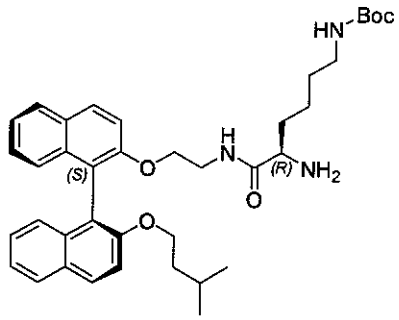
30(iii)



This compound was prepared *via* Protocol 1, using **30(ii)** (260 mg, 0.65 mmol) and (R)-Fmoc-Lys(Boc)-OH (305 mg, 0.65 mmol) to yield the desired product **30(iii)** as an off white solid (310 mg, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.41, d, J = 6.0 Hz, 3H; 0.53, d, J = 6.5 Hz, 3H; 1.27, m, 11H; 1.44, s, 9H; 2.85, m, 2H; 3.35, m, 2H; 3.81, m, 2H; 4.03, m, 2H; 4.12, m, 1H; 4.21, m, 1H; 4.38, m, 2H; 4.53, m, 1H; 5.38, br d, 1H; 5.78, br s, 1H; 7.09, d, J = 8.5 Hz, 1H; 7.25, m, 10H; 7.49, d, J = 9.0 Hz, 1H; 7.58, d, J = 7.0 Hz, 2H; 7.73, d, J = 7.5 Hz, 2H; 7.85, d, J = 8.0 Hz, 1H; 7.90, d, J = 7.5 Hz, 1H; 7.94, d, J = 9.0 Hz, 1H; 8.00, d, J = 9.0 Hz, 1H. MS (ES +ve) *m/z* 849 (100%) $[M+Na]^+$.

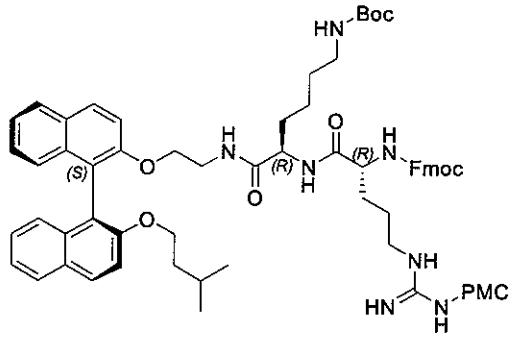
30(iv)



This compound was prepared *via* Protocol 2, using **30(iii)** (310 mg, 0.365 mmol) to yield the desired product **30(iv)** as an off white solid (172 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58, 3H, dd, J = 6.3, 1.5 Hz; 0.65, 3H, dd, J=6.6, 1.5 Hz; 1.51, m, 11H; 1.51, s, 9H; 2.93, m, 1H; 3.17, m, 3H; 3.30, m, 1H, 3.45, m, 1H; 3.92, m, 1H; 4.12, m, 3H; 4.79, br s, 1H; 6.73, m, 1H; 7.15, m, 1H; 7.25, m, 3H; 7.36, m, 2H; 7.48, m, 2H; 7.91, m, 2H; 7.99, m, 2H. MS (ES +ve) *m/z* 628 (100%).

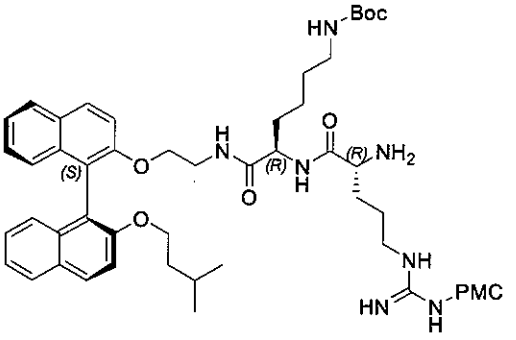
30(v)



This compound was prepared *via* Protocol 1, using **30(iv)** (172 mg, 0.274 mmol) and (*R*)-Fmoc-Arg(Pmc)-OH (182 mg, 0.274 mmol) to yield the desired product **30(v)** as an off white solid (165 mg, 47%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.41, d, J = 6.6 Hz, 3H; 0.52, d, J = 6.3 Hz, 3H; 1.25, s, 6H; 1.37, s, 9H; 1.30, m, 13H; 1.71, br t, 3H; 1.83, br s, 1H; 2.07, s, 3H; 2.55, s, 3H; 2.59, s, 3H; 2.84, m, 3H; 3.19, m, 4H; 3.81, m, 1H; 4.02, m, 3H; 4.12, m, 1H; 4.31, m, 3H; 4.84, br s, 1H, NH; 6.22, m, 5H, NH; 7.21, m, 10H; 7.48, m, 4H; 7.70, d, J = 7.5 Hz, 2H; 7.89, m, 4H. MS (ES +ve) *m/z* 1272 (5%) $[M+H]^+$.

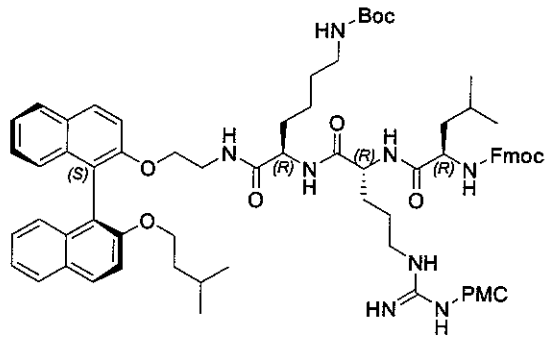
30(vi)



This compound was prepared *via* Protocol 2, using **30(v)** (165 mg, 0.130 mmol) to yield the desired product **30(vi)** as an off white solid (100 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.41, d, J = 6.6 Hz, 3H; 0.53, d, J = 6.3 Hz, 3H; 1.28, s, 6H; 1.41, s, 9H; 1.36, m, 14 H; 1.77, br t, 3H; 2.10, s, 3H; 2.56, s, 3H; 2.58, s, 3H; 2.92, m, 2H; 3.20, m, 3H; 3.37, m, 2H; 3.81, m, 1H; 4.08, m, 4H; 4.84, br s, 1H, NH; 6.22, m, 5H, NH; 7.23, m, 6H; 7.38, d, J = 9.0 Hz, 1H; 7.49, d, J = 9.0 Hz, 1H; 7.96, m, 4H.

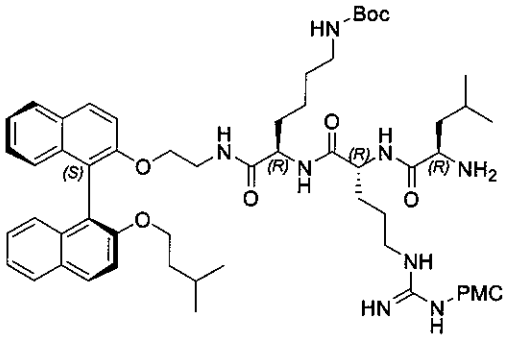
30(vii)



This compound was prepared *via* Protocol 1, using **30(vi)** (100 mg, 95 μmol) and (*R*)-Fmoc-Leu- OH (34 mg, 95 μmol) to yield the desired product **30(vii)** as an off white solid (120 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.41, br d, J = 6.0 Hz, 3H; 0.51, br d, J = 6.3 Hz, 3H; 0.88, br d, J = 5.7 Hz, 3H; 0.90, br d, J = 5.7 Hz, 3H; 1.24, s, 6H; 1.39, s, 9H; 1.56, m, 23H; 2.06, s, 3H; 2.51, s, 3H; 2.54, s, 3H; 2.71, s, 1H; 2.88, m, 2H; 3.11, m, 3H; 3.31, m, 1H; 3.77, m, 1H; 3.98, m, 2H; 4.11, m, 1H; 4.27, m, 2H; 4.54, br s, 1H, NH; 4.92, br s, 1H, NH; 6.35, m, 5H, NH; 7.26, m, 10H; 7.55, m, 4H; 7.70, d, J = 7.2 Hz, 2H; 7.89, m, 4H. MS (ES +ve) *m/z* 1385 (15%) $[M]^+$.

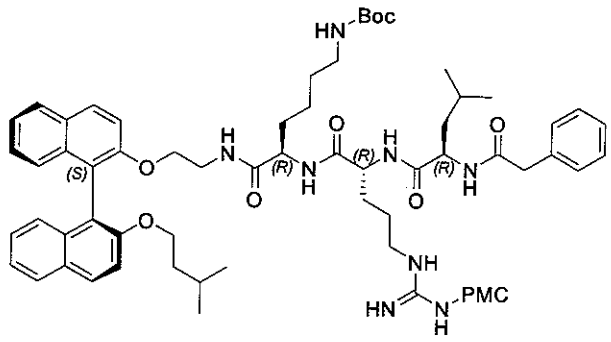
30(viii)



This compound was prepared *via* Protocol 2, using **30(vii)** (120 mg, 87 μmol) to yield the desired product **30(viii)** as an off white solid (80 mg, 79%).

MS (ES +ve) *m/z* 1163 (80%) $[M]^+$.

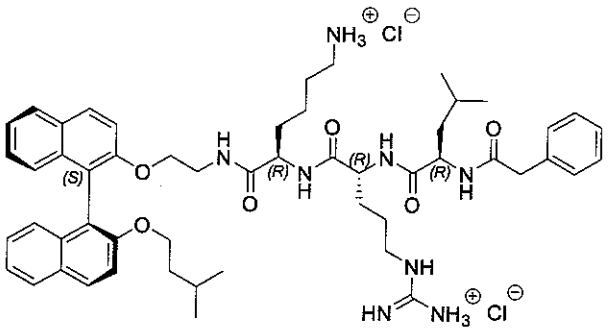
30(ix)



This compound was prepared *via* Protocol 1, using **30(viii)** (50 mg, 43 μmol) and phenylacetic acid (6 mg, 43 μmol) to yield the desired product **30(ix)** as a cream solid (50 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.43, d, J = 6.0 Hz, 3H; 0.53, d, J = 6.3 Hz, 3H; 0.80, br d, 3H; 0.83, br d, 3H; 1.28, s, 6H; 1.26, m, 14H; 1.41, s, 9H; 1.77, br t, 3H; 2.09, s, 3H; 2.53, s, 3H; 2.55, s, 3H; 2.90, m, 3H; 3.13, m, 2H; 3.29, m, 1H; 3.50, m, 2H; 3.62, s, 2H; 3.81, m, 1H; 3.99, m, 4H; 4.46, m, 2H; 4.86, br s, 1H, 6.25, m, 5H; 7.24, m, 11H, 7.89, m, 6H. MS (ES +ve) *m/z* 1303 (75%) $[M+Na]^+$.

Compound 30

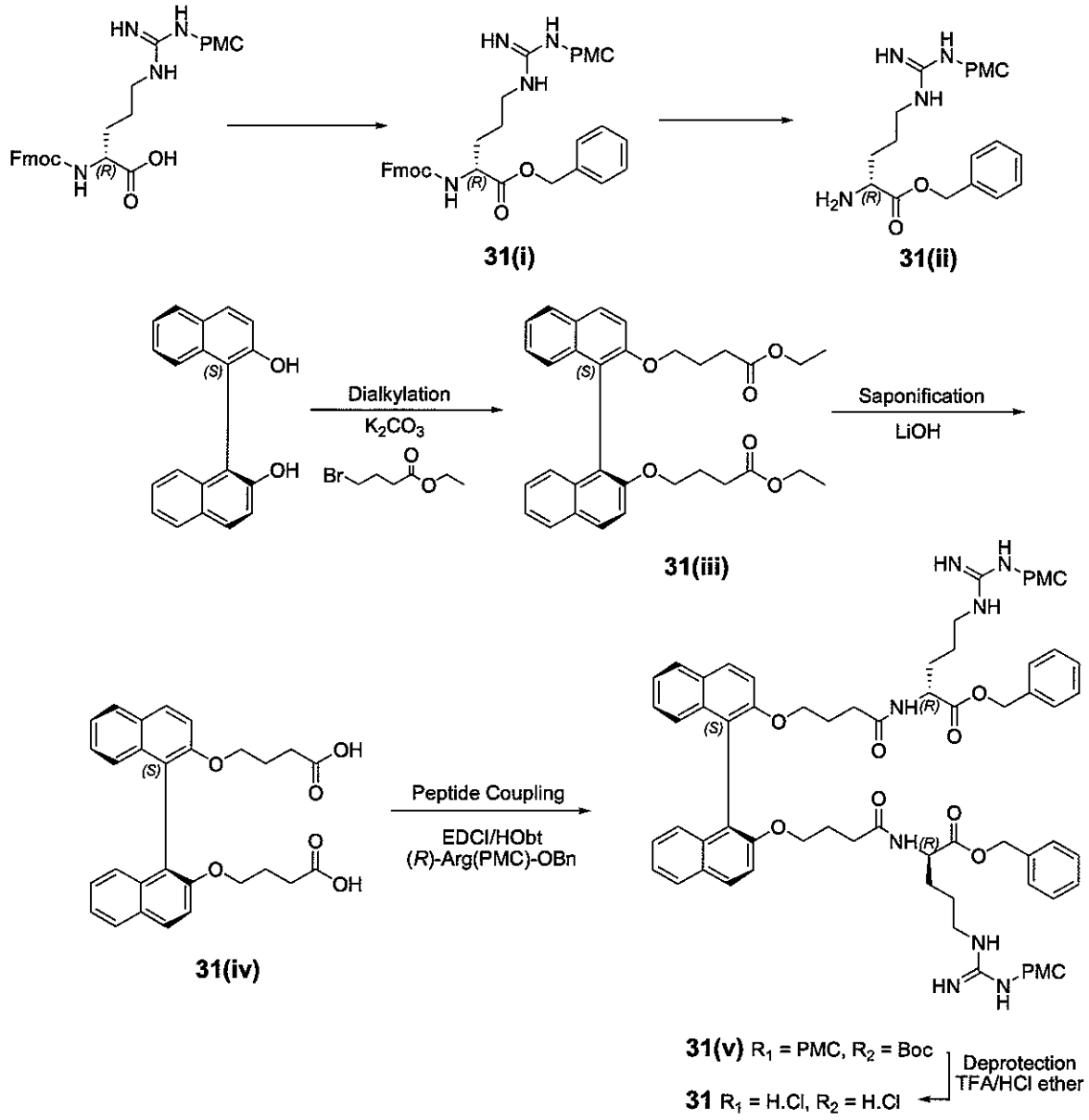


This compound was prepared *via* Protocol 3, using **30(ix)** (50 mg, 39 μmol) to yield the desired product **30** as a cream solid (20 mg, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48, d, J = 6.3 Hz, 3H; 0.57, d, J = 6.6 Hz, 3H; 0.88, br d, 3H; 0.95, br d, 3H; 1.19, m, 6H; 1.58, m, 7H; 2.82, br s, 2H; 3.27, m, 7H; 3.65, m, 2H; 3.87, m, 1H; 4.07, m, 4H; 4.27, m, 2H; 4.54, br s, 1H, NH; 4.92, br s, 1H, NH; 6.35, m, 5H, NH; 7.22, m, 10H; 7.55, m, 4H; 7.70, d, J = 7.2 Hz, 2H; 7.89, m, 4H. MS (ES +ve) *m/z* 915 (5%) $[M]^+$, 458 (100) $[M+2H]^{2+}$.

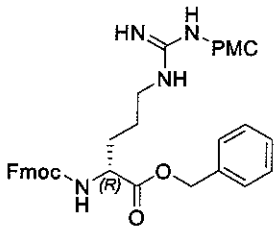
Compounds of Formula II

General Synthetic Scheme (Example - Compound 31)



Synthesis of Compound 31

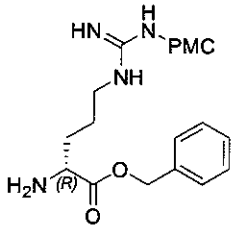
31(i)



To Fmoc-(*D*)-Arg(Pmc)-OH (400 mg, 604 mmol) suspended in DCM was added $SOCl_2$ (2 ml) at 0 °C. After stirring for an hour the solvent was removed and the resultant residue resuspended in DCM and BzOH (0.1 ml) added. The solution was then stirred overnight at 40 °C before being evaporated to dryness. The crude residue was then subjected to flash column chromatography over silica using 2%MeOH/DCM as the eluant to afford the desired product **31(i)** as a white solid (341 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29, s, 6H; 1.51, m, 2H; 1.74, m, 4H; 2.11, s, 3H; 2.58, m, 8H; 3.13, m, 2H; 4.14, m, 1H, 4.34, m, 3H; 5.11, s, 2H; 5.98, d, J = 9.2 Hz, NH; 6.16, br s, NH; 6.29, br s, NH; 7.30, m, 9H; 7.58, d, J = 7.5 Hz, 2H; 7.75, d, J = 7.2 Hz, 2H.

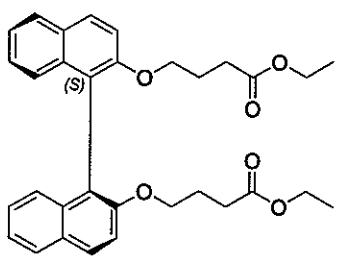
31(ii)



This compound was prepared *via* Protocol 2, using **31(i)** (341 mg, 0.463 mmol) to yield the desired product **31(ii)** as a white solid (159 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27, s, 6H; 1.51, m, 2H; 1.78, m, 4H; 2.07, s, 3H; 2.52, m, 8H; 3.11, m, 2H; 3.41, m, 1H; 5.07, s, 2H; 6.38, s, NH; 7.30, m, 5H.

31(iii)

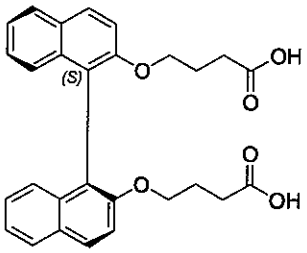


To a suspension of (*S*)-1,1'-binapth-2,2'-diol (1 g, 3.5 mmol) and anhydrous potassium carbonate (2.4 g, 5 equiv) dissolved in acetone (25 ml), was added ethyl bromobutyrate (1.15 ml, 2.3 equivalents) under an

N_2 atmosphere. The mixture was then heated at reflux for 24 hrs before being evaporated to dryness and the residue partitioned between ethyl acetate and water. The organic layer was then washed twice with water before being dried and evaporated to dryness to yield an oil **31(iii)** which was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17, t, J = 7.2 Hz, 6H; 1.70, m, 4H, 1.85, m, 4H; 3.98, m, 8H; 7.17, m, 4H; 7.30, m, 2H; 7.39, d, J = 8.8 Hz, 2H; 7.84, d, J = 8.0 Hz, 2H; 7.92, d, J = 8.8 Hz, 2H. MS (EI) *m/z* 514 (90%) $[M]^+$; 400 (80); 115 (100).

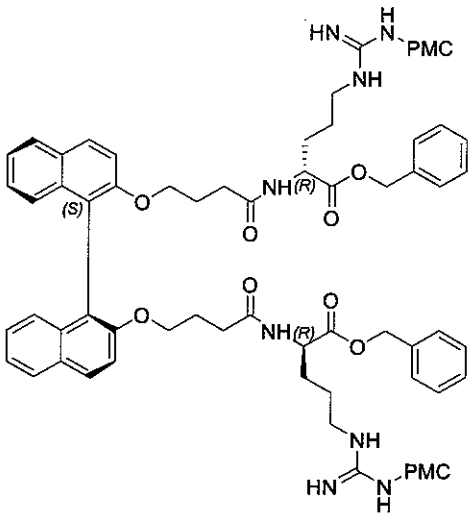
31(iv)



To **31(iii)** (598 mg, 1.52 mmol) dissolved in THF (30 ml), was added a solution of LiOH (250 mg, 10.5 mmol) in water (20 ml), After stirring at RT for 4 hrs, diethyl ether was added and the layers separated. The aqueous layer was then acidified with 1M HCl before being extracted with diethyl ether (3 x 20ml). The combined organic extracts were then dried ($MgSO_4$) and evaporated to dryness to yield the product **31(iv)** as a white foamy solid (342 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65, m, 4H, 1.82, m, 4H; 3.93, m, 2H; 3.98, m, 2H; 7.15, m, 4H; 7.27, m, 2H; 7.35, d, J = 9.1 Hz, 2H; 7.81, d, J = 8.2 Hz, 2H; 7.90, d, J = 8.8 Hz, 2H; 11.84, br s, 1H. MS (EI) *m/z* 458 (50%) $[M]^+$; 372 (25) $[M\text{-}CH_2CH_2CH_2COOH]^+$; 286 (100) $[M\text{-}2xCH_2CH_2CH_2COOH]^+$.

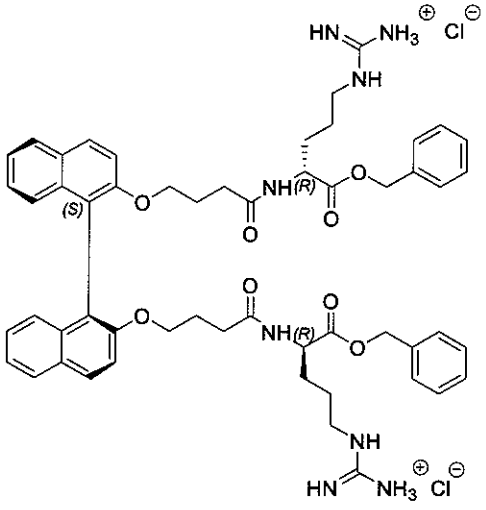
31(v)



This compound was prepared *via* protocol 1, using **31(ii)**(159 mg, 0.30 mmol) and **31(iv)**(68.7 mg, 0.15 mmol) to yield **31(v)** as a white solid (124 mg, 59%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25, s, 12H; 1.34, m, 8H; 1.70, m, 12H; 2.06, s, 6H; 2.51, m, 16H; 3.05, m, 4H; 3.75, m, 2H; 3.96, m, 2H; 4.34, m, 2H; 5.04, s, 4H; 6.11, br s, NH; 6.22, br s, NH; 6.42, d, J = 7.2 Hz; NH; 7.06, d, J = 8.5 Hz, 2H; 7.15, dist t, 2H; 7.25, m, 12H; 7.32, d, J = 9.1Hz; 2H; 7.79, d, J = 8.2 Hz, 2H; 7.85, d, J = 8.0 Hz, 2H. MS (ES +ve) *m/z* 742.7 (100%) $[M+H]^{2+}$.

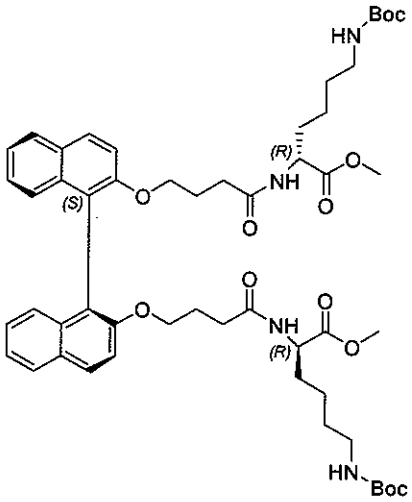
Compound 31



^{1}H NMR (300 MHz, CD_3OD) δ 1.58, m, 4H; 1.70, m, 6H; 1.85, m, 2H; 1.95, m, 4H; 3.12, m, 4H; 3.98, m, 4H; 4.38, m, 2H; 5.08, s, 4H; 7.06, m, 2H; 7.15, m, 2H; 7.25, m, 12H; 7.42, m, 2H; 7.83, m, 2H; 7.95, m, 2H. MS (ES +ve) *m/z* 951.2 (10%) $[M+H]^+$; 476.8 (100) $[M+H]^{2+}$.

Synthesis of Compound 32

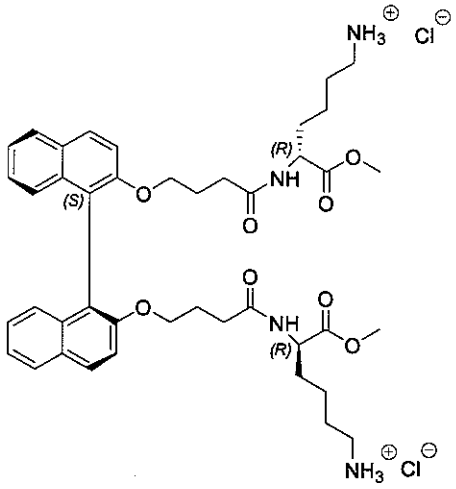
32(i)



This compound was prepared *via* protocol 1, using **31(iv)** (50 mg, 0.11 mmol) and (*D*)-lys(BOC)-OMe (68 mg, 0.23 mmol) to yield the desired product **32(i)** as an off white solid (90 mg, 87%). R_f = 0.44 (5% MeOH/DCM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18, m, 4H; 1.40, m, 4H; 1.43, s, 18H; 1.69, m, 12H; 3.01, m, 4H; 3.73, s, 6H; 3.87, m, 2H; 4.15, m, 2H; 4.47, m, 2H; 4.53, m, NH; 5.62, d, *J* = 8.2 Hz, NH; 7.19, m, 2H; 7.22, m, 2H; 7.35, m, 2H; 7.45, d, *J* = 9.1 Hz, 2H; 7.91, d, *J* = 8.2 Hz, 2H; 7.99, d, *J* = 8.8 Hz, 2H. MS (ES +ve) *m/z* 981.5 (30%) $[M+K]^+$; 968.6 (100) $[M+Na]^+$; 943.6 (10) $[M+H]^+$.

Compound 32

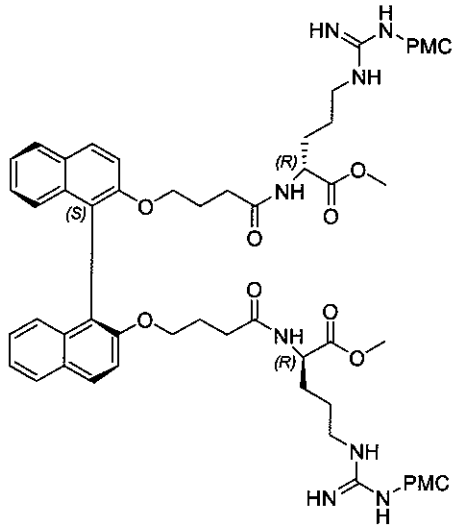


This compound was prepared *via* Protocol 3, using **32(i)** (88 mg, 0.093 mmol) to yield the desired product **32** as an off white solid (50 mg, 76%).

^{1}H NMR (300 MHz, CD_3OD) δ 1.39, m, 4H; 1.67, m, 12H; 1.96, m, 4H; 2.89, m, 4H; 3.35, s, 6H; 4.02, m, 4H, 4.30, m, 2H; 7.02, dist d; J = 8.0 Hz, 2H; 7.17, m, 2H; 7.29, m, 2H; 7.52, m, 2H; 7.87, m, 2H; 7.98, m, 2H. MS (ES +ve) *m/z* 743.3 (10%) $[M+H]^+$; 372.6 (100) $[M+2H]^{2+}$.

Synthesis of Compound 33

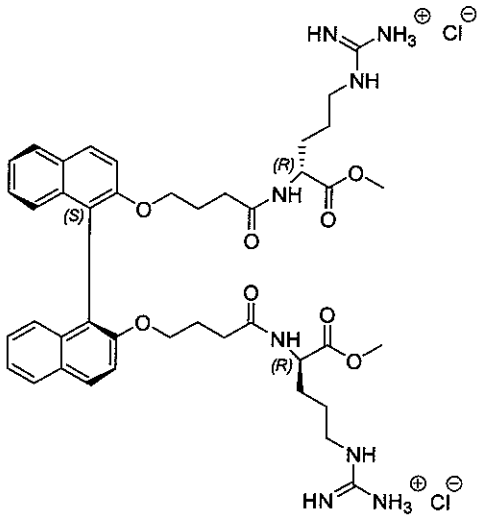
33(i)



This compound was prepared *via* Protocol 1, using (*D*)-arg(Pmc)-OMe (40 mg, 0.088 mmol) and **31(iv)** (20 mg, 0.044 mmol) to yield **33(i)** as a white solid (18 mg, 31%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28, s, 12H; 1.43, m, 4H; 1.77, m, 12H; 1.86, m, 4H; 2.09, s, 6H; 2.52, s, 6H; 2.55, s, 6H; 2.59, m, 2H; 3.12, m, 4H; 3.65, s, 6H; 3.84, m, 2H: 4.01, m, 2H; 4.37, m, 2H; 6.20, br s, NH; 6.42, m, NH; 7.02, dist d, NH; 7.09, d, J = 8.3 Hz, 2H; 7.19, dist t, 2H; 7.30, dist t, 2H; 7.39, d, J = 9.1 Hz, 2H; 7.85, m, 2H; 7.92, d, J = 9.1 Hz, 2H; 7.97, d, NH; 7.99, d, NH.

Compound 33

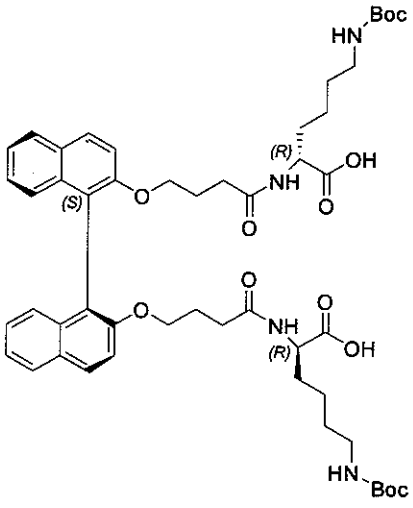


This compound was prepared *via* Protocol 3, using **33(i)** (20 mg, 0.015 mmol) to yield **33** as a white solid (9 mg, 64%).

^{1}H NMR (300 MHz, CD_3OD) δ 1.34, m, 10H; 1.61, m, 6H; 2.93, m, 4H; 3.46, s, 6H; 3.62, m, 2H; 3.75, m, 2H; 4.05, m, 2H; 6.53, m, 2H; 6.74, m, 4H; 7.16, d, J = 8.8 Hz, 2H; 7.42, d, J = 7.7 Hz, 2H; 7.57, d, J = 8.3 Hz, 2H. MS (ES +ve) *m/z:* 401 (100%) $[M+2H]^{2+}$.

Synthesis of Compound 34

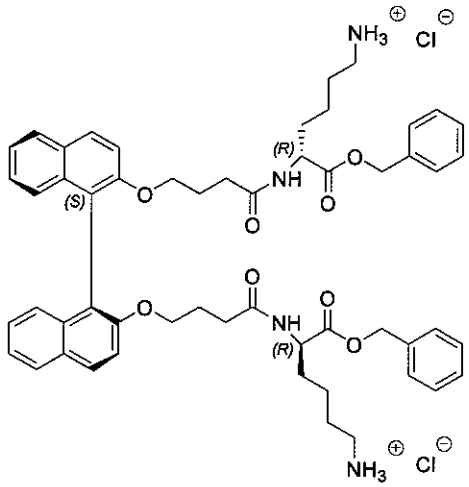
34(i)



To **32(i)** (200 mg, 0.212 mmol) dissolved in THF (20 ml), was added a solution of LiOH (75 mg, 3.14 mmol) in water (10 ml). After stirring at RT for 90 minutes, ethyl acetate was added and the layers separated. The aqueous layer was then acidified with a dilute potassium bisulphate solution. This was then extracted with DCM (3 x 20ml) and the combined organic extracts then dried and evaporated to dryness to yield the product **34(i)** as a white foamy solid (178mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24, m, 4H; 1.40, s, 18H; 1.44, m, 4H; 1.76, m, 12H; 3.00, m, 4H; 3.77, m, 2H; 4.09, m, 2H; 4.46, m, 2H; 4.85, m, NH; 6.29, m, NH; 7.16, m, 2H; 7.21, m, 2H; 7.28, m, 2H; 7.30, d, J = 9.0 Hz, 2H; 7.84, d, J = 7.8 Hz, 2H; 7.87, d, J = 8.7 Hz, 2H. MS (ES +ve) *m/z* 937.2 (15%) $[M+Na]^+$; 915.2 (15) $[M+H]^+$. MS (ES -ve) *m/z* 913.1 (100%) $[M-H]^-$.

Compound 34

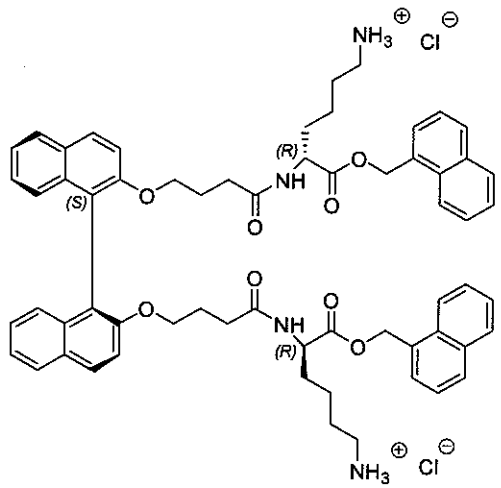


This compound was prepared *via* Protocol 4, using **34(i)** (120 mg, 0.131 mmol), triphenyl phosphine (73 mg, 0.278 mmol), DIAD (0.055 ml, 0.275 mmol) and BzOH (0.05 ml, 0.275 mmol). The BOC- protected intermediate **34(ii)** eluted at the same time as a reaction by product, and so this material was then deprotected *via* protocol 3 to yield the desired product **34** as a pale yellow hydrochloride salt (101 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32, m, 4H; 1.68, m, 10H; 1.79, m, 2H; 1.93, m, 4H; 2.82, m, 4H; 3.97, m, 4H; 4.33, m, 2H; 5.11, ABq, J = 12.3 Hz, 4H; 7.01, dist d, J = 8.5 Hz, 2H; 7.14, app t, 2H; 7.31, m, 14H; 7.48, m, 2H; 7.62, m, 2H; 7.85, d, J = 7.9 Hz, 2H; 7.94, d, J = 8.8 Hz, 2H. MS (ES +ve) *m/z* 895.5 (10%) $[M+H]^+$; 825.4 (40) $[M-lys]^+$; 448.7 (100) $[M+2H]^{2+}$.

Synthesis of Compound 35

Compound 35

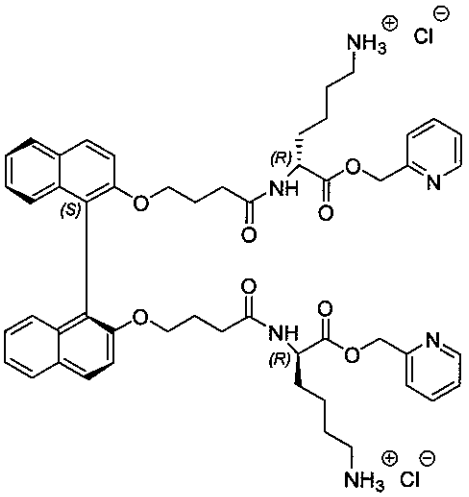


This compound was prepared *via* Protocol 4, using **34(i)** (60 mg, 0.066 mmol), triphenylphosphine (73 mg, 278 mmol), DIAD (0.055 ml, 0.275 mmol) and 1-naphthalene methanol (45 mg, 0.0.28 mmol). The BOC- protected intermediate **35(i)** eluted at the same time as a reaction by product, and so this material was then deprotected *via* Protocol 3 to yield the desired product **35** as a pale yellow hydrochloride salt (58 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10, m, 4H; 1.40, m, 4H; 1.51, m, 4H; 1.63, m, 4H; 1.76, m, 4H; 2.58, m, 4H; 3.73, m, 2H; 3.80, m, 2H; 4.19, m, 2H; 6.90, dist t, 2H; 7.00, t, J = 7.1 Hz, 2H; 7.13, dist t, 2H; 7.30, m, 4H; 7.37, m, 6H; 7.38, m, 8H, 7.84, d, J = 8.0 Hz; 2H. MS (ES +ve) *m/z* 995.5 (10%) $[M+H]^+$; 825.4 (40) $[M\text{-lys}]^+$; 448.7 (100) $[M+2H]^{2+}$.

Synthesis of Compound 36

Compound 36

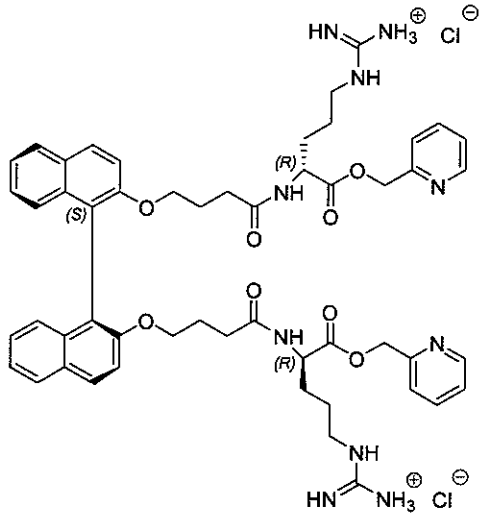


The crude PMC protected precursor **36(i)** was prepared *via* Protocol 1 using **34(i)** (120 mg, 0.131 mmol) and 2-pyridyl carbinol (0.026 ml) to yield an impure light brown solid. This was then deprotected *via* protocol 3 to yield **36** as an off white solid (68 mg, 54%).

^{1}H NMR (300 MHz, CD_3OD) δ 1.41, m, 4H; 1.65, m, 8H; 1.95, m, 4H; 2.87, m, 4H; 3.97, m 4H; 4.31, m, 2H; 5.41, ABq, J = 14.4 Hz, 2H; 5.52, ABq, J = 14.4 Hz, 2H; 6.96, dist d, 2H; 7.14, dist t, 2H; 7.26, dist t, 2H; 7.46, dist d, 2H; 7.83, d, J = 7.9 Hz, 2H; 7.92, m, 4H; 8.00, dist d, 2H; 8.47, dist t 2H, 8.76, br d, 2H. MS (ES +ve) *m/z* 449.4 (100%) $[M+2H]^{2+}$.

Synthesis of Compound 37

Compound 37

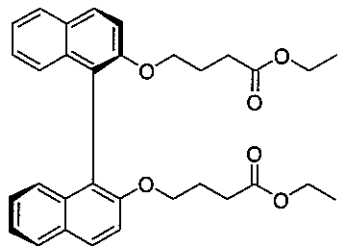


To **33(i)** (200 mg, 0.2 mmol) dissolved in THF (20 ml), was added a solution of LiOH (75 mg, 3.1 mmol) in water (10 ml). After stirring at RT for 90 minutes, ethyl acetate was added and the layers separated. The aqueous layer was then acidified with a dilute potassium bisulphate solution. This was then extracted with DCM (3 x 20ml) and the combined organic extracts then dried and evaporated to dryness to yield the product **37(i)** as a white foamy solid (145 mg, 88%). The protected precursor was prepared *via* Protocol 1 using **37(i)** (60 mg, 0.046 mmol) and 2-pyridyl carbinol (0.02 ml) to yield **37(ii)** as an impure light brown solid (MS (ES +ve) *m/z* 1485.5 (10%) $[M+H]^+$; 743.3 (20) $[M+H]^{2+}$). This was then deprotected *via* Protocol 3 to yield **37** as an off white solid (28 mg, 64%).

^{1}H NMR (300 MHz, CD_3OD) δ 1.69, m, 10H; 2.00, m, 6H; 3.20, m, 4H; 4.00, m, 4H; 4.39, m, 2H; 5.44, ABq, J = 14.9 Hz, 2H; 5.53, ABq, J = 14.9 Hz, 2H; 6.99, m, 2H; 7.16, m, 2H; 7.28, m, 2H; 7.50, m, 2H; 7.94, m, 8H; 8.47, m, 2H; 8.78, m, 2H. MS (ES +ve) *m/z* 477.5 (100%) $[M+2H]^{2+}$.

Synthesis of Compound 38

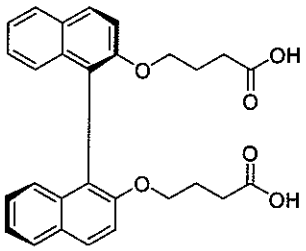
38(i)



To a suspension of (*R*)-1,1'-binapth-2,2'-ol (1 g, 3.5 mmol) and anhydrous potassium carbonate (2.4 g, 5 equiv) dissolved in acetone (25 ml), was added ethyl bromobutyrate (1.15 ml, 2.3 equivalents) under an N_2 atmosphere. The mixture was then heated at reflux for 4 days before being evaporated to dryness and the residue partitioned between ethyl acetate and water. The organic layer was then washed twice with water before being dried and evaporated to dryness. The crude residue was subjected to flash column chromatography to yield the desired compound **38(i)** (1.05 g, 68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15, t, *J* = 7.2 Hz, 6H; 1.70, m, 4H, 1.86, m, 4H; 3.98, m, 8H; 7.16, m, 4H; 7.27, m, 2H; 7.38, d, *J* = 9.1 Hz, 2H; 7.82, d, *J* = 8.2 Hz, 2H; 7.90, d, *J* = 9.1 Hz, 2H.

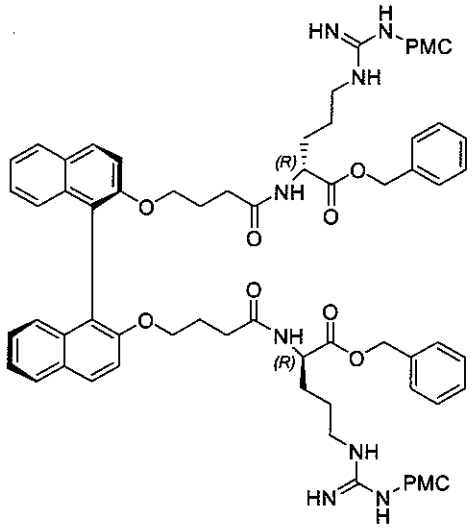
38(ii)



To **38(i)** (1.0 g, 1.94 mmol) dissolved in THF (30 ml), was added a solution of LiOH (300 mg, 12.5 mmol) in water (20 ml), After stirring at RT overnight, diethyl ether was added and the layers separated. The aqueous layer was then acidified with a dilute HCl solution. This was then extracted with diethyl ether (3 x 20ml), the combined organic extracts were then dried and evaporated to dryness to yield **38(ii)** as a white foamy solid (646 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71, m, 4H, 1.90, m, 4H; 3.91, m, 2H; 3.99, m, 2H; 7.11, dist d, *J* = 8.3 Hz, 2H; 7.18, m, 2H; 7.27, m, 2H; 7.37, d, *J* = 8.8 Hz, 2H; 7.83, d, *J* = 8.0 Hz, 2H; 7.90, d, *J* = 8.8 Hz, 2H; 9.34, bs s, COOH.

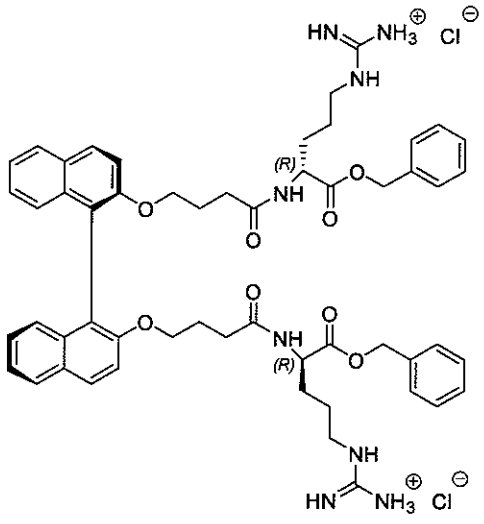
38(iii)



This compound was prepared *via* Protocol 1, using **31(ii)** (125 mg, 0.236 mmol) and **38(ii)** (45 mg, 0.098 mmol) to yield **38(iii)** as a white solid (123 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25, s, 12H; 1.34, m, 4H; 1.70, m, 16H; 2.06, s, 6H; 2.51, m, 16H; 3.04, m, 4H; 3.79, m, 2H; 3.96, m, 2H; 4.37, m, 2H; 5.04, s, 4H; 6.05, br s, NH; 6.21, br s, NH; 7.06, d, J = 8.5 Hz, 2H; 7.15, dist t, 2H; 7.25, m, 12H; 7.32, d, J = 9.1Hz; 2H; 7.79, d, J = 7.9 Hz, 2H; 7.87, d, J = 9.1 Hz, 2H. MS (ES +ve) *m/z* 1483.4 (10%) $[M+H]^+$; 742.4 (20) $[M+H]^{2+}$.

Compound 38

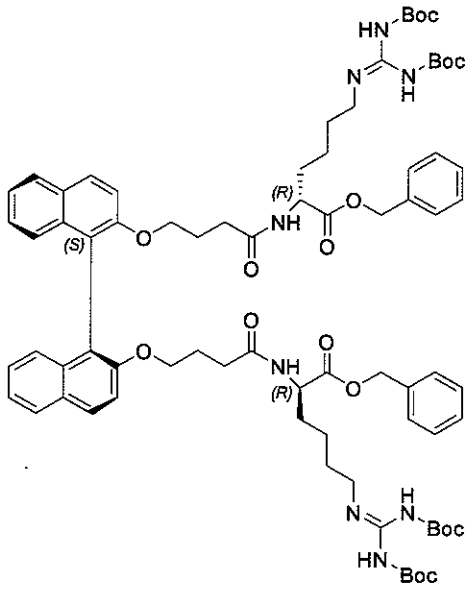


This compound was prepared *via* Protocol 3, using **38(iii)** (120 mg, 0.081 mmol) to yield **38** as a white solid (71 mg, 86%).

^{1}H NMR (300 MHz, CD_3OD) δ 1.56, m, 4H; 1.67, m, 6H; 1.83, m, 2H; 1.93, m, 4H; 3.12, m, 4H; 3.93, m, 2H; 4.02, m, 2H; 4.34, m, 2H; 5.07, ABq, *J* = 12.3 Hz, 2H; 5.12, ABq, *J* = 12.3 Hz, 2H; 7.00, m, 2H; 7.12, m, 2H; 7.27, m, 12H; 7.46, m, 2H; 7.83, d, *J* = 7.9 Hz, 2H; 7.93, d, *J* = 9.1 Hz, 2H. MS (ES +ve) *m/z* 476.5 (100%) $[M+H]^{2+}$.

Synthesis of Compound 39

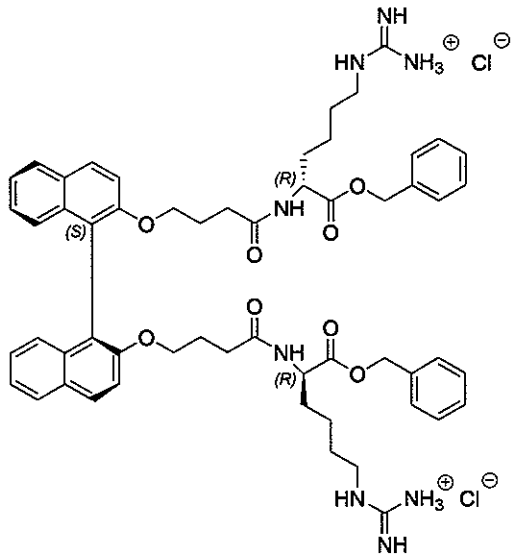
39(i)



To **34** (20 mg, 0.021 mmol) in DCM (2 ml) was added triethylamine (0.09 ml) and N,N'-bis(tert-butoxycarbonyl)-N''-triflyl guanadine (25 mg, 0.062 mmol) under N_2. The solution was allowed to stir overnight before being evaporated to dryness. The resultant residue was then subjected to flash column chromatography (over silica), using 2% MeOH/DCM as the eluant to yield the desired compound **39(i)** as a pale yellow oil (23 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18, m, 4H; 1.48, m, 40H; 1.59, m, 4H; 1.70, m, 8H; 3.27, m, 4H; 3.82, m, 2H; 4.09, m, 2H; 4.45, m, 2H; 5.15, ABq, *J* = 12.3 Hz, 4H; 5.54, d, *J* = 8.2 Hz, NH; 7.16, dist d, *J* = 8.2 Hz, 2H; 7.24, m, 2H; 7.31, m, 11H; 7.49, m, 1H; 7.62, m, 2H; 7.87, d, *J* = 7.9 Hz, 2H; 7.94, d, *J* = 9.1 Hz, 2H; 8.28, m, NH. MS (ES +ve) *m/z* 1401.7 (40%) $[M+Na]^+$; 1379 (100) $[M+H]^+$.

Compound 39

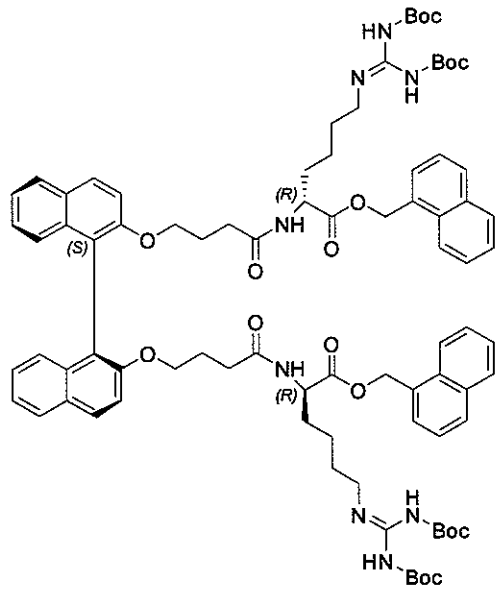


This compound was prepared *via* Protocol 3, using **39(i)** (20 mg, 0.014 mmol) to yield the desired product **39** as a light brown solid (15 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18, m, 4H; 1.48, m, 40H; 1.59, m, 4H; 1.70, m, 8H; 3.27, m, 4H; 3.82, m, 2H; 4.09, m, 2H; 4.45, m, 2H; 5.15, ABq, J = 12.3 Hz, 4H; 5.54, d, J = 8.2 Hz, NH; 7.16, dist d, J = 8.2 Hz, 2H; 7.24, m, 2H; 7.31, m, 11H; 7.49, m, 1H; 7.62, m, 2H; 7.87, d, J = 7.9 Hz, 2H; 7.94, d, J = 9.1 Hz, 2H; 8.28, m, NH. MS (ES +ve) *m/z* 490.5 (60%) $[M+2H]^{2+}$; 452.4 (100) $[M+H-Ph]^{2+}$; 414.5 (80) $[M+2H-2Ph]^{2+}$.

Synthesis of Compound 40

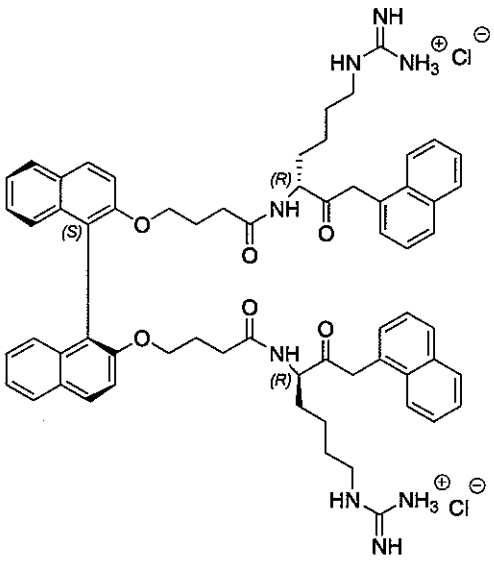
40(i)



To **35** (47 mg, 0.044 mmol) in DCM (2 ml) was added triethylamine (0.19 ml) and N,N'-bis(tert-butoxycarbonyl)-N''-triflylguanadine (53 mg, 0.13 mmol) under N2. The solution was allowed to stir overnight before being evaporated to dryness. The resultant residue was then subjected to flash column chromatography (over silica), eluting with 2% MeOH/DCM to yield the desired compound **40(i)** as an off white solid (40 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01, m, 2H; 1.32, m, 2H; 1.48, m, 44H; 1.54, m, 4H; 1.70, m, 8H; 3.14, m, 4H; 3.73, m, 2H; 4.00, m, 2H; 4.42, m, 2H; 5.51, d, J = 7.9 Hz, NH; 5.61, ABq, J = 12.3 Hz, 4H; 7.12, dist d, J = 7.9 Hz, 2H; 7.26, m, 6H; 7.53, m, 8H; 7.80, m, 4H; 7.88, m, 4H; 7.97, dist d, J = 7.9 Hz, 2H; 8.24, m, NH. MS (ES +ve) *m/z* 1501.8 (10%) [M+Na]+; 1479.7 (10) $[M+H]^+$; 740.5 (20) $[M+2H]^{2+}$.

Compound 40

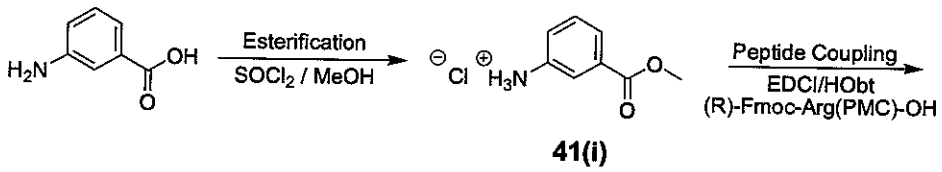


This compound was prepared *via* Protocol 3, using **40(i)** (38 mg, 0.026 mmol) to yield the desired product **40** as a light brown solid (18 mg, 61%).

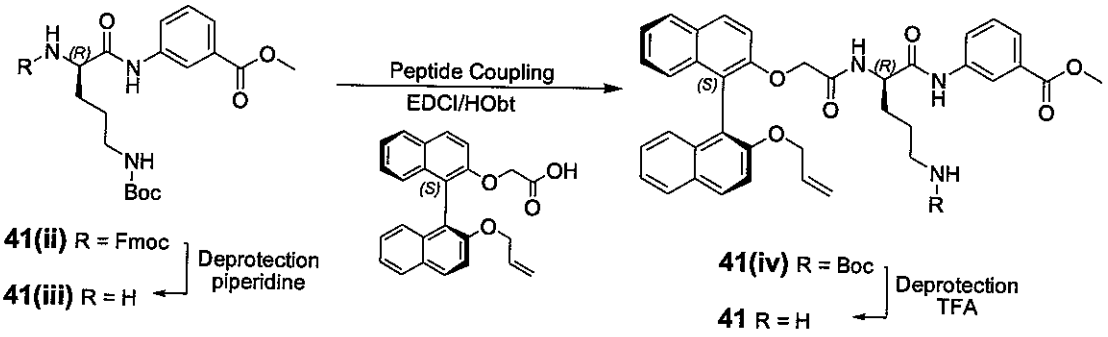
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32, m, 6H; 1.62, m, 10H; 1.92, m, 4H; 2.95, m, 2H; 3.10, m, 2H; 3.97, m, 4H; 4.30, m, 2H; 5.57, m, 4H; 7.02, m, 2H; 7.17, m, 2H; 7.229, m, 2H; 7.50, m, 10H; 7.88, m, 10H. MS (ES +ve) *m/z* 540.4 (20%) $[M+2H]^{2+}$; 477.3 (95) $[M+H\text{-nap}]^{2+}$; 414.4 (100) $[M+H\text{-}2nap]^{2+}$.

Compounds of Formula III

General Synthetic Scheme (Example - Compound 41)

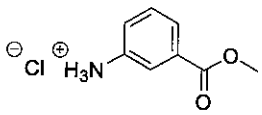


41(i)



Synthesis of Compound 41

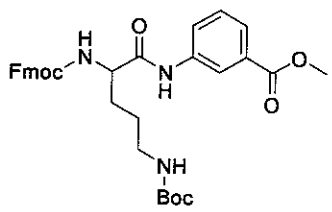
41(i)



To a suspension of 3-aminobenzoic acid (1.03 g mg, 7.52 mmol) in MeOH (80 ml) at 0 °C was added dropwise thionyl chloride (5 ml). The resulting solution was allowed to stir for 16 h before the solvent was removed by evaporation and the product precipitated with diethyl ether. The diethyl ether was removed by evaporation to yield the title compound **41(i)** as a white solid (1.38 g, 98%). Mp 176-178 °C.

^{1}H NMR (300 MHz, D_2O) δ 3.66, s, 3H; 7.37, m, 1H; 7.42, m, 1H; 7.71, m, 1H; 7.75, dt, J = 1.8, 3.3, 7.2 Hz, 1H. MS (CI) *m/z* 152 (100%) $[M]^+$.

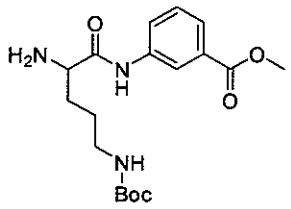
41(ii)



This compound was prepared *via* Protocol 1, from **41(i)** (220 mg, 2.27 mmol) and (*R*)-Fmoc-Lys(Boc)-OH (578 mg, 1.27 mmol) to afford **41(ii)** as a white solid (277 mg, 36%). Mp 96-98°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42, s, 9H; 1.60, m, 2H; 1.78, m, 2H; 3.08, m, 2H; 3.86, s, 3H; 4.17, t, J = 6.9 Hz, 1H; 4.36, d, J = 6.9 Hz, 2H; 4.63, m, 1H; 6.03, d, J = 8.1 Hz, 2H; 7.26, m, 2H; 7.36, m, 2H; 7.56, d, J = 7.2, Hz, 2H; 7.72, d, J = 7.8 Hz, 2H; 7.77, m, 1H; 7.88, d, J = 8.1 Hz, 1H; 8.17, s, 1H; 9.15, s, 1H. MS (ES +ve) *m/z* 610 (100%) $[M+Na]^+$; 588 (70) $[M+H]^+$.

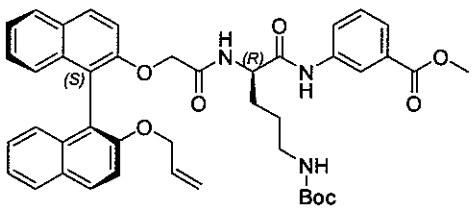
41(iii)



This compound was prepared *via* Protocol 2, from **41(ii)** (555 mg, 0.95 mmol) to yield **41(iii)** as a colourless viscous oil (285 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43, s, 9H; 1.65, m, 4H; 2.08, m, 2H; 3.19, m, 2H; 3.69, m, 1H; 3.91, s, 3H; 5.11, m, 1H; 7.36, m, 1H; 7.51, t, J = 7.8 Hz, 1H; 7.84, t, J = 1.8 Hz, 1H; 8.04, m, 1H. MS (ES +ve) *m/z* 264 (100%) $[M-Boc+H]^+$.

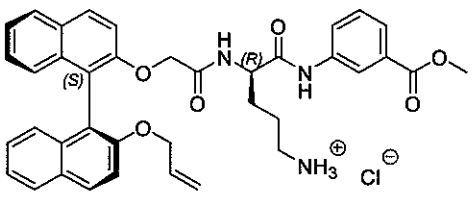
41(iv)



This compound was prepared *via* Protocol 1, from **22(ii)** (288 mg, 0.75 mmol) and **41(iii)** (275 mg, 0.75 mmol) to afford **41(iv)** as a white foam (434 mg, 79%). Mp 70°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04, m, 2H; 1.44, s, 9H; 1.62, m, 2H; 2.96, m, 2H; 3.87, s, 3H; 4.55, m, 5H; 4.94, m, 2H; 5.69, m, 1H; 6.45, d, J = 8.1 Hz, 1H; 7.85, m, 8H; 7.91, m, 7H; 9.08, s, 1H. MS (ES +ve) *m/z* 732 (50%) $[M+H]^+$; 351 (100).

Compound 41

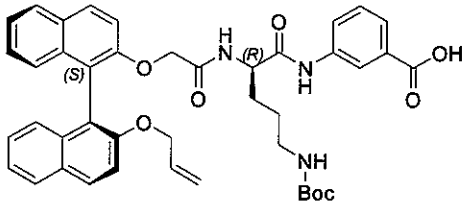


This compound was prepared *via* Protocol 3, from **41(iv)** (56 mg, 0.077 mmol) to yield **41** as a highly hydroscopic cream solid (38 mg, 74%).

^{1}H NMR (300 MHz, CD_3OD) δ 1.30, m, 2H; 1.67, m, 2H; 2.76, m, 2H; 3.93, s, 3H; 4.59, m, 5H; 4.90, m, 2H; 5.71, m, 1H; 7.06, m, 2H; 7.34, m, 8H; 7.75, m, 2H; 7.92, m, 2H; 8.02, m, 2H. MS (ES +ve) *m/z* 632 (100%) $[M]^+$.

Synthesis of Compound 42

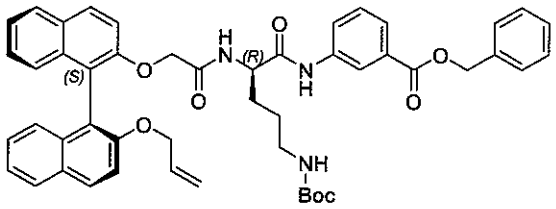
42(i)



To a solution of **41(iv)** (370 mg, 0.51 mmol) in THF/water, 3:1 (8 ml) was added lithium hydroxide monohydrate (43 mg, 0.51 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 ml) and the THF was removed by evaporation before the remaining aqueous layer was washed with diethyl ether (40 ml) to remove unreacted starting material. The aqueous phase was acidified with dilute potassium bisulfate and the resulting precipitate was extracted with DCM (3 x 40 ml). The combined DCM fractions were dried and evaporated to yield the title compound **42(i)** as a white solid (350 mg, 96%). Mp 86-90°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15, m, 2H; 1.49, s, 9H; 1.65, m, 2H; 3.03, m, 2H; 4.59, m, 5H; 5.01, m, 2H; 5.71, m, 1H; 6.63, d, J = 9.0 Hz, 1H; 7.34, m, 8H; 7.97, m, 7H; 9.26, s, 1H; 9.70, br s, 1H. MS (ES +ve) *m/z* 740 (100%) $[M+Na]^+$; 718 (20) $[M+H]^+$.

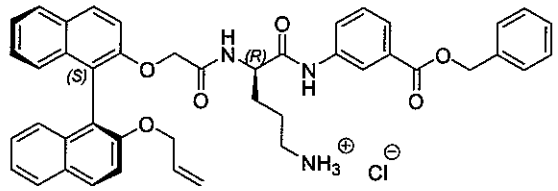
42(ii)



To a solution of **42(i)** (40 mg, 0.056 mmol) in acetone (2 ml) was added K_2CO_3 (17 mg, 0.12 mmol) and benzyl bromide (21 mg, 0.12 mmol). The resulting suspension was allowed to stir for 16 h before concentration and purification by flash column chromatography (5% MeOH/DCM) to yield the title compound **42(ii)** as a white solid (36 mg, 80%). Mp 145-152°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05, m, 2H; 1.42, s, 9H; 1.52, m, 2H; 3.00, m, 2H; 4.50, m, 5H; 4.87, m, 2H; 5.30, s, 2H; 5.68, m, 1H; 6.27, d, J = 8.4 Hz, 1H; 7.30, m, 11H; 7.90, m, 7H; 8.63, s, 1H. MS (ES +ve) *m/z* 808 (30%) $[M+H]^+$; 414 (100%).

Compound 42

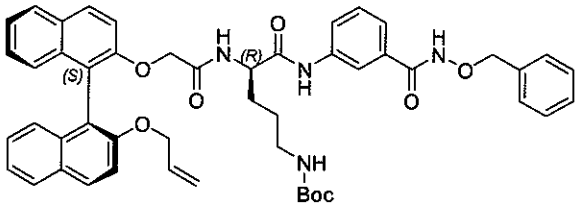


This compound was prepared *via* Protocol 3, from **42(ii)** (35 mg, 0.043 mmol) to yield **42** as a highly hydroscopic cream solid (30 mg, 93%).

^{1}H NMR (500 MHz, CD_3OD) δ 1.22, m, 2H; 1.59, m, 2H; 2.68, m, 2H; 4.46, m, 5H; 4.79, m, 2H; 5.27, s, 2H; 5.58, m, 1H; 7.28, m, 11H; 7.80, m, 7H; 8.25, s, 1H. MS (ES +ve) *m/z* 750 (35%) $[M+K]^+$; 360 (100%).

Synthesis of Compound 43

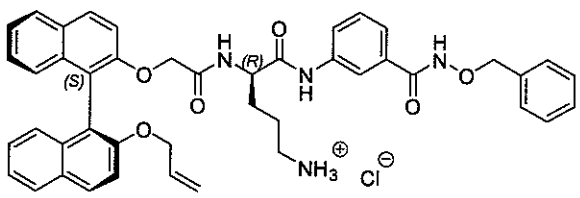
43(i)



This compound was prepared *via* Protocol 1, from **42(i)** (91 mg, 0.127 mmol) and *O*-benzylhydroxylamine (20 mg, 1.27 mmol) to afford **43(i)** as a white solid (82 mg, 78%). Mp 141-144°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06, m, 2H; 1.43, s, 9H; 1.54, m, 2H; 2.93, m, 2H; 4.30, m, 1H; 4.54, m, 4H; 4.66, t, J = 5.1 Hz, 1H; 4.95, m, 4H; 5.66, m, 1H; 6.41, d, J = 7.5 Hz, 1H; 7.31, m, 10H; 7.88, m, 2H; 7.97, m, 2H; 9.14, s, 1H. MS (ES +ve) *m/z* 823 (100%) $[M+H]^+$.

Compound 43

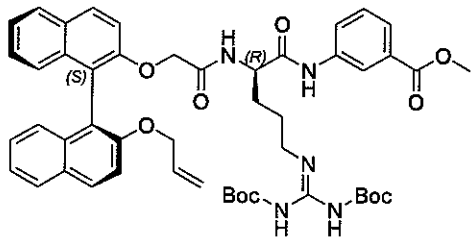


This compound was prepared *via* Protocol 3, from **43(i)** (73 mg, 0.089 mmol) to yield **43** as a hydroscopic white solid (67 mg, 99%).

^{1}H NMR (500 MHz, CD_3OD) δ 1.15, m, 2H; 1.62, m, 2H; 3.23, m, 2H; 3.90, m, 1H; 4.46, m, 6H; 4.90, m, 2H; 5.63, m, 1H; 7.50, m, 20H. MS (ES +ve) *m/z* 723 (20%) $[M]^+$; 360 (100%).

Synthesis of Compound 44

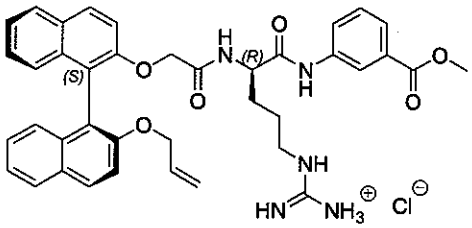
44(i)



To a solution of **41** (32 mg, 0.048 mmol) in DCM (3 ml) was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (28 mg, 0.072 mmol), triethylamine (7.3 mg, 0.072 mmol). The resulting solution was allowed to stir for 16 h under a nitrogen atmosphere. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the title compound **44(i)** as a white solid (41 mg, 98%). Mp 74-76°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14, m, 2H; 1.46, s, 9H; 1.51, s, 9H; 1.65, m, 2H; 3.26, m, 2H; 3.91, s, 3H; 4.34, m, 1H; 4.48, m, 2H; 4.57, d, J = 3.3 Hz, 2H; 4.67, m, 2H; 5.59, m, 1H; 6.34, d, J = 8.4 Hz, 1H; 7.26, m, 8H; 7.77, m, 7H; 8.27, br s, 1H; 8.55, s, 1H. MS (ES +ve) *m/z* 896 (100%) $[M+Na]^+$; 875 (95%) $[M+H]^+$.

Compound 44

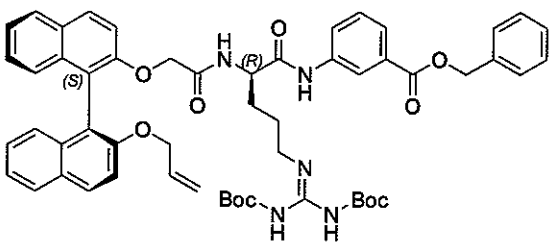


This compound was prepared *via* Protocol 3, from **44(i)** (49 mg, 0.056 mmol) to yield **44** as a cream solid (32 mg, 0.045 mmol, 80%). Mp 124-126°C.

^{1}H NMR (300 MHz, CD_3OD) δ 1.17, m, 2H; 1.63, m, 2H; 3.01, m, 2H; 3.92, s, 3H; 4.52, m, 5H; 4.97, m, 2H; 5.73, m, 1H; 7.07, m, 2H; ; 7.32, m, 9H; 7.90, m, 4H; 8.28, s, 1H. MS (ES +ve) *m/z* 698 (25%) $[M+Na]^+$; 413 (100%).

Synthesis of Compound 45

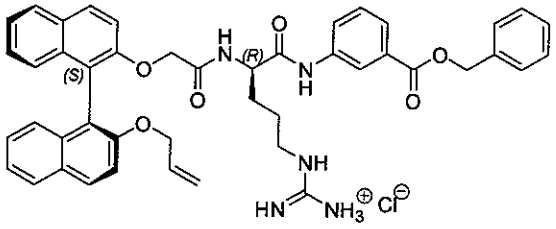
45(i)



To a solution of **42** (20 mg, 0.027 mmol) in DCM (2 ml) was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (16 mg, 0.041 mmol), and triethylamine (4 mg, 0.041 mmol). The resulting solution was allowed to stir for 16 h under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the title compound **45(i)** as a white solid (15 mg, 58%). Mp 122-126°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15, m, 2H; 1.46, s, 9H; 1.50, s, 9H; 1.63, m, 2H; 3.25, m, 2H; 4.32, m, 1H; 4.45, m, 2H; 4.56, m, 2H; 4.85, m, 2H; 5.37, s, 2H; 5.56, m, 1H; 6.31, d, J = 8.1 Hz, 1H; 7.32, m, 8H; 7.85, m, 7H; 8.26, br s, 1H; 8.41, s, 1H. MS (ES +ve) *m/z* 950 (100%) $[M+H]^+$.

Compound 45

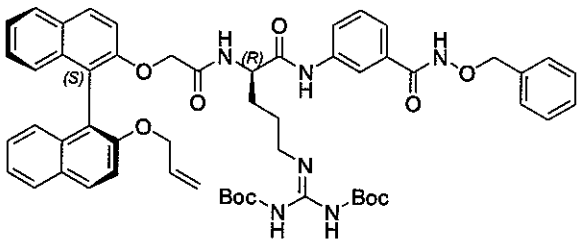


This compound was prepared *via* Protocol 3, from **45(i)** (15 mg, 0.016 mmol) to yield **45** as a highly hydroscopic cream solid (6 mg, 48%).

^{1}H NMR (500 MHz, CD_3OD) δ 1.08, m, 2H; 1.54, m, 2H; 2.92, m, 2H; 4.28, dd, J = 5.0, 7.0 Hz, 1H; 4.47, m, 4H; 4.80, m, 2H; 5.27, s, 2H; 5.59, m, 1H; 7.25, m, 13H; 7.79, m, 7H; 8.22, s, 1H. MS (ES +ve) *m/z* 750 (100%) $[M]^+$.

Synthesis of Compound 46

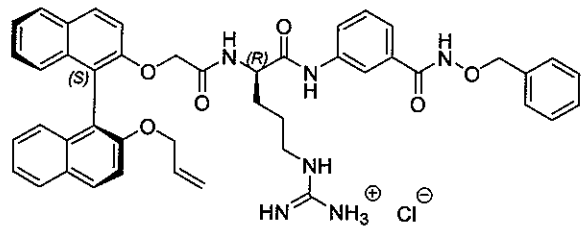
46(i)



To a solution of **43** (51 mg, 0.067 mmol) in DCM (3 ml) was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (39 mg, 0.10 mmol), and triethylamine (0.1 ml). The resulting solution was allowed to stir for 16 hr under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the title compound **46(i)** as a white solid (58 mg, 90%). Mp 112°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10, m, 2H; 1.44, s, 9H; 1.50, s, 9H; 1.65, m, 2H; 3.23, m, 2H; 4.25, m, 1H; 4.51, m, 4H; 4.89, m, 2H; 5.00, s, 2H; 5.63, m, 1H; 6.34, d, J = 7.5 Hz, 1H; 7.31, m, 16H; 7.90, m, 4H; 8.25, br s, 1H; 9.05, s, 1H. MS (ES +ve) *m/z* 987 (100%) $[M+Na]^+$; 965 (90%) $[M+H]^+$.

Compound 46

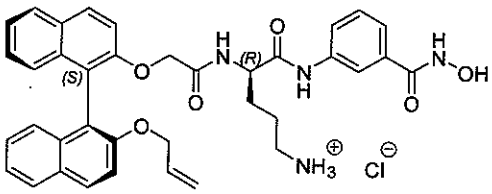


This compound was prepared *via* Protocol 3, from **46(i)** (16 mg, 0.017 mmol) to yield **46** as a cream solid (7 mg, 51%). Mp 142 °C.

^{1}H NMR (300 MHz, CD_3OD) δ 1.20, m, 2H; 1.66, m, 2H; 3.04, m, 2H; 3.97, m, 1H; 4.49, m, 6H; 4.96, m, 2H; 5.60, m, 1H; 7.33, m, 16H; 7.95, m, 4H. MS (ES +ve) *m/z* 765 (20%) $[M]^+$; 102 (100).

Synthesis of Compound 47

Compound 47

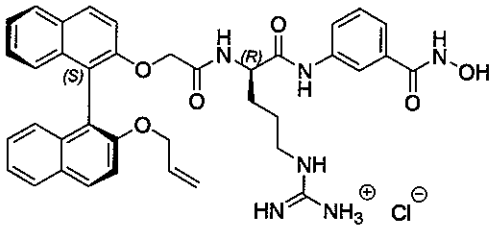


To a solution of **43(i)** (28 mg, 0.034 mmol) in THF (3 ml) was added palladium on activated carbon (15 mg). The resulting mixture was flushed with hydrogen gas and allowed to stir for 16 h. The mixture was filtered through celite and evaporated to dryness. This intermediate product was then subjected to the Protocol 3 to yield the title compound **47** as a white solid (16 mg, 70%). Mp 116°C.

^{1}H NMR (500 MHz, CD_3OD) δ 0.76, m, 3H; 1.35, m, 4H; 1.67, m, 2H; 3.66, m, 2H; 3.88, m, 2H; 4.08, m, 1H; 4.56, m, 2H; 7.30, m, 9H; 7.89, m, 5H. MS (ES +ve) *m/z* 636 (50%) $[M]^+$; 623 (100).

Synthesis of Compound 48

Compound 48



To a solution of **46(i)** (39 mg, 0.040 mmol) in THF (3 ml) was added palladium on activated carbon. The resulting mixture was flushed with hydrogen gas and allowed to stir for 16 h. The mixture was filtered through celite and

evaporated to dryness. This intermediate product was then subjected to Protocol 3 to yield the title compound **48** as a white solid (24 mg, 84%). Mp 158-160°C.

^{1}H NMR (300 MHz, CD_3OD) δ 0.51, t, J = 7.2 Hz, 3H; 1.17, m, 2H; 1.40, m, 2H; 1.62, m, 2H; 3.03, m, 2H; 3.92, m, 2H; 4.09, m, 1H; 4.45, ABq, J = 14.1 Hz, 2H; 7.24, m, 9H; 7.95, m, 5H; 9.96, br s, 1H. MS (ES +ve) *m/z* 677 (100%) $[M]^+$.

ACTIVITY

Antibacterial assay method for *Staphylococcus aureus* (ATCC 6538P) and *Enterococcus faecium*

Bacterial strains:

Staphylococcus aureus (ATCC 6538P)

Enterococcus faecium

VRE strains: #243 E.faecium van B ST17 #449 E.faecium van B ST17

#820 E.faecium van A ST17 #987 E.faecium van B ST39

The S. aureus assay is performed in the PC2 lab and the E. faecium assay is performed in the PC3 lab.

Compound preparation:

Compounds are accurately weighed out (between approx. 1-2mg) and dissolved in either 10%methanol/water (v/v) or 100%DMSO to a final stock concentration of 5mg/ml.

Compounds are then diluted 1/10 in H2O to a test conc of 500ug/ml ready for immediate use, or storage at -20°C.

Starter culture:

Grow up an o/n starter culture of Staphylococcus aureus and each VRE strain by diluting previous culture (stored at 4°C) 1/1000 into ~ 50mls Luria Broth (LB) for S. aureus or Enterococossel Broth (EB) for the VRE strains.

Incubate o/n at 37°C + shaking.

*A glycerol stock (0.6mls bacterial culture, 0.3mls glycerol) of each strain is kept at -80°C if needed.

Assay set up:

In a 96well round bottom plate add 50ul LB / well for the S. aureus plate and add 50ul EB / well for the VRE plates.

Add 50ul of compound dilution (500ug/ml test conc) to each of three top row wells (ie: tested in triplicate) and dilute 1in 2 from the top row to the bottom row.

After the compound dilution, add to each well 50ul of a 1/1000 dilution of the appropriate overnight bacterial culture, either S. aureus or the different VRE strains.

Plates are incubated at 37°C on a slowly rotating plate incubator.

- test concentrations are (in ug/ml) 125, 62.5, 31.25, 15.6, 7.8, 3.9, 1.9, 0.98

- final DMSO concentration in the first row of wells of the assay is 2.5%
- Vancomycin is included in the assay (in triplicate) at a starting test concentration of 5ug/ml for S. aureus and 125ug/ml for the VRE strains

Reading results of assay:

After incubation for 24hrs the plates are removed and read. Inhibition of bacterial growth is indicated by lack of bacterial pellet or a clear well. In the VRE plates bacterial growth is indicated by black coloured media (EB) as well as a bacterial pellet.

Untreated control wells are included in the assay to check they all contain bacterial pellets. Uninoculated untreated control wells are included to check they all contain clear medium.

The plates are analysed for MIC and the results tabulated.

Antibacterial assay results for *Staphylococcus aureus* (ATCC 6538P) and *Enterococcus faecium*

Activity for Compounds was determined in the assays described. The minimum inhibitory concentration (μg/ml) was determined to be in a given range if at least two of three values fell within that range.

- MIC of the compound in the range of less than 0.98 (μg/ml) is designated in the table by ++++
- MIC of the compound in the range of greater than or equal to 0.99 (μg/ml) and less than or equal to 15.6 (μg/ml) is designated in the table by +++
- MIC of the compound in the range of greater than or equal to 15.7 (μg/ml) and less than or equal 62.5 (μg/ml) is designated in the table by ++
- MIC of the compound in the range of greater than or equal to 62.6 (μg/ml) is designated in the table by +

Compound	Sa	243	449	820	987
Van	+++	++++	++	+	++++
1	+++	++	++	+++	++
2	+++	++	++	++	++
3	+++	++	++	++	++
4	+++	++	++	++	++
5	+++	++	++	++	++
6	+++	++	++	++	++
7	+++	++	++	++	++

8	++	+	+	+	+
9	+++	+	++	++	++
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11	+++	++	++	++	++
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31	+++	++	++	++	++
32	+	+	+	+	+
33	+++		+	+	
34	+++	+	++	++	+

35	+++	+	+	++	+
36	+	+	+	+	+
37	+++	+	+	+	+
38	+++	++	++	++	++
39	+++	+	++	++	+
40	+++	+	+	++	+
41	+++	+	+	+	+
42	++	+	+	+	.+
43	+++	+	+	++	+
44	+++	+	+	++	+
45	+++	++	++	++	++
46	+++	+	+	+	+
47	+++	+	+	+	+

Antibacterial assay methods for *Staphylococcus aureus* Mu50 (ATCC 700699), Methicillin-Resistant *Staphylococcus aureus* (ATCC 43300), Multi-Drug-Resistant *Staphylococcus epidermidis* (ATCC 700562)

Compounds

The compounds were stored at room temperature in the dark prior to use. Each compound was solubilized in DMSO to a final concentration of 40 mg/mL. The stock material was diluted to a concentration equivalent to two times the final in-well high test concentration (100 µg/mL for all experimental compounds) in Mueller Hinton II broth. Precipitation was observed in the wells at 100 and 50 µg/mL with all eight compounds. Vancomycin and oxacillin were obtained from Sigma Aldrich Chemical Company and were used as positive and/or negative control compounds in the reported assays at high test concentrations of 100, 25 and 100 µg/mL respectively.

Bacterial Strains

The bacterial strains employed in these assays were obtained from the American Type Culture Collection (ATCC). All of the bacterial strains were propagated as recommended by the ATCC. Each strain was stored as a frozen glycerol stock at -80°C and a 10 µL loop of the frozen stocks was used to inoculate each culture for these assays. The strains with their classification and properties are listed in the table below.

Bacteria Strain	**ATCC #**	**Classification**	**Properties**

Staphylococcus aureus	700699	Gram Positive	Mu50, Reduced Vancomycin Susceptibility
Staphylococcus aureus	43300	Gram Positive	Methicillin-Resistant
Staphylococcus epidermidis	700562	Gram Positive	Multi-Drug-Resistant

MIC Determination

The susceptibility of the above microorganisms to the test compounds was evaluated by determining the MIC of each compound using micro-broth dilution analysis according to the methods recommended by the NCCLS. All microbial strains were obtained from American Type Culture Collections (ATCC) and cultured according to the suppliers recommendations. Evaluation of the susceptibility of each organism against the test compounds included a positive control antibiotics Vancomycin and Oxacillin. For each organism, a standardized inoculum was prepared by direct suspension of freshly plated colonies in Mueller Hinton II broth to an optical density 625 nm (OD_{625}) of 0.1 (equivalent to a 0.5 McFarland standard). The suspended inoculum was diluted to a concentration of approximately 1 x 10^6 colony forming units per milliliter (CFU/mL) and 100 µL placed into triplicate wells of a 96-well plate containing 100 µL of test compound serially diluted 2-fold in Mueller Hinton II broth. One hundred microliters of the inoculum was also added to triplicate wells containing 100 µL of two-fold serial dilutions of a positive control antibiotic and to wells containing 100 µL of media only. This dilution scheme yielded final concentrations for each microbial organism estimated to be 5 x 10^5 CFU/mL (verified by colony quantification on appropriate agar plates, data is not presented). Test compound concentrations ranged from a high-test of 1:2 (100 µg/mL)) to a low test of 1:2048 (0.1 µg/mL) using a two-fold dilution scheme. The plates were incubated for 24 hours at 37°C, and the microbial growth at each concentration of compound was determined by measuring the optical density at 625 nm on a Molecular Devices SpectraMax Plus-384 plate reader. The MIC for each compound was determined as the lowest compound dilution that completely inhibited microbial growth.

Antibacterial assay results for *Staphylococcus aureus* Mu50 (ATCC 700699), Methicillin-Resistant *Staphylococcus aureus* (ATCC 43300), Multi-Drug-Resistant *Staphylococcus epidermidis* (ATCC 700562)

Microsoft Excel 2003 was used to analyze and graph the data, and the MIC (minimal inhibitory concentration) was determined from the resulting data. The MIC is defined as the lowest concentration of compound that completely inhibited bacterial.

Activity for Compounds was determined in the assays described. The minimum inhibitory concentration (µg/ml) was determined to be in a given range if at least two of three values fell within that range.

- MIC of the compound in the range of less than 0.98 (µg/ml) is designated in the table by ++++
- MIC of the compound in the range of greater than or equal to 0.99 (µg/ml) and less than or equal to 15.6 (µg/ml) is designated in the table by +++

- MIC of the compound in the range of greater than or equal to 15.7 (μg/ml) and less than or equal 62.5 (μg/ml) is designated in the table by ++

MIC of the compound in the range of greater than or equal to 62.6 (μg/ml) is designated in the table by +

Compound	***Staphylococcus aureus* Mu50 (ATCC 700699)**	**Methicillin-Resistant *Staphylococcus aureus* (ATCC 43300)**	**Multi-Drug-Resistant *Staphylococcus epidermidis* (ATCC 700562**
1	+++	+++	+++
12	+++	+++	+++
15	+++	+++	+++
16	+++	+++	+++
17	+++	+++	+++
21	+++	+++	+++
30	+++	+++	+++
31	++	+++	+++

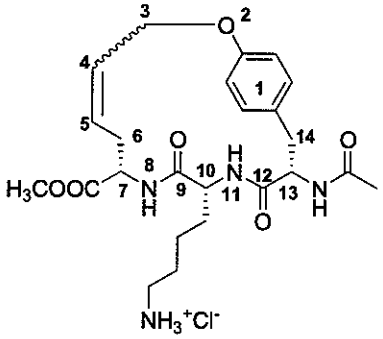
Example 2: Preparation and Biological Activity of Further Compounds according to the Present Invention

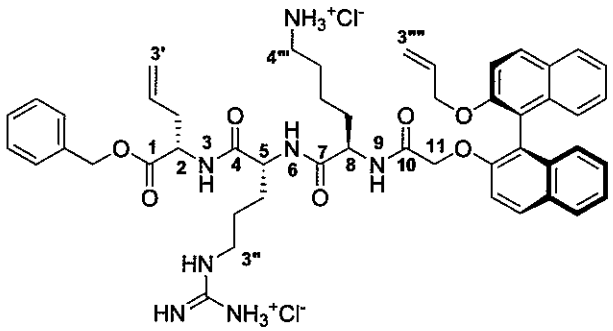
General Notes

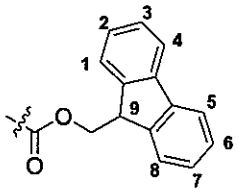
Melting point determinations were carried out on a Gallenkamp melting point apparatus. Chemical ionization (CI) and electron impact (EI) mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer by a direct insertion technique with an electron beam energy of 70 eV. Electrospray (ES) mass spectra were obtained on a VG Autospec spectrometer. High-resolution mass spectra (HRMS) were determined on a micromass QTof2 spectrometer using polyethylene glycol or polypropylene glycol as the internal standard. The *m/z* values are stated with their peak intensity as a percentage in parentheses. Optical rotations were measured using a Jasco polarimeter with a 10 mm path length. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained as specified on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer. Spectra were recorded in the specified deuterated solvent, and referenced to the residual non-deuterated solvent signal. Chemical shifts (δ) in ppm were measured relative to the internal standard. Where samples exhibited (*E*) and (*Z*) isomers the chemical shifts are separated by (/). In general, the two forms could not be separated by flash chromatography. Multiplet (m) signals are reported from the centre of the peak. Proton and carbon assignments were determined through the interpretation of two dimentional spectra (COSY, gHSQC and gHMBC). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} pre-coated aluminium plates with a thickness of 0.2 mm. All column chromatography was performed under 'flash' conditions on Merck silica gel 60 (230-400 mesh). Chromatography solvent mixtures

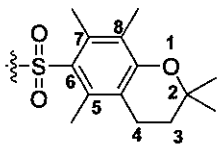
were measured by volume. Organic solvent extracts were dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure with a Buchi rotary evaporator. Solvents were purified and dried based upon standard techniques.[120] All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and TLC analysis. Starting materials and reagents were purchased from Sigma-Aldrich Pty Ltd or Auspep Pty Ltd and were used as received. The Grubbs' first generation catalyst used was specifically benzylidene bis(tricyclohexylphosphene)dichlororuthenium.

Proton and carbon NMR spectra for all compounds were assigned using the numbering systems illustrated below. Cyclic peptoids were named using the IUPAC "superatom" convention, in which the aromatic ring is considered equivalent to, and sequentially numbered like all other atoms in the macrocycle.[121]









General Synthetic Procedures

***N*-Boc and Pmc Deprotection (Procedure A)**

The *N*-Boc or Pmc protected amine was stirred for 3 h in 1:1 DCM/TFA (10 mL) solution at RT. The solvent was removed under reduced pressure, and the residue was resuspended in a minimal volume of methanol. The solution was then treated with an excess of 1M HCl/ether solution and the solvent evaporated. The crude product was purified by precipitation from DCM and/or MeOH by addition of diethyl ether.

Peptide Coupling (Procedure B)

To a solution of the acid (1 equiv.) in DMF or CH_3CN (10 mL) at room temperature was added HOBt (1.1 equiv.), EDCI (1 equiv.) and the amine (1.2 equiv.). If the amine was a hydrochloride salt, DIPEA (1 equiv.) was also added. The mixture was allowed to stir for 16 h before dilution with EtOAc (30 mL) and washing with water (30 mL) and brine (30 mL). The organic fraction was dried ($MgSO_4$) and further purified by column chromatography if required.

***N*-Fmoc Deprotection (Procedure C)**

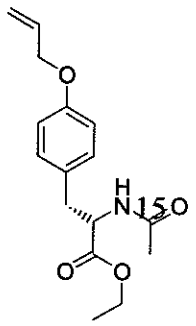
The Fmoc protected amine was stirred in 1% piperidine/acetonitrile (10 mL) for 3 h at RT. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the free amine.

Macrocyclization by Olefin Metathesis (Procedure D)

To a solution of the precursor tripeptide (1 equiv.) in DCM (to 0.004 M) was added Grubbs' first generation catalyst (15 mol%) and the resulting solution was heated at reflux for 48 h before the solvent was removed by evaporation and the product isolated by flash column chromatography (15:1, DCM/MeOH) to yield the corresponding macrocycle.

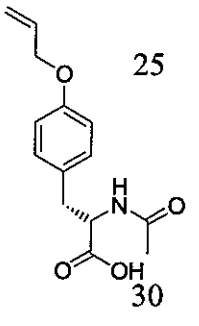
Experimental

Ethyl (2*S*)-2-acetamido-3-(4-allyloxyphenyl)propanoate (15)



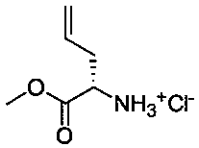
To a solution of ethyl (2*S*)-2-acetamido-3-(4-hydroxyphenyl) propanoate monohydrate **13** (2.69 g, 9.98 mmol) and anhydrous K_2CO_3 (2.75 g, 20.0 mmol) in DMF (15 mL) was added allyl bromide (2.42 g, 19.96 mmol). The resulting mixture was allowed to stir for 16 h under nitrogen before the reaction was quenched with water (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with water (5 x 50 mL), dried and the solvent was evaporated to yield the title compound (2.91 g, 9.98 mmol, 100%) as a white solid, which had spectral data in agreement with that reported.[122] $[\alpha]_D^{25}$ +23.1 (*c*. 0.1, EtOH). Mp 69-70°C (lit. 69.5°C)[122] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.02 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 6.83 (d, *J* = 8.8 Hz, 2H, ArH3' and ArH5'); 6.14 (d, *J* = 8.0 Hz, 1H, NH); 6.06 (m, 1H, H2"); 5.31 (m, 2H, H3"); 4.81 (dd, *J* = 13.5, 6.0 Hz, 1H, H2); 4.50 (d, *J* = 5.1 Hz, 2H, H1"); 4.16 (dd, *J* = 13.9, 6.7 Hz, 2H, $OC\underline{H}_2CH_3$); 3.04 (m, 2H, H3); 1.98 (s, 3H, $NCOCH_3$); 1.25 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$). Mass Spectrum (CI, +ve) *m/z* 292 (100%) [MH^+]. HRMS calcd for $C_{16}H_{22}NO_4$ 292.1549, found 292.1559.

(2*S*)-2-Acetamido-3-(4-allyloxyphenyl)propanoic acid (16)



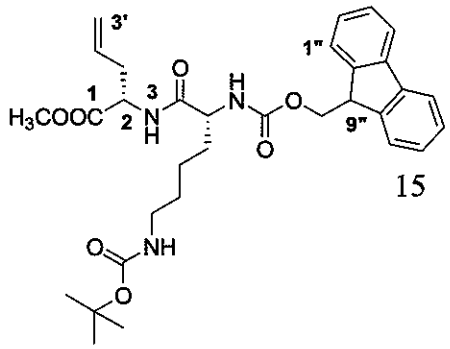
To a solution of **15** (2.90 g, 9.98 mmol) in THF/water, (3:1, 80 mL) was added lithium hydroxide monohydrate (838 mg, 20.0 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation. The aqueous layer was extracted with DCM (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with DCM (3 x 40 mL). The combined organic fractions were dried and evaporated to yield the title compound (2.62 g, 9.98 mmol, 100%) as white needles, which had spectral data in agreement with that reported.[122] Mp 170-172°C (lit. 200°C)[122] ^{1}H NMR (D_6 acetone, 300 MHz): δ 7.09 (s, 1H, NH); 7.04 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 6.73 (d, *J* = 8.4 Hz, 2H, ArH3'and ArH5'); 5.94 (m, 1H, H2"); 5.27 (dd *J* = 1.3 Hz, 17.3 Hz, 1H, $H3_a$"); 5.10 (dd *J* = 1.3, 10.5 Hz, 1H, $H3_b$"); 4.52 (m, 1H, H2); 4.41 (d *J* = 5.5 Hz, 2H, H1"); 2.98 (dd, *J* = 5.7, 14.1 Hz, 2H, $H3_a$); 2.79 (dd, *J* = 8.1, 14.1 Hz, 2H, $H3_b$); 1.75 (s, 3H, $NCOC\underline{H}_3$). Mass Spectrum (CI, +ve) *m/z* 264 (100%) [MH^+]. HRMS calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1246.

Methyl (2*S*)-2-amino-4-pentenoate hydrochloride (18)



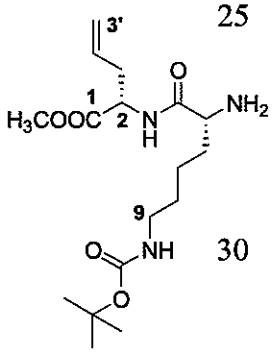
To a suspension of (2*S*)-2-amino-4-pentanoic acid **17** (200 mg, 1.74 mmol) in MeOH (6 mL) at 0°C was added dropwise thionyl chloride (1 mL). The resulting solution was allowed to stir for 16 h before the solvent was removed by evaporation and the product crystallized with ether. The ether was removed by evaporation to yield the title compound (287 mg, 1.74 mmol, 100%) as a white solid, which had spectral data in agreement with that reported.[82] Mp 172-174°C (lit. 174-176°C)[82] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.74 (bs, 3H, NH_3^+); 5.88 (m, 1H, H4); 5.32 (d, J = 16.8 Hz, 1H, $H5_a$); 5.25 (d, J = 10.2 Hz, 1H, $H5_b$); 4.29 (t, J = 5.1 Hz, 1H, H2); 3.81 (s, 3H, OCH_3); 2.86 (t, J = 5.7 Hz, 2H, H3). Mass Spectrum (ES, +ve) *m/z* 130 (100%) [M^+]. HRMS calcd for $C_6H_{12}NO_2$ 130.0868, found 130.0876.

Methyl (2*S*,5*R*)-2-allyl-3-aza-9-(*tert*-butoxycarboxamido)-5-(9*H*-9-fluorenylmethyloxycarboxamido)-4-oxononanoate (19)



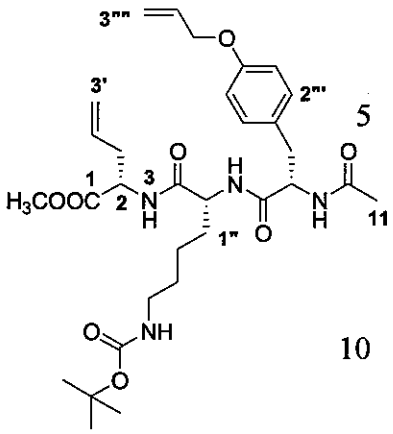
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **18** (186 mg, 1.62 mmol) and (2*R*)-6-*tert*-butoxycarboxamido-2-(9*H*-9-fluorenylmethyloxy carboxamido)hexanoic acid (633 mg, 1.35 mmol) to afford **19** (733 mg, 1.27 mmol, 94%) as a cream solid. Mp 117-120°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (d, J = 7.6 Hz, 2H, ArH1" and ArH8"); 7.59 (d, J = 7.6 Hz, 2H, ArH4" and ArH5"); 7.39 (t, J = 7.6 Hz, 2H, ArH3" and ArH6"); 7.31 (dd, J = 9.0, 7.2, 1.2 Hz, 2H, ArH2" and ArH7"); 6.75 (d, J = 7.2 Hz, 1H, NH); 5.65 (m, 1H, H2'); 5.07 (m, 2H, H3'); 4.65 (m, 2H, H2 and NH); 4.38 (d, J = 6.7 Hz, 2H, $OC\underline{H}_2$-H9"); 4.21 (m, 2H, H5 and H9"); 3.71 (s, 3H, OCH_3); 3.10 (d, J = 6.3 Hz, 2H, H9); 2.52 (m, 2H, H1'); 1.85 (m, 2H, H8); 1.66 (m, 2H, H7); 1.39 (m 2H, H7); 1.43 (s, 9H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 579.9 (80%) [MH^+], 479.9 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{32}H_{42}N_3O_7$ 580.3023, found 580.3041.

Methyl (2*S*,5*R*)-2-allyl-5-amino-3-aza-9-(*tert*-butoxycarboxamido)-4-oxononanoate (20)



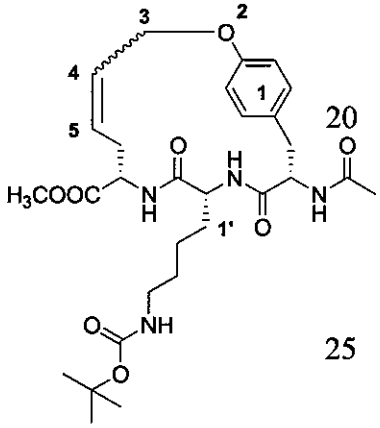
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **19** (715 mg, 1.23 mmol) to yield **20** (436 mg, 1.22 mmole, 99%) as a cream oil, and is in agreement with the literature.[78] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75 (d, J = 8.0 Hz, 1H, NH); 5.70 (m, 1H, H2'); 5.13 (m, 2H, H3'); 4.80 (bs, 1H, NH); 4.64 (m, 1H, H2); 3.74 (s, 3H, OCH_3); 3.38 (dd, J = 4.6, 7.6 Hz, 1H, H5); 3.12 (d, J = 6.3 Hz, 2H, H9); 2.57 (m, 2H, H1'); 1.61 (m, 8H, H6, H7, H8 and NH_2); 1.44 (s, 9H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 358.5 (70%) [MH^+], 258.4 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{17}H_{32}N_3O_5$ 358.2342, found 358.2334.

Methyl (2*S*,5*R*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate (21)



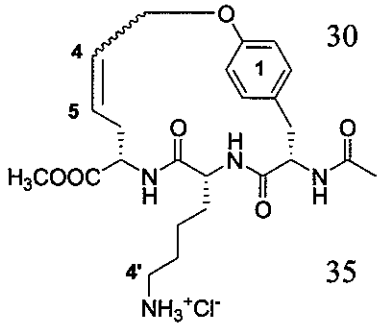
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **20** (440 mg, 1.20 mmol) and **16** (270 mg, 1.03 mmol) to afford **21** (424 mg, 0.70 mmol, 69%) as a white solid. Mp 149-150°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (d, J = 8.0 Hz, 1H, NH); 7.11 (d, J = 8.4 Hz, 2H, ArH2''' and ArH6'''); 6.84 (d, J = 8.4 Hz, 2H, ArH3''' and ArH5'''); 6.67 (d, J = 8.0 Hz, 1H, NH); 6.48 (d, J = 7.2 Hz, 1H, NH); 6.04 (m, 1H, H2''''); 5.67 (m, 1H, H2'); 5.41 (dd, J = 1.3, 17.3 Hz, 1H, $H3_a$''''); 5.28 (dd, J = 1.3, 10.5 Hz, 1H, $H3_b$''''); 5.10 (m, 2H, H3'); 4.75 (t, J = 5.9 Hz, 1H, H2); 4.60 (m, 1H, H8); 4.50 (d, J = 5.5 Hz, 2H, H1''''); 4.42 (dd, J = 7.6, 13.1 Hz, 1H, H5); 3.71 (s, 3H, OCH_3); 2.97 (m, 4H, H4" and $ArCH_2$); 2.52 (m, 2H, H1'); 1.97 (s, 3H, H11); 1.44 (s, 9H, $C(CH_3)_3$); 1.34 (m, 6H, H1", H2" and H3"). Mass Spectrum (ES, +ve) *m/z* 603.4 (40%) [MH^+], 503.4 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{31}H_{47}N_4O_8$ 603.3394, found 603.3389.

(7*S*,10*R*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(4-[*tert*-butoxycarboxamido]butyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (22)



The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **21** (277 mg, 0.46 mmol) to yield **22** (199 mg, 0.35 mmol, 75%) as a brown solid. Mp 178-180°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (m, 2H, NH); 7.07 (m, 2H, ArH); 6.71 (m, 2H, ArH); 5.63 (m, 2H, H4 and H5); 4.48 (m, 4H, H7, H13 and H3); 4.13 (m, 2H, NH and H10); 3.60 (m, 3H, OCH_3); 2.79 (bs, 4H, H4' and H14); 2.38 (m, 2H, H6); 1.80 (m, 3H, $NCOCH_3$); 1.10 (m, 6H, H1', H2' and H3'); 1.26 (s, 9H, $C(CH_3)_3$).. Mass Spectrum (ES, +ve) *m/z* 575.3 (20%) [MH^+], 475.3 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{29}H_{43}N_4O_8$ 575.3081, found 575.3091.

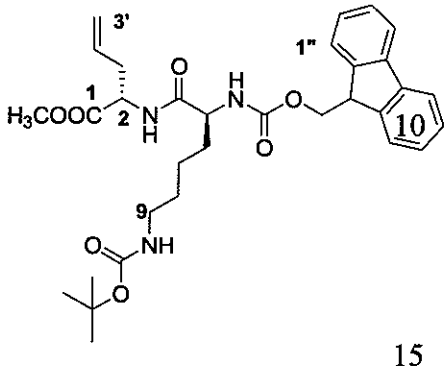
(7*S*,10*R*,13*S*,4*E*/*Z*)-13-Acetamido-10-(4-aminobutyl)-8,11-diaza-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (12)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **22** (49 mg, 0.084 mmol) to yield **12** (17 mg, 0.033 mmol, 49%) as a highly hydroscopic yellow solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.10 (m, 3H, ArH and NH); 6.85 (bs, 1H, NH); 6.71 (d, J = 7.5 Hz, 2H, ArH); 5.75 (m, 2H, H4 and H5); 4.39 (m, 5H, H3, H7, H10 and H13); 3.68 (s, 3H, OCH_3); 2.85 (m, 4H, H6 and H4'); 2.52 (m, 2H, H14); 1.93 (s, 3H, $NCOCH_3$); 1.50 (m, 6H, H1', H2' and H3'). ^{13}C NMR (CD_3OD, 75 MHz): δ

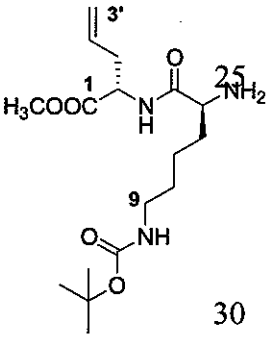
173.5, C9; 173.1, 7-CO; 173.0, 13-NCO; 172.6, C12; 157.7, 1-ArC1; 132.4, 1-ArCH2 and 1-ArCH6; 131.1, C4; 129.6, C5; 129.3, 1-ArC4; 116.8, 1-ArCH3 and 1-ArCH5; 70.0, C3; 57.9, C13; 54.9, C10; 53.5, C4'; 53.0, OCH_3; 40.7, C7; 38.2, C14; 32.1, C1'; 31.7, C6; 28.0, C3'; 23.5, $NCO\underline{C}H_3$; 22.6, C2'. Mass Spectrum (ES, +ve) *m/z* 475.3 (100%) [M^+]. HRMS calcd for $C_{24}H_{35}N_4O_6$ 475.2557, found 475.2534.

Methyl (2*S*,5*S*)-2-allyl-3-aza-9-(*tert*-butoxycarboxamido)-5-(9*H*-9-fluorenylmethyloxycarboxamido)-4-oxononanoate (23)



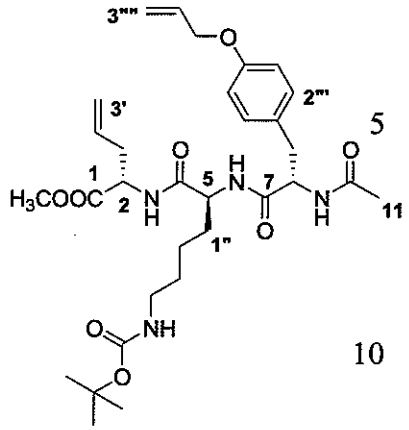
To a solution of **18** (430 mg, 2.61 mmol) and (2*S*)-6-*tert*-butoxycarboxamido-2-(9*H*-9-fluorenylmethyloxy)carboxamido hexanoic acid (1.22 g, 2.61 mmol) in DCM (10 mL) was added EDCI (500 mg, 2.61 mmol) and a catalytic quantity of DMAP. The resulting mixture was allowed to stir at RT for 16 h. The reaction was diluted with DCM (25 mL), then the organic layer was washed with brine (2 x 25 mL) and water (2 x 25 mL) and dried, before being concentrated. The crude product was purified by flash column chromatography (25:1 DCM/MeOH) to afford the title compound (1.31 g, 2.27 mmol, 87%) as a cream coloured solid. Mp 123-126°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (d, *J* = 7.6 Hz, 2H, ArH1" and ArH8"); 7.59 (d, *J* = 7.6 Hz, 2H, ArH4" and ArH5"); 7.40 (t, *J* = 7.6 Hz, 2H, ArH3" and ArH6"); 7.31 (ddd, *J* = 9.0, 7.2, 1.2 Hz, 2H, ArH2" and ArH7"); 6.46 (bs, 1H, NH); 5.64 (m, 1H, H2'); 5.44 (s, 1H, NH); 5.10 (m, 2H, H3'); 4.65 (m, 1H, H2); 4.39 (d, *J* = 7.2 Hz, 2H, $OC\underline{H}_2$-H9"); 4.22 (m, 1H, H5); 4.17 (bs, 1H, H9"); 3.74 (s, 3H, OCH_3); 3.11 (m, 2H, H9); 2.55 (m, 2H, H1'); 1.85 (m, 2H, H7); 1.65 (m, 2H, H6); 1.50 (m 2H, H8); 1.44 (s, 9H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 580.5 (10%) [MH^+], 130.5 (100%) [MH^+ (less allylgly)]. HRMS calcd for $C_{32}H_{42}N_3O_7$ 580.3023, found 580.3025.

Methyl (2*S*,5*S*)-2-allyl-5-amino-3-aza-9-(*tert*-butoxycarboxamido)-4-oxononanoate (24)



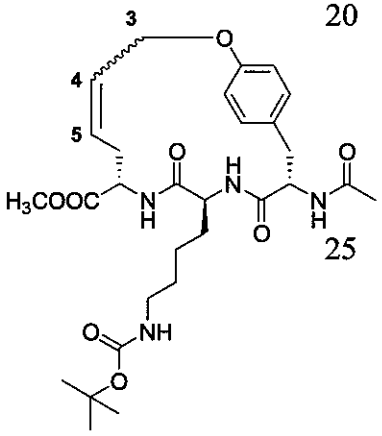
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **23** (1.27 g, 2.19 mmol) to yield **24** (778 mg, 2.18 mmole, 100%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, *J* = 8.0 Hz, 1H, NH); 5.69 (m, 1H, H2'); 5.11 (m, 2H, H3'); 4.76 (bs, 1H, NH); 4.67 (m, 1H, H2); 3.75 (s, 3H, OCH_3); 3.39 (dd, *J* = 4.6, 7.6 Hz, 1H, H5); 3.12 (d, *J* = 6.3 Hz, 2H, H9); 2.54 (m, 2H, H1'); 1.52 (m, 8H, H6, H7, H8 and NH_2); 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.8, C4; 172.1, C1; 156.0, NCO_2; 132.2, C2'; 118.9, C3'; 78.9, $\underline{C}(CH_3)_3$; 54.8, C5; 52.2, C2; 51.1, OCH_3; 40.0, C9; 36.4, C1'; 34.4, C6; 29.7, C8; 28.3, $C(\underline{C}H_3)_3$; 22.6, C7. Mass Spectrum (ES, +ve) *m/z* 358.5 (85%) [MH^+], 258.4 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{17}H_{32}N_3O_5$ 358.2342, found 358.2339.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate (25)



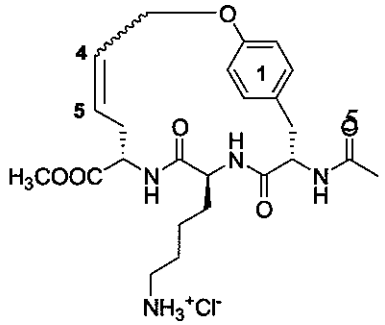
To a solution of **24** (782 mg, 2.19 mmol) and **16** (576 mg, 2.19 mmol) in DCM (10 mL) was added EDCI (420 mg, 2.19 mmol) and a catalytic quantity of DMAP. The resulting mixture was allowed to stir at RT for 16 h. The reaction was diluted with DCM (25 mL) and the organic layer was washed with brine (2 x 25 mL) and water (2 x 25 mL) and dried, before being concentrated by evaporation. The crude product was purified by flash column chromatography (25:1 DCM/ MeOH) to afford the title compound (664 mg, 1.10 mmol, 50%) as a 1:1 mixture of 2 epimers, as a white solid. Mp 112-114°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.09 (m, 2H, ArH2''' and ArH6'''); 6.91 (d, *J* = 8 Hz, 1H, NH); 6.82 (m, 2H, ArH3''' and ArH5'''); 6.69 (d, *J* = 8.0 Hz, 1H, NH); 6.55 (bs, 1H, NH); 6.03 (m, 1H, H1''''); 5.68 (m, 1H, H2'); 5.25 (m, 4H, H3' and H3''''); 4.96 (bs, 1H, H2); 4.86 (bs, 1H, H8); 4.67 (m, 2H, H2''''); 4.48 (dd, *J* = 3.0, 8.4 Hz, 1H, H5); 3.74/3.71 (s, 3H, OCH_3); 3.04 (m, 4H, H4'' and $ArCH_2$); 2.51 (m, 2H, H1'); 1.98/1.96 (s, 3H, H11); 1.79 (s, 2H, H2''); 1.60 (s, 2H, H1''); 1.43 (s, 9H, $C(CH_3)_3$); 1.28 (s, 2H, H3''). Mass Spectrum (ES, +ve) *m/z* 603.4 (35%) [MH^+], 503.4 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{31}H_{47}N_4O_8$ 603.3394, found 603.3397.

(7*S*,10*S*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(4-[*tert*-butoxycarboxamido]butyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (26)



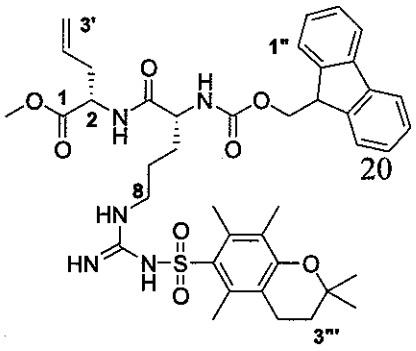
The title compound was prepared using the general procedure for olefin metathesis (Procedure D) using **25** (311 mg, 0.52 mmol) to yield **26** as a mixture of epimers and *E*/*Z* iosomers (228 mg, 0.40 mmol, 76%) as a brown solid. Mp 196-201°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.54 (m, 2H, NH); 7.34 (bs, 1H, NH); 7.06 (m, 2H, ArH); 6.81/6.73 (d, *J* = 8.0 Hz, 2H, ArH); 5.66 (d, *J* = 16.4 Hz, 1H, H4-*trans*); 5.55 (m, 1H, H5); 4.90 (m, 2H, H7 and H13); 4.64 (m, 3H, H2 and H10); 3.80/3.77 (s, 3H, OCH_3); 3.10 (m, 4H, H6 and H4'); 2.70 (m, 2H, H14); 2.10 (s, 3H, $NCOCH_3$); 1.51 (m, 6H, H1', H2' and H3'); 1.44/1.40 (s, 9H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 575.3 (25%) [MH^+], 475.3 (40%) [MH^+ (less Boc)]. HRMS calcd for $C_{29}H_{43}N_4O_8$ 575.3081, found 575.3092.

(7*S*,10*S*,13*S*,4*E*/*Z*)-13-Acetamido-10-(4-aminobutyl)-8,11-diaza-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (27)



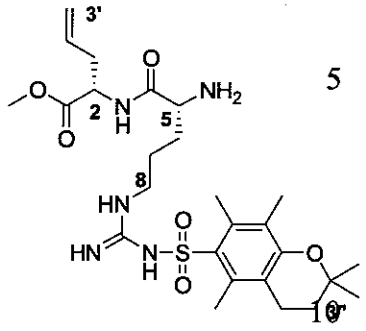
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **26** (220 mg, 0.380 mmol) to yield **27** as a mixture of epimers and *E*/*Z* iosomers (152 mg, 0.300 mmol, 79%) as a highly hydroscopic yellow solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.19 (d, *J* = 8.4 Hz, 1H, NH); 6.98/6.92 (d, *J* = 8.0 Hz, 2H, ArH); 6.74/6.64 (d, *J* = 8.0 Hz, 2H, ArH); 5.57 (d, *J* = 16.0 Hz, 2H, H4-*trans*); 5.39 (m, 1H, H5); 4.53 (m, 4H, H7, H13 and H2); 4.21 (m, 1H, H10); 3.93 (bs, 1H, NH); 3.63/3.60 (s, 3H, OCH_3); 2.76 (m, 6H, H6, H4' and H14); 1.99/1.89 (s, 3H, $NCOC\underline{H}_3$); 1.64 (m, 2H, H2'); 1.51 (bs, 2H, H3'); 1.22 (m, 2H, H1'). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.5, C9; 173.3, 7-CO; 173.1, 13-NCO; 172.5, C12; 157.7, 1-ArC1; 131.4, 1-ArCH2 and 1-ArCH6; 131.1, C4; 129.5, C5; 129.1, 1-ArC4; 116.4, 1-ArCH3 and 1-ArCH5; 66.9, C3; 57.7, C13; 53.9, C10; 53.1, C4'; 53.0, OCH_3; 40.5, C7; 38.1, C14; 32.0, C1'; 31.8, C6; 28.0, C3'; 23.5, $NCO\underline{C}H_3$; 22.5, C2'. Mass Spectrum (ES, +ve) *m/z* 475.4 (100%) [M^+]. HRMS calcd for $C_{24}H_{35}N_4O_6$ 475.2557, found 475.2581.

Methyl (2*S*,5*R*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (28)



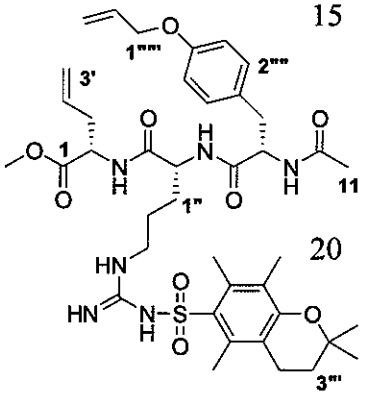
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **18** (287 mg, 1.74 mmol) and (2*R*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]pentanoic acid (961 mg, 1.45 mmol) to afford **28** (1.01 g, 1.31 mmol, 90%) as a brown solid. Mp 96-100°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, *J* = 7.5 Hz, 2H, ArH1" and ArH8"); 7.52 (d, *J* = 7.2 Hz, 2H, ArH4" and ArH5"); 7.35 (bs, 1H, NH); 7.33 (dd, *J* = 7.2, 7.2 Hz, 2H, ArH3" and ArH6"); 7.20 (t, *J* = 7.2 Hz, 2H, ArH2" and ArH7"); 6.35 (s, 2H, NH); 6.26 (bs, 2H, NH); 5.62 (m, 1H, H2'); 5.03 (d, *J* = 18.0 Hz, 1H, $H3_a$'); 4.98 (d, *J* = 10.2 Hz, 1H, $H3_b$'); 4.53 (dd, *J* = 7.2, 12.9 Hz, 1H, H2); 4.27 (d, *J* = 6.6 Hz, 2H, $OC\underline{H}_2$-H9"); 4.10 (m, 2H, H5 and H9"); 3.63 (s, 3H, OCH_3); 3.23 (m, 2H, H8); 2.57 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.49 (m, 4H, H1' and H4"'); 2.06 (s, 3H, 8"'-CH_3); 1.88 (m, 2H, H7); 1.71 (t, *J* = 6.6 Hz, 2H, H3"'); 1.61 (m, 2H, H6); 1.24 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 774 (100%) [MH^+]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3559.

Methyl (2*S*,5*R*)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (29)



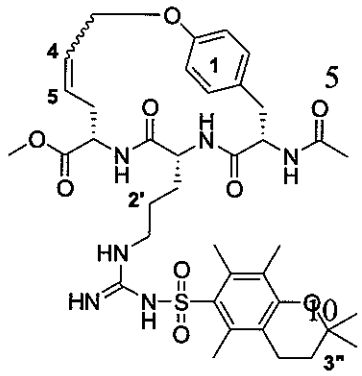
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **28** (717 mg, 0.93 mmol) to yield **29** (407 mg, 0.74 mmol, 80%) as a cream oil, and is in agreement with the literature.[80] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87 (d, *J* = 8.1 Hz, 1H, NH); 6.36 (bs, 3H, NH); 5.68 (m, 1H, H2'); 5.10 (m, 2H, H3'); 4.52 (dd, *J* = 6.9, 12.9 Hz, 1H, H2); 3.71 (s, 3H, OCH_3); 3.42 (m 1H, H5); 3.19 (dd, *J* = 6.9, 11.1 Hz, 2H, H8); 2.62 (t, *J* = 6.9 Hz, 2H, H4"); 2.56 (s, 3H, 7"-CH_3); 2.54 (s, 3H, 5"-CH_3); 2.49 (m, 2H, H1'); 2.10 (s, 3H, 8"-CH_3); 1.80 (t, *J* = 6.9 Hz, 2H, H2"); 1.74 (m, 2H, H7); 1.58 (m, 2H, H6); 1.30 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, +ve) *m/z* 552 (100%) [MH^+]. HRMS calcd for $C_{26}H_{42}N_5O_6S$ 552.2856, found 552.2839.

Methyl (2*S*,5*R*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (30)



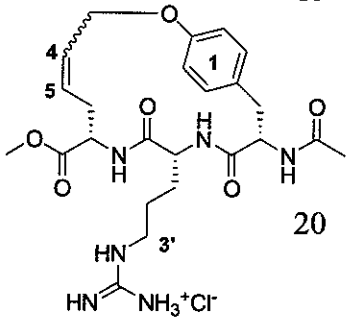
The title compound was synthesised using the general peptide coupling procedure (Procedure B) using **29** (387 mg, 0.70 mmol) and **16** (153 mg, 0.58 mmol) to afford **30** (336 mg, 0.42 mmol, 73%) as a light brown solid. Mp 172-176°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, *J* = 7.5 Hz, 1H, NH); 7.11 (d, *J* = 8.7 Hz, 2H, ArH2"" and ArH6""); 6.78 (d, *J* = 8.4 Hz, 2H, ArH3"" and ArH5""); 6.36 (bs, 2H, NH); 6.18 (bs, 1H, NH); 5.98 (m, 1H, H2""'); 5.69 (m, 1H, H2'); 5.36 (dd, *J* = 1.5, 17.4 Hz, 1H, $H3_a$""'); 5.24 (dd, *J* = 1.5, 10.5 Hz, 1H, $H3_b$""'); 5.08 (d, *J* = 15.6 Hz, 1H, $H3_a$'); 5.04 (d, *J* = 8.4 Hz, 1H, $H3_b$'); 4.48 (m, 2H, H2 and H5); 4.42 (d, *J* = 4.8 Hz, 1H, H1""'); 4.29 (m, 1H, H8); 3.69 (s, 3H, OCH_3); 3.05 (m, 2H, H3"); 2.99 (m, 2H, $ArCH_2$); 2.63 (t, *J* = 6.9 Hz, 2H, H4"'); 2.59 (s, 3H, 7"'-CH_3); 2.57 (s, 3H, 5"'-CH_3); 2.54 (m, 2H, H1'); 2.09 (s, 3H, 8"'-CH_3); 1.93 (s, 3H, H11); 1.80 (t, *J* 6.6 Hz, 2H, H3"'); 1.51 (m, 4H, H1" and H2"); 1.30 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 797 (100%) [MH^+]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3913.

(7*S*,10*R*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (31)



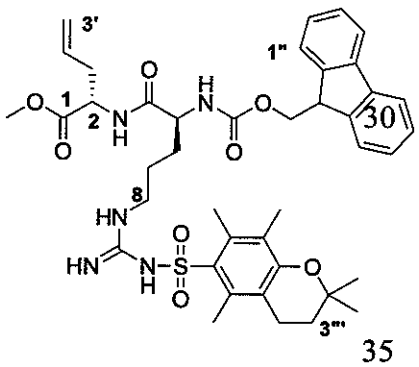
The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **30** (104 mg, 0.13 mmol) to yield **31** (103 mg, 0.13 mmol, 100%) as a grey solid. Mp 172-175°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04 (m, 2H, ArH); 6.72 (m, 2H, ArH); 6.37 (bs, 1H, NH); 5.45 (m, H4 and H5); 4.79 (m, 2H, H3); 4.57 (m, 3H, H7, H10 and H13); 3.63 (s, 3H, OCH_3); 2.97 (m, 4H, H3' and H6); 2.54 (m, 10H, H14, 7"-CH_3, 5"-CH_3 and H4"); 2.06 (s, 3H, 8"-CH_3); 1.90 (s, 3H, NCOC$\underline{H}_3$); 1.76 (m, 2H, H1'); 1.48 (m, 2H, H3"); 1.27 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, -ve) *m/z* 767 (100%) [MH^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3558.

(7*S*,10*R*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (32)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **31** (60 mg, 0.078 mmol) to yield **32** (38 mg, 0.071 mmol, 91%) as a white solid. Mp 218-224°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.10 (m, 2H, ArH); 6.79 (m, 2H, ArH); 5.70 (m, 1H, H5); 5.51 (m, 1H, H4); 4.44 (m, 5H, H3, H7, H10 and H13); 3.69 (m, 3H, OCH_3); 3.10 (m, 2H, H3'); 2.94 (m, 2H, H14); 2.49 (m, 2H, H6); 1.94 (s, 3H, NCOC$\underline{H}_3$); 1.71 (m, 2H, H1'); 1.33 (m, 2H, H2'). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.6, $\underline{C}OOCH_3$; 173.5, C11; 173.1, C9; 172.4, N$\underline{C}OCH_3$; 158.4, CN_3; 157.4, 1-ArC4; 131.5, C4; 129.5, C5; 129.1, 1-ArCH2 and 1-ArCH6; 129.0, 1-ArC1; 116.5, 1-ArCH3 and 1-ArCH5; 66.9, C3; 57.5, C7; 56.2, C10; 54.3, C10; 53.6, C3'; 52.5, OCH_3; 42.1, C6; 38.7, C14; 35.3, NCO$\underline{C}H_3$; 26.6, C1'; 22.7, C2'. Mass Spectrum (ES, +ve) *m/z* 503 (100%) [M^+]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2626.

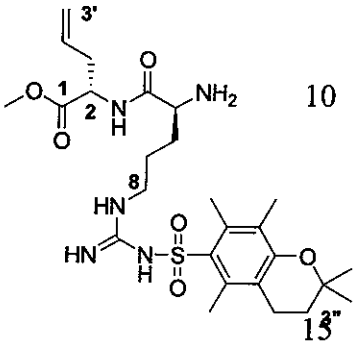
Methyl (2*S*,5*S*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (33)



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **18** (287 mg, 1.74 mmol) and (2*S*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]pentanoic acid (961 mg, 1.45 mmol) to afford **33** (936 mg, 1.21 mmol, 83%) as a brown solid. Mp 90-94°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, J = 7.5 Hz, 2H, ArH1" and ArH8"); 7.54 (d, J = 7.0 Hz, 2H, ArH4" and ArH5"); 7.39 (bs, 1H, NH) 7.34 (t, J = 7.5 Hz, 2H, ArH3" and ArH6"); 7.22 (t, J = 7.5 Hz, 2H, ArH2" and ArH7"); 6.34 (bs, 1H, NH); 6.12 (d, J = 7.5 Hz 1H, NH); 5.65 (m, 1H, H2'); 5.03 (d, J = 17.0 Hz, 1H, $H3_a$'); 4.98 (d,

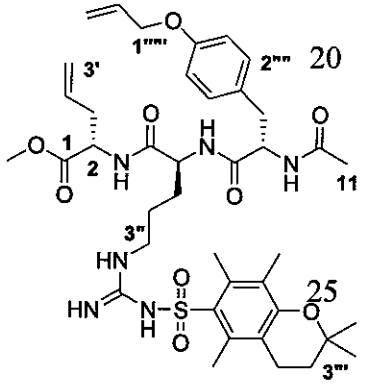
J = 10.0 Hz, 1H, H3$_b$'); 4.54 (m, 1H, H2); 4.36 (m, 1H, H5); 4.29 (d, J = 7.2 Hz, 2H, OC<u>H$_2$</u>-H9"); 4.11 (m, 1H, H9"); 3.65 (s, 3H, OCH$_3$); 3.25 (m, 2H, H8); 2.58 (s, 3H, 7"'-CH$_3$); 2.55 (s, 3H, 5"'-CH$_3$); 2.48 (m, 4H, H1' and H4"'); 2.07 (s, 3H, 8"'-CH$_3$); 1.93 (m, 2H, H6); 1.73 (t, J = 6.5 Hz, 2H, H3"'); 1.60 (m, 2H, H7); 1.26 (s, 6H, 2 x 2"'-CH$_3$). Mass Spectrum (ES, +ve) *m/z* 774 (20%) [MH$^+$], 130 (100%) [allylGly]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3517.

Methyl (2*S*,5*S*)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (34)



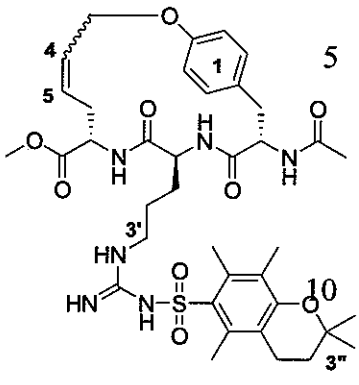
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **33** (749 mg, 0.97 mmol) to yield **34** (259 mg, 0.47 mmol, 48%) as a cream oil, which had spectral data in agreement with that reported.[80] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, J = 8.1 Hz, 1H, NH); 6.33 (bs, 3H, NH); 5.66 (m, 1H, H2'); 5.09 (m, 2H, H3'); 4.54 (m, 1H, H2); 3.73 (s, 3H, OCH$_3$); 3.43 (m, 1H, H5); 3.20 (m, 2H, H8); 2.63 (t, J = 6.9 Hz, 2H, H4"); 2.57 (s, 3H, 7"-CH$_3$); 2.55 (s, 3H, 5"-CH$_3$); 2.50 (m, 2H, H1'); 2.10 (s, 3H, 8"-CH$_3$); 1.80 (m, 4H, H7 and H3"); 1.60 (m, 2H, H6); 1.30 (s, 6H, 2 x 2"-CH$_3$). Mass Spectrum (ES, +ve) *m/z* 552 (100%) [MH$^+$]. HRMS calcd for $C_{26}H_{42}N_5O_6S$ 552.2856, found 552.2856.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (35)



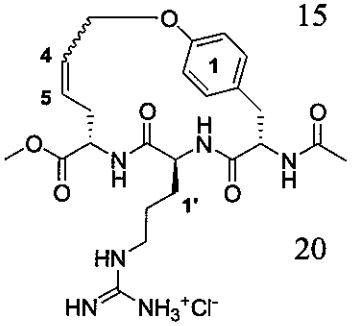
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **34** (236 mg, 0.43 mmol) and **16** (95 mg, 0.36 mmol) to afford **35** (207 mg, 0.25 mmol, 72%) as a light brown solid. Mp 99-104°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, J = 7.8 Hz, 1H, NH); 7.69 (bs, 1H, NH); 7.14 (d, J = 7.5 Hz, 1H, NH); 7.04 (d, J = 8.4 Hz, 2H, ArH2"" and ArH6""); 6.74 (d, J = 8.4Hz, 2H, ArH3"" and ArH5""); 6.41 (bs, 2H, NH); 6.01 (m, 1H, H2""'); 5.70 (m, 1H, H2'); 5.37 (dd, J = 1.5, 17.4 Hz, 1H, H3$_a$""'); 5.25 (dd, J = 1.5, 10.5 Hz, 1H, H3$_b$""'); 5.07 (d, J = 15.3 Hz, 1H, H3$_a$'); 5.03 (d, J = 9.3 Hz, 1H, H3$_b$'); 4.74 (m, 1H, H2); 4.64 (bs, 1H, H5); 4.56 (dd, J = 6.9, 13.5 Hz, 2H, H8); 4.44 (d, J = 5.4 Hz, 2H, H1""'); 3.68 (s, 3H, OCH$_3$); 3.17 (d, J = 4.5 Hz, 2H, H3"); 2.95 (m, 2H, ArCH$_2$); 2.59 (t, J = 6.3 Hz, 2H, H4"'); 2.55 (s, 3H, 7"'-CH$_3$); 2.53 (s, 3H, 5"'-CH$_3$); 2.50 (m, 2H, H1'); 2.08 (s, 3H, 8"'-CH$_3$); 1.88 (s, 3H, H11); 1.78 (t, J = 6.3 Hz, 2H, H3"'); 1.72 (m, 2H, H7); 1.55 (m, 2H, H6); 1.29 (s, 6H, 2 x 2"'-CH$_3$). Mass Spectrum (ES, +ve) *m/z* 797 (100%) [MH$^+$]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3890.

(7*S*,10*S*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (36)



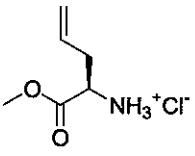
The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **35** (127 mg, 0.16 mmol) to yield **36** (117 mg, 0.15 mmol, 95%) as a grey solid. Mp 224-228°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.97 (m, 2H, ArH); 6.71 (m, 2H, ArH); 6.41 (bs, 1H, NH); 5.50 (m, H4 and H5); 4.57 (bs, 5H, H3, H7, H10 and H13); 3.67 (s, 3H, OCH_3); 3.16 (m, 2H, H3'); 2.56 (m, 10H, H14, 7"-CH_3, 5"-CH_3 and H4"); 2.08 (s, 3H, 8"-CH_3); 1.78 (s, 3H, $NCOC\underline{H}_3$); 1.52 (m, 2H, H1'); 1.35 (m, 2H, H3"); 1.30 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, +ve) *m/z* 769 (100%) [MH^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3574.

(7*S*,10*S*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (37)



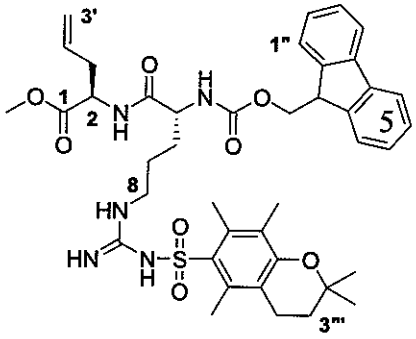
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **36** (91 mg, 0.12 mmol) to yield **37** as a white solid (38 mg, 0.071, 59%). Mp 218-220°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.05 (m, 2H, ArH); 6.74 (m, 2H, ArH); 5.80 (m, 1H, H5); 5.55 (m, 1H, H4); 4.51 (m, 5H, H3, H7, H10 and H13); 3.68 (m, 3H, OCH_3); 3.18 (m, 2H, H3'); 2.84 (m, 2H, H14); 2.49 (m, 2H, H6); 1.99 (s, 3H, $NCOC\underline{H}_3$); 1.76 (m, 2H, H1'); 1.64 (m, 2H, H2'). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.5, $\underline{C}OOCH_3$; 173.3, C11; 173.2, C9; 172.2, $N\underline{C}OCH_3$; 158.9, CN_3; 157.8, 1-ArC4; 131.5, C4; 129.9, C5; 129.1, 1-ArCH2 and 1-ArCH6; 129.0, 1-ArC1; 116.2, 1-ArCH3 and 1-ArCH5; 66.8, C3; 57.6, C7; 56.0, C10; 54.1, C10; 53.6, C3'; 52.9, OCH_3; 42.0, C6; 38.0, C14; 35.3, $NCO\underline{C}H_3$; 26.2, C1'; 22.6, C2'. Mass Spectrum (ES, +ve) *m/z* 503 (100%) [M^+]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2603.

Methyl (2*R*)-2-amino-4-pentenoate hydrochloride (38)



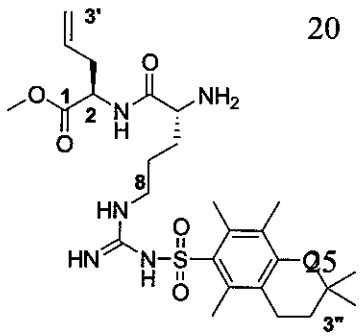
To a suspension of (2*R*)-2-amino-4-pentenoic acid (200 mg, 1.74 mmol) in methanol (6 mL) at 0°C was added dropwise thionyl chloride (1 mL). The resulting solution was allowed to stir for 16 h before the solvent was removed by evaporation and the product crystallized with diethyl ether. The diethyl ether was removed by evaporation to yield the title compound (287 mg, 1.74 mmol, 100%) as a white solid which had spectral data in agreement with that reported.[123] Mp 135-140°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.70 (bs, 3H, NH_3^+); 5.89 (m, 1H, H4); 5.32 (d, J = 17.3 Hz, 1H, $H5_a$); 5.24 (d, J = 10.1 Hz, 1H, $H5_b$); 4.31 (m, 1H, H2); 3.81 (s, 3H, OCH_3); 2.87 (t, J = 6.3 Hz, 2H, H3). Mass Spectrum (ES, +ve) *m/z* 130 (100%) [M^+]. HRMS calcd for $C_6H_{12}NO_2$ 130.0868, found 130.0870.

Methyl (2*R*,5*R*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (39)



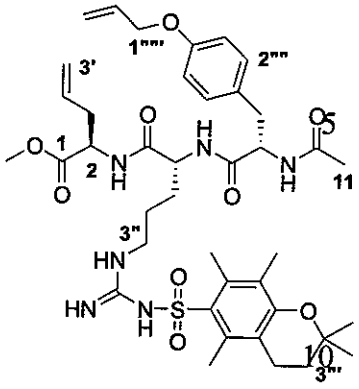
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **38** (287 mg, 1.74 mmol) and (2*R*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]pentanoic acid (961 mg, 1.45 mmol) to afford **39** (1.01 g, 1.31 mmol, 90%) as a brown solid. Mp 96-98°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, J = 7.5 Hz, 2H, ArH1" and ArH8"); 7.53 (d, J = 5.0 Hz, 2H, ArH4" and ArH5"); 7.40 (d, J = 4.5 Hz, 1H, NH); 7.34 (t, J = 7.5 Hz, 2H, ArH3" and ArH6"); 7.22 (t, J = 7.5 Hz, 2H, ArH2" and ArH7"); 6.34 (s, 2H, NH); 6.12 (bs, 2H, NH); 5.64 (m, 1H, H2'); 5.03 (d, J = 17.0 Hz, 1H, $H3_a$'); 4.98 (d, J = 10.0 Hz, 1H, $H3_b$'); 4.53 (m, 1H, H2); 4.36 (dd, J = 8.5, 12.5 Hz, 1H, H5); 4.29 (d, J = 7.0 Hz, 2H, 9"-CH_2); 4.10 (m, 1H, H9"); 3.65 (s, 3H, OCH_3); 3.28 (m, 2H, H8); 3.22 (bs, 1H, NH); 2.58 (s, 3H, 7"'-CH_3); 2.55 (s, 3H, 5"'-CH_3); 2.47 (m, 4H, H1' and H4"'); 2.07 (s, 3H, 8"'-CH_3); 1.91 (m, 2H, H7); 1.73 (t, J = 6.5 Hz, 2H, H3"'); 1.60 (m, 2H, H6); 1.25 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 774 (100%) [MH^+]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3524.

Methyl (2*R*,5*R*)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (40)



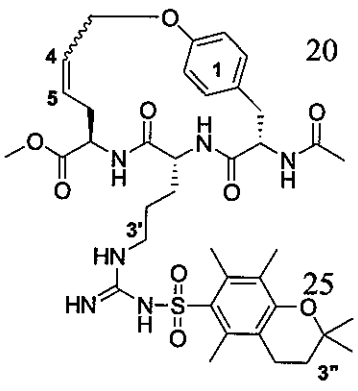
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **39** (693 mg, 0.900 mmol) to yield **40** (387 mg, 0.0700 mmole, 78%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87 (d, J = 7.5 Hz, 1H, NH); 6.35 (bs, 3H, NH); 5.67 (m, 1H, H2'); 5.09 (d, J = 16.2 Hz, 1H, $H3_a$'); 5.09 (d, J = 12.0 Hz, 1H, $H3_b$'); 4.54 (m, 1H, H2); 3.72 (s, 3H, OCH_3); 3.42 (m 1H, H5); 3.19 (d, J = 5.4 Hz, 2H, H8); 2.56 (s, 3H, 7"-CH_3); 2.54 (s, 3H, 5"-CH_3); 2.51 (m, 2H, H1'); 2.10 (s, 3H, 8"-CH_3); 2.05 (bs, 2H, H7); 1.80 (t, J = 6.3 Hz, 2H, H2"); 1.57 (m, 2H, H6); 1.30 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, +ve) *m/z* 552.1 (40%) [MH^+], 243.0 (100%) [MH^+ less allylGly]. HRMS calcd for $C_{26}H_{42}N_5O_6S$ 552.2856, found 552.2829.

Methyl (2*R*,5*R*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (41)



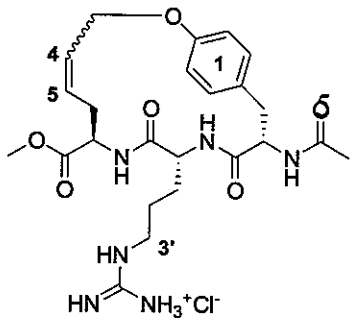
The title compound was synthesised using the general peptide coupling procedure (Procedure B) using **40** (387 mg, 0.700 mmol) and **16** (153 mg, 0.580 mmol) to afford **41** (297 mg, 0.37 mmol, 64%) as a light brown solid. Mp 217-220°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (bs, 1H, NH); 7.10 (d, J = 8.0 Hz, 2H, ArH2"" and ArH6""); 6.88 (bs, 1H, NH); 6.82 (d, J = 8.5 Hz, 2H, ArH3"" and ArH5""); 6.31 (d, J = 7.0 Hz, 1H, NH); 6.17 (bs, 1H, NH); 6.01 (m, 1H, H2""'); 5.69 (m, 1H, H2'); 5.38 (d, J = 17.0 Hz, 1H, $H3_a$""'); 5.26 (d, J = 10 Hz, 1H, $H3_b$""'); 5.11 (d, J = 17.0 Hz, 1H, $H3_a$'); 5.08 (d, J = 10.5 Hz, 1H, $H3_b$'); 4.56 (m, 1H, H2); 4.99 (m, 3H, H5 and H1""'); 4.43 (d, J = 7.5 Hz, 1H, H8); 3.71 (s, 3H, OCH_3); 3.15 (bs, 2H, H3"); 3.00 (m, 2H, $ArCH_2$); 2.63 (t, J = 6.5 Hz, 2H, H4"'); 2.59 (s, 3H, 7"'-CH_3); 2.57 (s, 3H, 5"'-CH_3); 2.51 (m, 2H, H1'); 2.11 (s, 3H, 8"'-CH_3); 1.97 (s, 3H, H11); 1.80 (t, J 6.5 Hz, 2H, H3"'); 1.58 (s, 6H, 2 x 2"'-CH_3); 1.30 (s, 4H, H1" and H2"). Mass Spectrum (ES, +ve) *m/z* 797.4 (100%) [MH^+]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3915.

(7*R*,10*R*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-imino[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (42)



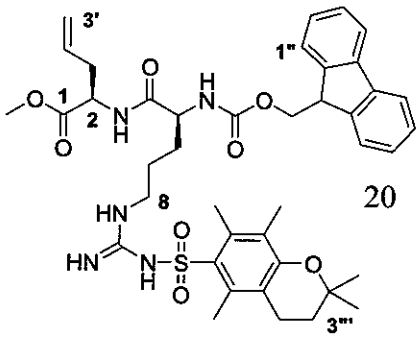
The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **41** (170 mg, 0.210 mmol) to yield **42** (160 mg, 0.210 mmol, 99%) as a grey solid. Mp 205-207°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.05 (m, 2H, NH); 7.02 (m, 2H, ArH); 6.72 (m, 2H, ArH); 6.48 (bs, 1H, NH); 5.75 (m, 2H, NH); 5.42 (m, H4 and H5); 4.62 (bs, 2H, H3); 4.30 (m, 3H, H7, H10 and H13); 3.66 (s, 3H, OCH_3); 2.90 (m, 4H, H3' and H14); 2.60 (m, 6H, 5"-CH_3 and 7"-CH_3); 2.55 (m, 2H, H4"); 2.00 (s, 3H, 8"-CH_3); 1.75 (s, 3H, $NCOCH_3$); 1.55 (m, 2H, H1'); 1.34 (bs, 2H, H3"); 1.27 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, -ve) *m/z* 769.5 (85%) [M^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3631.

(7*R*,10*R*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (43)



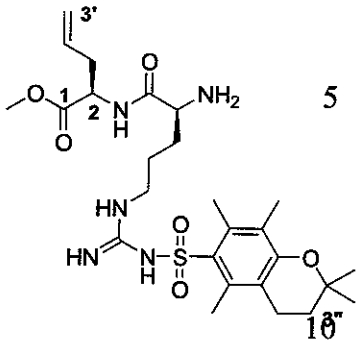
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **42** (108 mg, 0.140 mmol) to yield **43** (25 mg, 0.049 mmol, 35%) as a white solid. Mp 170-176°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.08 (m, 2H, ArH); 6.76 (m, 2H, ArH); 5.90 (m, 1H, H5); 5.54 (m, 1H, H4); 4.45 (m, 5H, H3, H7, H10 and H13); 3.69 (m, 3H, OCH_3); 3.07 (m, 2H, H3'); 2.92 (m, 2H, H14); 2.49 (m, 2H, H6); 1.94 (s, 3H, $NCOCH_3$); 1.65 (m, 2H, H1'); 1.33 (m, 2H, H2'). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.8, $COOCH_3$; 173.5, C11; 173.2, C9; 172.6, $NCOCH_3$; 158.4, CN_3; 157.2, 1-ArC4; 131.4, C4; 130.6, C5; 129.7, 1-ArCH2 and 1-ArCH6; 129.3, 1-ArC1; 115.9, 1-ArCH3 and 1-ArCH5; 67.3, C3; 57.2, C7; 54.0, C10; 53.7, C13; 53.2, C3'; 52.9, OCH_3; 42.0, C6; 37.9, C14; 35.2, $NCOCH_3$; 26.1, C1'; 22.6, C2'. Mass Spectrum (ES, +ve) *m/z* 503 (35%) [M^+]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2644.

Methyl (2*R*,5*S*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (44)



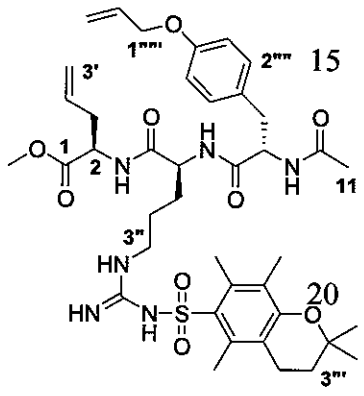
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **38** (287 mg, 1.74 mmol) and (2*S*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]pentanoic acid (961 mg, 1.45 mmol) to afford **44** (1.00 g, 1.29 mmol, 89%) as a brown foam. Mp 90-92°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, *J* = 7.6 Hz, 2H, ArH1" and ArH8"); 7.51 (d, *J* = 7.6 Hz, 2H, ArH4" and ArH5"); 7.33 (t, *J* = 7.2 Hz, 2H, ArH3" and ArH6"); 7.20 (t, *J* = 7.2 Hz, 2H, ArH2" and ArH7"); 6.42 (d, *J* = 7.6 Hz, 1H, NH); 6.34 (s, 1H, NH); 6.20 (bs, 1H, NH); 5.61 (m, 1H, H2'); 5.02 (d, *J* = 18.1 Hz, 1H, $H3_a$'); 4.97 (d, *J* = 10.5 Hz, 1H, $H3_b$'); 4.53 (dd, *J* = 7.6, 13.1 Hz, 1H, H2); 4.26 (d, *J* = 7.2 Hz, 3H, H5 and 9"-CH_2); 4.06 (t, *J* = 7.2 Hz, 1H, H9"); 3.63 (s, 3H, OCH_3); 3.23 (bs, 2H, H8); 2.57 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.47 (m, 4H, H1' and H4"'); 2.07 (s, 3H, 8"'-CH_3); 1.88 (m, 2H, H6); 1.70 (t, *J* = 6.7 Hz, 2H, H3"'); 1.60 (m, 2H, H7); 1.23 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 774 (12%) [MH^+], 130 (100%) [allylGly]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3536.

Methyl (2*R*,5*S*)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (45)



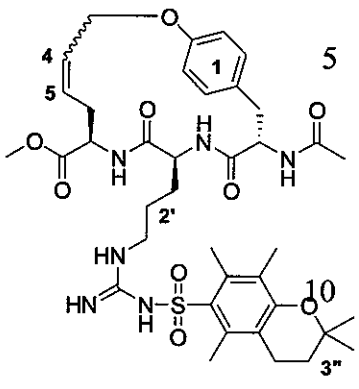
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **44** (788 mg, 1.01 mmol) to yield **45** (552 mg, 1.00 mmole, 99%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, J = 7.5 Hz, 1H, NH); 6.33 (bs, 3H, NH); 5.69 (m, 1H, H2'); 5.12 (d, J = 16.8 Hz, 1H, $H3_a$'); 5.11 (d, J = 10.8 Hz, 1H, $H3_b$'); 4.53 (dd, J = 7.2, 12.9 Hz, 1H, H2); 3.71 (s, 3H, OCH_3); 3.41 (d, J = 7.2 Hz, 1H, H5); 3.19 (m, 2H, H8); 2.57 (m, 2H, H1'); 2.57 (s, 3H, 7"-CH_3); 2.55 (s, 3H, 5"-CH_3); 2.10 (s, 3H, 8"-CH_3); 1.80 (m, 4H, H7 and H3"); 1.58 (m, 2H, H6); 1.30 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, +ve) *m/z* 552.1 (50%) [MH^+], 162.7 (100%). HRMS calcd for $C_{26}H_{42}N_5O_6S$ 552.2856, found 552.2834.

Methyl (2*R*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (46)



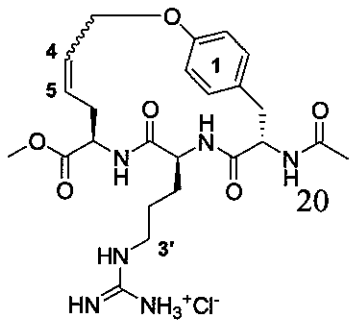
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **45** (513 mg, 0.930 mmol) and **16** (204 mg, 0.78 mmol) to afford **46** (496 mg, 0.622 mmol, 80%) as a light brown solid. Mp 98-102°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71 (d, J = 7.0 Hz, 1H, NH); 7.40 (d, J = 7.0 Hz, 1H, NH); 7.06 (d, J = 8.5 Hz, 2H, ArH2"" and ArH6""); 6.99 (bs, 1H, NH); 6.76 (d, J = 9.0 Hz, 2H, ArH3"" and ArH5""); 6.38 (bs, 2H, NH); 6.20 (bs, 1H, NH); 6.02 (m, 1H, H2""'); 5.69 (m, 1H, H2'); 5.38 (dd, J = 1.5, 17.0 Hz, 1H, $H3_a$""'); 5.25 (dd, J = 1.0, 11.0 Hz, 1H, $H3_b$""'); 5.09 (d, J = 17.5 Hz, 1H, $H3_a$'); 5.06 (d, J = 10.5 Hz, 1H, $H3_b$'); 4.66 (m, 1H, H2); 4.55 (m, 2H, H5 and H8); 4.45 (d, J = 5.5 Hz, 2H, H1""'); 3.67 (s, 3H, OCH_3); 3.20 (d, J = 4.5 Hz, 2H, H3"); 2.97 (m, 2H, $ArCH_2$); 2.61 (t, J = 6.0 Hz, 2H, H4"'); 2.57 (s, 3H, 7"'-CH_3); 2.55 (s, 3H, 5"'-CH_3); 2.53 (m, 2H, H1'); 2.09 (s, 3H, 8"'-CH_3); 1.88 (s, 3H, H11); 1.79 (t, J = 7.0 Hz, 2H, H3"'); 1.74 (m, 2H, H7); 1.57 (m, 2H, H6); 1.30 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 819 (100%) [MNa^+]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3873.

(7*R*,10*S*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-imino[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (47)



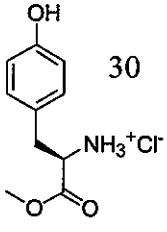
The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **46** (262 mg, 0.330 mmol) to yield **47** (217 mg, 0.280 mmol, 86%) as a grey solid. Mp 174-176°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.10 (m, 2H, NH); 7.06 (m, 2H, ArH); 6.73 (m, 2H, ArH); 6.44 (bs, 1H, NH); 5.70 (m, 2H, NH); 5.40 (m, H4 and H5); 4.62 (bs, 2H, H3); 4.28 (m, 3H, H7, H10 and H13); 3.55 (s, 3H, OCH_3); 3.00 (m, 2H, H3'); 2.80 (m, 2H, H14); 2.44 (m, 6H, 5"-CH_3 and 7"'-CH_3); 2.55 (m, 2H, H4"); 2.00 (s, 3H, 8"-CH_3); 1.73 (s, 3H, $NCOC\underline{H}_3$); 1.51 (m, 2H, H1'); 1.35 (bs, 2H, H3"); 1.23 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, +ve) *m/z* 767 (65%) [MH^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3630.

(7*R*,10*S*,13*S*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (48)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from 47 (129 mg, 0.16 mmol) to yield 48 as a white solid (71 mg, 0.14 mmol, 86%). Mp 134-138°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.10 (m, 2H, ArH); 6.78 (m, 2H, ArH); 5.85 (m, 1H, H5); 5.46 (m, 1H, H4); 4.43 (m, 5H, H3, H7, H10 and H13); 3.69 (m, 3H, OCH_3); 3.30 (m, 2H, H3'); 2.95 (m, 2H, H14); 2.53 (m, 2H, H6); 1.94 (s, 3H, $NCOC\underline{H}_3$); 1.80 (m, 2H, H1'); 1.62 (m, 2H, H2'). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.0, $\underline{C}OOCH_3$; 173.6, C11; 173.3, C9; 173.0, $N\underline{C}OCH_3$; 158.4, CN_3; 157.2, 1-ArC4; 131.3, C4; 130.6, C5; 129.7, 1-ArCH2 and 1-ArCH6; 129.5, 1-ArC1; 115.8, 1-ArCH3 and 1-ArCH5; 67.7, C3; 57.8, C7; 54.9, C10; 54.0, C10; 53.2, C3'; 52.9, OCH_3; 42.0, C6; 37.7, C14; 33.2, $NCO\underline{C}H_3$; 26.5, C1'; 22.3, C2'. Mass Spectrum (ES, +ve) *m/z* 503.4 (100%) [M^+]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2666.

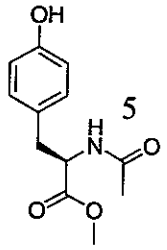
Methyl (2*R*)-2-amino-(4-hydroxyphenyl)-2-propanoate hydrochloride (50)



To a solution of (2*R*)-2-amino-3-(4-hydroxyphenyl)propanoic acid **49** (1.07 g, 5.9 mmol) in anhydrous MeOH (10 mL) at 0°C was added dropwise thionyl chloride (2 mL). The resulting mixture was allowed to stir for 16 h before the solvent was removed by evaporation to yield the title compound (1.36 g, 5.9 mmol, 100%) as a white solid, which had spectral data in agreement with that reported.[124] $[\alpha]_D^{23}$ -27.7 (*c*. 0.1, EtOH). (lit. $[\alpha]_D^{24}$ -27.1 (*c*. 2.0, MeOH)[124] Mp 176°C (lit. 134-136°C)[124] ^{1}H NMR (CD_3OD, 300 MHz): δ 7.05 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 6.82 (d, *J* = 8.4 Hz, 2H, ArH3' and ArH5'); 4.13 (t, *J* = 6.9 Hz, 1H, H2), 3.83 (s, 3H, OCH_3); 3.22 (dd, *J* = 6.0, 14.4 Hz, 1H, $3H_a$); 3.12 (dd, *J* = 6.9, 14.7 Hz, 1H, $3H_b$). Mass Spectrum (CI, +ve) *m/z* 196 (100%) [M^+]. HRMS calcd for $C_{10}H_{14}NO_3$ 196.0974, found 196.0985.

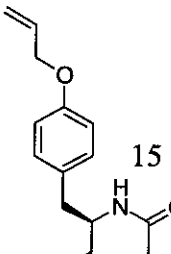
Methyl (2*R*)-2-acetamido-3-(4-hydroxyphenyl)propanoate (51)

A solution of the HCl salt **50** (1.09 g, 6.02 mmol) in water (3 mL) was cooled to 0°C before the addition of 5M sodium acetate solution (35 mL) and a small amount of ice. Acetic anhydride (10 mL) was added and the resulting precipitate was collected by vacuum filtration and dried to yield the title compound (1.09 g, 4.58 mmol, 76%) as a white solid, which had spectral data in agreement with that reported.[124] $[\alpha]_D^{25}$ -27.2 (*c*. 0.1, EtOH) (lit. $[\alpha]_D^{25}$ -26.6 (*c*. 0.1, MeOH)[124] Mp 132-133°C (lit. 134-135.5°C)[124] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.94 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 6.75 (d, *J* = 8.4 Hz, 2H, ArH3' and ArH5'); 4.77 (m, 1H, H2); 3.71 (s, 3H, OCH_3); 3.04 (dd, *J* = 5.7, 14.1 Hz, 1H, $3H_a$); 2.95 (dd, *J* = 6.6, 14.1 Hz, 1H, $3H_b$); 1.96 (s, 3H, $NCOCH_3$). Mass Spectrum (CI, +ve) *m/z* 238 (100%) [MH^+]. HRMS calcd for $C_{12}H_{16}N_1O_4$ 238.107933, found 238.108226.



Methyl (2*R*)-2-acetamido-3-(4-allyloxyphenyl)propanoate (52)

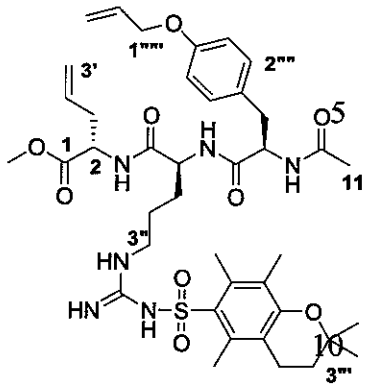
To a solution of **51** (989 mg, 4.17 mmol), and anhydrous K_2CO_3 (1.15 g, 8.34 mmol) in DMF (10 mL) was added allyl bromide (1.01 g, 8.34 mmol) and the resulting mixture was allowed to stir for 16 h under a nitrogen atmosphere. The reaction was quenched with water (30 mL), extracted with ethyl acetate (3 x 30 mL), and the combined organics were washed with water (5 x 20 mL) before drying. The solvent was evaporated to yield the title compound (985 mg, 3.56 mmol, 85%) as a pale yellow solid. $[\alpha]_D^{25}$ -24.2 (*c*. 0.1, EtOH). Mp 90°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.97 (d, *J* = 8.7 Hz, 2H, ArH2' and ArH6'); 6.80 (d, *J* = 8.7 Hz, 2H, ArH3' and ArH5'); 6.09 (d, *J* = 7.8 Hz, 1H, NH); 6.01 (m, 1H, H2"); 5.37 (dd, *J* = 1.8, 17.4 Hz, 1H, $H3_a$"); 5.25 (dd, *J* = 1.8, 10.5 Hz, 1H, $H3_b$"); 4.80 (m, 1H, H2); 4.47 (d, *J* = 5.5 Hz, 2H, H1"); 3.68 (s, 3H, OCH_3); 3.04 (m, 2H, H3); 1.99 (s, 3H, $NCOCH_3$). Mass Spectrum (CI, +ve) *m/z* 278 (100%) [MH^+]. HRMS (EI) calcd for $C_{15}H_{19}NO_4$ 277.131408, found 277.130309.



(2*R*)-2-Acetamido-3-(4-Allyloxyphenyl)propanoic acid (53)

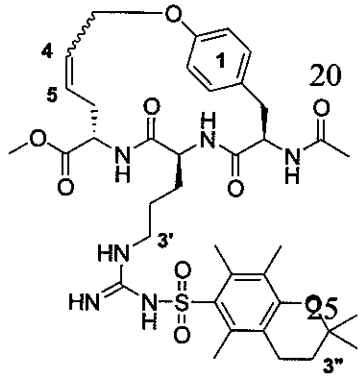
To a solution of **52** (900 mg, 3.25 mmol) in THF/water, 3:1 (10 mL) was added lithium hydroxide monohydrate (273 mg, 6.5 mmol), and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed *in vacuo*. The aqueous layer was extracted with diethyl ether (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with DCM (3 x 40 mL). The combined DCM fractions were dried and evaporated to yield the title compound (750 mg, 2.85 mmol, 88%) as a white solid. $[\alpha]_D^{23}$ -23.2 (*c*. 0.1, EtOH). Mp 75°C. ^{1}H NMR (D_6 acetone, 300 MHz): δ 7.27 (d, *J* = 7.8 Hz, 1H, NH); 7.17 (d, *J* = 8.7 Hz, 2H, ArH2' and ArH6'); 6.86 (d, *J* = 8.7 Hz, 2H, ArH3'and ArH5'); 6.06 (m, 1H, H2"); 5.40 (dd *J* = 1.5 Hz, 17.5 Hz, 1H, $H3_a$"); 5.23 (dd, *J* = 1.5, 10.5 Hz, 1H, $H3_b$"); 4.67 (dd, *J* = 5.1, 8.1, 10.5 Hz 1H, H2); 4.53 (d, *J* = 5.1 Hz, 2H, H1"); 3.11 (dd, *J* = 5.4, 14.1 Hz, 1H, $3H_a$); 2.93 (dd, J = 8.1, 14.1, 1H, $3H_b$); 1.89 (s, 3H, $NCOCH_3$). Mass Spectrum (CI, +ve) *m/z* 264 (100%) [MH^+]. HRMS calcd for $C_{14}H_{18}NO_4$ 264.123583, found 264.123770.

Methyl (2*S*,5*S*,8*R*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (54)



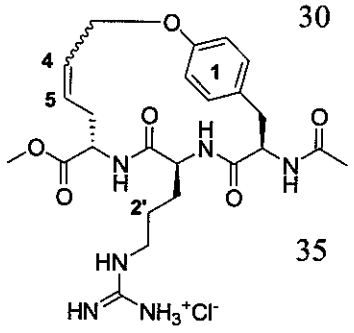
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **34** (654 mg, 1.19 mmol) and **53** (260 mg, 0.99 mmol) to afford **54** (683 mg, 0.86 mmol, 87%) as a light brown solid. Mp 200-204°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (d, J = 8.4 Hz, 2H, ArH2"" and ArH6""); 6.90 (d, J = 4.8 Hz, 1H, NH); 6.57 (d, J = 8.4 Hz, 2H, ArH3"" and ArH5""); 6.34 (d, J = 7.5 Hz, 1H, NH); 6.19 (bs, 2H, NH); 6.00 (m, 1H, H2""'); 5.70 (m, 1H, H2'); 5.37 (dd, J = 1.8, 17.1 Hz, 1H, $H3_a$""'); 5.26 (dd, J = 1.8, 10.5 Hz, 1H, $H3_b$""'); 5.11 (d, J = 12.0 Hz, 1H, $H3_a$'); 5.03 (d, J = 10.0 Hz, 1H, $H3_b$'); 4.49 (m, 5H, H2, H5, H8 and H1""'); 3.70 (s, 3H, OCH_3); 3.16 (m, 2H, H3"); 2.99 (m, 2H, $ArCH_2$); 2.63(t, J = 6.3 Hz, 2H, H4"'); 2.59 (s, 3H, 7"'-CH_3); 2.57 (s, 3H, 5"'-CH_3); 2.54 (m, 2H, H1'); 2.11 (s, 3H, 8"'-CH_3); 1.96 (s, 3H, H11); 1.80 (t, J = 6.3 Hz, 2H, H3"'); 1.72 (m, 2H, H7); 1.58 (m, 2H, H6); 1.30 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 797 (40%) [MH^+], 106 (100%). HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3926.

(7*S*,10*S*,13*R*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (55)



The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **54** (366 mg, 0.46 mmol) to yield **55** (307 mg, 0.40 mmol, 87%) as a grey solid. Mp 186-190°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.17 (m, 3H, NH); 7.02 (m, 2H, ArH); 6.75 (m, 2H, ArH); 6.41 (bs, 1H, NH); 5.75 (m, 1H H5); 5.45 (m, 1H, H4); 4.42 (m, 5H, H3, H7, H10 and H13); 3.69 (s, 3H, OCH_3); 3.06 (m, 2H, H3'); 2.62 (m, 2H, H4"); 2.56 (m, 8H, H14, 7"-CH_3, and 5"-CH_3); 2.08 (s, 3H, 8"-CH_3); 1.85 (s, 3H, NCO$\underline{CH_3}$); 1.60 (m, 2H, H1'); 1.40 (m, 2H, H3"); 1.26 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, +ve) *m/z* 769 (40%) [MH^+], 106 (100%). HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3600.

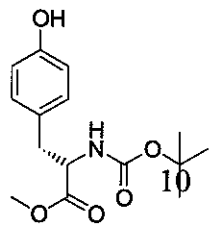
(7*S*,10*S*,13*R*,4*E*/*Z*)-13-Acetamido-8,11-diaza-10-(3-[amino{imino}methylamino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (56)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **55** (128 mg, 0.17 mmol) to yield **56** as a highly hydroscopic solid (29 mg, 0.058 mmol, 34%). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.19 (m, 3H, NH); 7.63 (bs, 1H, NH); 7.05 (m, 2H, ArH); 6.67 (m, 2H, ArH); 5.78 (m, 1H, H5); 5.25 (m, 1H, H4); 4.43 (m, 5H, H3, H7, H10 and H13); 3.58 (m, 3H, OCH_3); 3.06 (m, 2H, H3'); 2.85 (m, 2H, H14); 2.51 (m, 2H, H6); 1.77 (s, 3H, NCO$\underline{CH_3}$); 1.65 (m, 2H, H1'); 1.37 (m, 2H, H2'). ^{13}C NMR (CD_3OD, 75

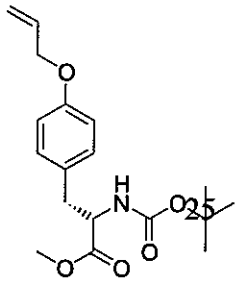
MHz): δ 171.3, $\underline{C}OOCH_3$; 171.6, C11; 171.3, C9; 169.4, $N\underline{C}OCH_3$; 156.8, CN_3; 155.8, 1-ArC4; 130.2, C4; 128.8, C5; 128.2, 1-ArCH2 and 1-ArCH6; 127.9, 1-ArC1; 114.9, 1-ArCH3 and 1-ArCH5; 67.1, C3; 55.2, C7; 54.7, C10; 52.9, C10; 51.8, C3'; 51.6, OCH_3; 42.0, C6; 36.9, C14; 33.9, $NCO\underline{C}H_3$; 29.0, C1'; 22.4, C2'. Mass Spectrum (ES, +ve) *m/z* 503 (30%) [M^+], 102 (100%). HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2638.

Methyl (2*S*)-(4-hydroxyphenyl)-2-*tert*-butoxycarboxamido propanoate (58)



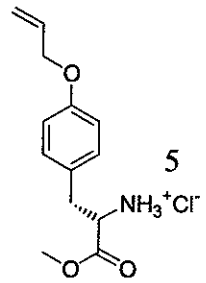
To a solution of (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid **57** (5.23 g, 28.9 mmol) in anhydrous MeOH (20 mL) at 0^0C was added dropwise thionyl chloride (2 mL). The resulting mixture was allowed to stir for 40 h before the solvent was removed by evaporation and the resulting hydrochloride salt was dissolved in DMF (15 mL). To this solution was added di-*tert*-butyl-dicarbonate (9.44 g, 43.3 mmol) and the reaction mixture was allowed to reach RT whilst stirring. After 16 h the reaction was quenched with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with water (5 x 20 mL), dried and evaporated. The crude product was purified by flash column chromatography (25: 1, DCM/MeOH) to yield the title compound (1.32 g, 4.48 mmol, 16%) as a yellow oil, which had spectral data in agreement with that reported.[125] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.95 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 6.73 (d, *J* = 8.4 Hz, 2H, ArH3' and ArH5'); 6.51 (bs, OH); 5.05 (d, *J* = 8.4 Hz, 1H, NH); 4.53 (m, 1H, H2), 3.71 (s, 3H, OCH_3); 2.99 (m, 2H, H3); 1.42 (s, 9H, $C(CH_3)_3$). Mass Spectrum (CI, +ve) *m/z* 196 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{16}H_{22}NO_5$ 296.1498, found 296.1503.

Methyl (2*S*)-3-(4-allyloxyphenyl)-2-*tert*-butoxycarboxamidopropanoate (59)



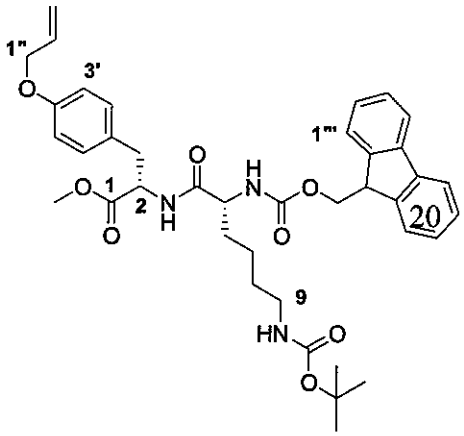
To a solution of **58** (1.30 g, 4.39 mmol) in DMF (15 mL) under an N_2 atmosphere was added K_2CO_3 (1.21g, 8.79 mmol) and the resulting suspension was allowed to stir for 20 min before the addition of allyl bromide (0.76 mL, 8.79 mmol). The reaction mixture was allowed to stir for 16 h before quenching with water (40 mL) and extracting with EtOAc (3 x 40mL). The combined organic fractions were washed with water (4 x 40 mL), dried and evaporated to yield the title compound (1.21 g, 3.35 mmol, 76%) as a clear solid, which had spectral data in agreement with that reported.[126] Mp 142-144°C (lit. 145°C)[126] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.03 (d, *J* = 8.8 Hz, 2H, ArH2' and ArH6'); 6.84 (d, *J* = 8.4 Hz, 2H, ArH3' and ArH5'); 6.04 (m, 1H, H2"); 5.34 (m, 2H, H3"); 4.97 (d, *J* = 8.0 Hz, 1H, NH); 4.50 (m, 3H, H1" and H2); 3.70 (s, 3H, OCH_3); 3.02 (m, 2H, H3); 1.42 (s, 9H, $C(CH_3)_3$). Mass Spectrum (CI, +ve) *m/z* 320 (100%) [MH^+]. HRMS calcd for $C_{17}H_{24}N_2O_4$ 320.1736, found 320.1714.

Methyl (2S)-2-(4-allyloxyphenyl)-2-aminopropanoate hydrochloride (60)



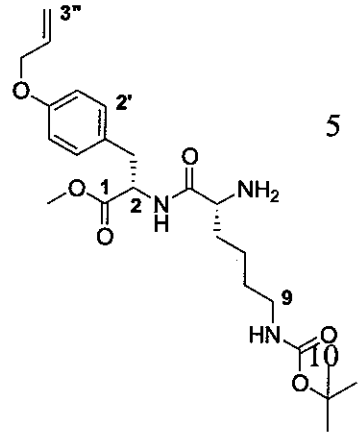
To a solution of **59** (1.10 g, 3.28 mmol) in DCM (5 mL) was added TFA (5 mL) dropwise. After stirring for 16 h the solvent was removed by evaporation and the resulting trifluoroacetate salt was resuspended in methanol (2 mL) and treated with 1M HCl/diethyl ether (2 mL). The solution was stirred for 5 min before the solvent was evaporated to yield the crude hydrochloride salt. The crude product was purified by precipitation (DCM/diethyl ether) to give the title compound (889 mg, 3.28 mmol, 100%) as a white solid. Mp 216-220°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.16 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.93 (d, J = 8.8 Hz, 2H, ArH3' and ArH5'); 6.05 (m, 1H, H2"); 5.38 (dd, J = 17.3, 1.7 Hz, 1H, $H3_a$"); 5.24 (dd, J = 11.8, 1.3 Hz, 1H, $H3_b$"); 4.54 (m, 2H, H1"); 4.26 (m, 1H, H2); 3.81 (s, 3H, OCH_3); 3.14 (m, 2H, H3). ^{13}C NMR (CD_3OD, 75 MHz): δ 170.3, C1; 159.6, ArC4'; 139.6, C2"; 131.4, ArCH2'and ArCH6'; 127.0, ArC1; 117.4, C3"; 116.2, ArCH3'and ArCH5'; 69.7, C1"; 55.3, C2; 53.6, OCH_3; 36.6, C3. Mass Spectrum (CI, +ve) *m/z* 236 (90%) [M^+]. HRMS calcd for $C_{13}H_{18}NO_3$ 236.1287, found 236.1276.

Methyl (2*S*,5*R*)-2-(4-allyloxybenzyl)-3-aza-9-(*tert*-butoxycarboxamido)-5-(9*H*-9-fluorenylmethylcarboxamido)-4-oxononanoate (61)



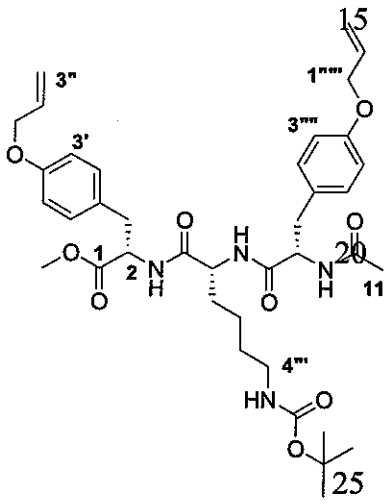
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **60** (200 mg, 0.74 mmol) and (2*R*)-6-*tert*-butoxycarboxamido-2-[(9*H*-9-fluorenylmethyloxy)carboxamido]hexanoic acid (291 mg, 0.62 mmol) to afford **61** (317 mg, 0.47 mmol, 75%) as a pale yellow solid. Mp 114-116°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (d, J = 7.6 Hz, 2H, ArH1"' and ArH8"'); 7.57 (d, J = 6.3 Hz, 2H, ArH4"' and ArH5"'); 7.38 (t, J = 7.2 Hz, 2H, ArH3"' and ArH6"'); 7.28 (t, J = 7.6 Hz, 2H, ArH2"' and ArH7"'); 6.99 (d, J = 7.6 Hz, 2H, ArH2' and ArH6'); 6.82 (d, J = 7.2 Hz, 1H, NH); 6.76 (d, J = 8.0 Hz, 2H, ArH3' and ArH5'); 5.97 (m, 1H, H2"); 5.67 (d, J = 7.2 Hz, 1H, NH); 5.34 (d, J = 16.8 Hz, 1H, $H3_a$"); 5.23 (d, J = 10.5 Hz, 1H, $H3_b$"); 4.81 (d, J = 5.8 Hz, 1H, H2); 4.70 (t, J = 5.9 Hz, 1H, H5); 4.36 (m, 3H, OCH_2 and $OC\underline{H}_2$-H9"'); 4.19 (m, 2H, H1"); 3.68 (s, 3H, OCH_3); 3.05 (m, 4H, H9 and $ArCH_2$); 1.73 (m, 2H, H6); 1.56 (m, 2H, H7); 1.42 (s, 9H $C(CH_3)_3$); 1.24 (m, 2H, H8). Mass Spectrum (ES, +ve) *m/z* 708.4 (100%) [MNa^+]. HRMS calcd for $C_{39}H_{48}N_3O_8$ 686.3439, found 686.3441.

Methyl (2*S*,5*R*)-2-(4-allyloxybenzyl)-5-amino-3-aza-9-(*tert*-butoxycarboxamido)-4-oxononanoate (62)



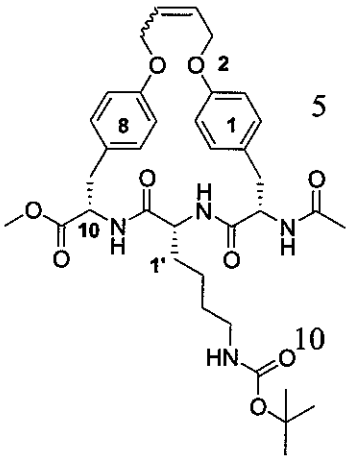
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **61** (198 mg, 0.290 mmol) to yield **62** (131 mg, 0.280 mmole, 97%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (d, J = 8.4 Hz, 1H, NH); 7.04 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.83 (d, J = 8.4 Hz, 2H, ArH3' and ArH5'); 6.05 (m, 1H, H2"); 5.40 (dd, J = 1.7, 17.3 Hz, 1H, $H3_a$"); 5.28 (dd, J = 1.7, 11.8 Hz, 1H, $H3_b$"); 4.78 (m, 1H, H2); 4.66 (bs, 1H, NH); 4.50 (m, 2H, H1"); 3.71 (s, 3H, OCH_3); 3.32 (dd, J = 4.2, 7.6 Hz, 1H, H5); 2.61 (m, 4H, $ArCH_2$ and H8); 1.52 (m, 6H, H6, H7 and H8); 1.43 (s, 9H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 464.3 (100%) [MH^+]. HRMS calcd for $C_{24}H_{38}N_3O_6$ 464.2761, found 464.2749.

Methyl (2*S*,5*R*,8*S*)-2,8-di(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate (63)



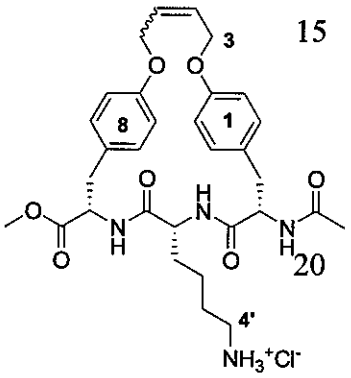
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **62** (220 mg, 0.600 mmol) and **16** (132 mg, 0.500 mmol) to yield **63** (130 mg, 0.180 mmol, 37%) as a white solid. Mp 185-186°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (d, J = 7.6 Hz, 2H, NH); 7.08 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 7.02 (d, J = 8.4 Hz, 2H, ArH2"" and ArH6""); 6.82 (d, J = 8.4 Hz, 4H, ArH3', ArH5', ArH3"" and ArH5""); 6.63 (d, J = 7.2 Hz, 1H, NH); 6.02 (m, 2H, H2" and H2""'); 5.34 (m, 4H, H3" and H3""'); 4.78 (m, 2H, H2 and H8); 4.60 (m, 1H, H5); 4.47 (m, 4H, H1" and H1""'); 3.67 (s, 3H, OCH_3); 2.97 (m, 6H, Ar'-CH_2, Ar""-CH_2 and H4"'); 1.93 (s, 3H, H11); 1.43 (s, 9H, $C(CH_3)_3$); 1.19 (m, 6H, H1"', H2"' and H3"'). Mass Spectrum (ES, +ve) *m/z* 709.3 (100%) [MH^+]. HRMS calcd for $C_{38}H_{52}N_4O_9$ 709.3813, found 709.3793.

(10*S*,13*R*,16*S*,4*E/Z*)-16-Acetamido-11,14-diaza-13-([*tert*-butoxycarboxamido]butyl)-10-methoxycarbonyl-2,7-dioxa-12,15-dioxo-1(1,4),8(4,1)-diphenylenecycloheptadecaphane-4-ene (64)



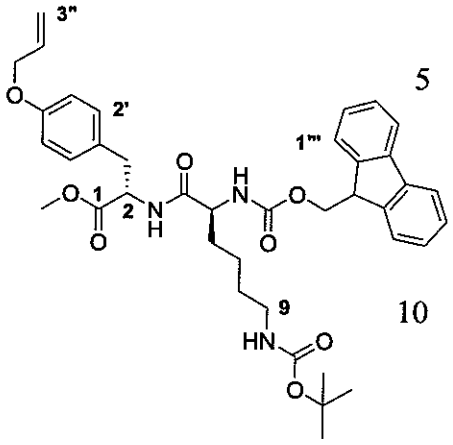
The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **63** (56 mg, 0.079 mmol) to yield **64** (22 mg, 0.032 mmol, 41%) as a brown solid. Mp 190-194°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.96 (m, 8H, ArH); 5.93 (m, 2H, H4 and H5); 4.18 (m, 1H, H10); 4.83 (m, 1H, H16); 4.56 (m, 4H, H3 and H6); 4.13 (m, 1H, H13); 3.74 (s, 3H, OCH_3); 3.28 (m, 2H, H4'); 2.84 (m, 4H, H9 and H17); 1.97 (s, 3H, $NCOCH_3$); 1.25 (s, 9H, $C(CH_3)_3$); 1.40 (m, 6H, H1', H2' and H3'). Mass Spectrum (ES, -ve) *m/z* 725.4 (100%) [MH^+ + formate], 681 (85%) [MH^+]. HRMS calcd for $C_{36}H_{49}N_4O_9$ 681.3500, found 681.3521.

(10*S*,13*R*,16*S*,4*E/Z*)-16-Acetamido-13-(4-aminobutyl)-11,14-diaza-10-methoxycarbonyl-2,7-dioxa-12,15-dioxo-1(1,4),8(4,1)-diphenylenecycloheptadecaphane-4-ene (65)



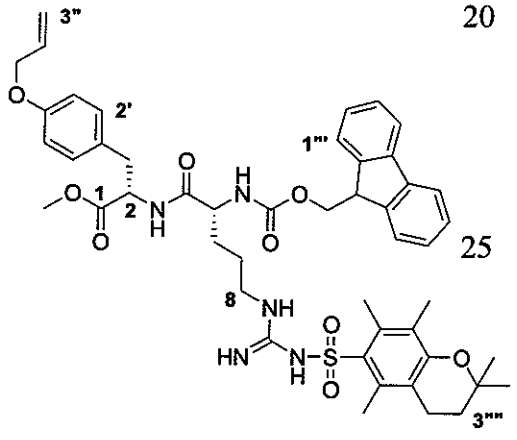
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **64** (22 mg, 0.038 mmol) to yield **65** (20 mg, 0.034 mg, 89%) as a yellow solid. Mp >260°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.06 (m, 3H, NH); 7.07 (m, 4H, ArH); 6.78 (m, 4H, ArH); 5.95 (m, 2H, H4 and H5); 4.66 (bs, 4H, H3 and H6); 4.56 (m, 1H, H10); 4.40 (m, 1H, H16); 4.11 (m, 1H, H13); 3.75 (m, 3H, OCH_3); 2.90 (m, 6H, H9, H17 and H4'); 1.92 (s, 3H, $NCOCH_3$); 1.45 (m, 4H, H1' and H2'); 0.90 (m, 2H, H3'). ^{13}C NMR (CD_3OD, 75 MHz): δ 171.1, C12; 170.3, $NCOCH_3$; 169.9, 10-CO; 169.4, C15; 157.3, 1-ArC1; 157.13, 8-ArC1; 130.9, 8-ArC4; 130.5, 8-ArCH2 and 8-ArCH6; 130.1, 1-ArCH2 and 1-ArCH6; 128.8, C4; 128.4, C5; 126.3, 1-ArCH4; 115.5, 8-ArCH3 and 8-ArCH5; 114.4, 1-ArCH3 and 1-ArCH5; 68.6, C3; 67.9, C6; 54.8, C16; 52.6, C13; 52.4, OCH_3; 52.2, C10; 39.5, C4'; 38.0, C9'; 35.8, C17; 34.9, C1'; 32.0, C3'; 26.5, 16-$NCO\underline{C}H_3$; 23.3, C2'. Mass Spectrum (ES, -ve) *m/z* 581.6 (100%) [M^+]. HRMS calcd for $C_{31}H_{41}N_3O_7$ 581.2975, found 581.2980.

Methyl (2*S*,5*S*)-2-(4-allyloxybenzyl)-3-aza-9-(*tert*-butoxycarboxamido)-5-(9*H*-9-fluorenylmethylcarboxamido)-4-oxononanoate (66)



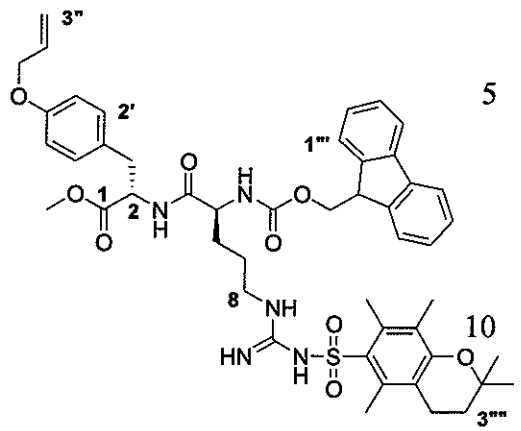
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **60** (200 mg, 0.74 mmol) and (2*S*)-6-*tert*-butoxycarboxamido-2-[(9*H*-9-fluorenylmethyloxy)carboxamido]hexanoic acid (291 mg, 0.62 mmol) to afford **66** (328 mg, 0.48 mmol, 77%) as a pale yellow solid. Mp 52-54°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75 (d, J = 7.5 Hz, 2H, ArH1''' and ArH8'''); 7.59 (d, J = 6.9 Hz, 2H, ArH4''' and ArH5'''); 7.39 (t, J = 7.5 Hz, 2H, ArH3''' and ArH6'''); 7.30 (dd, J = 1.2, 7.5 Hz, 2H, ArH2''' and ArH7'''); 6.98 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.77 (d, J = 8.7 Hz, 2H, ArH3' and ArH5'); 6.58 (d, J = 7.2 Hz, 1H, NH); 5.98 (m, 1H, H2''); 5.56 (d, J = 6.9 Hz, 1H, NH); 5.35 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$''); 5.24 (dd, J = 1.5, 10.8 Hz, 1H, $H3_b$''); 4.81 (dd, J = 6.0, 13.8 Hz, 1H, H2); 4.70 (t, J = 5.1 Hz, 1H, H5); 4.40 (m, 4H, H1'' and $OC\underline{H_2}$-H9'''); 4.20 (d, J = 7.2 Hz, 2H, H1''); 3.70 (s, 3H, OCH_3); 3.04 (m, 4H, H9 and $ArCH_2$); 1.80 (m, 2H, H6); 1.64 (m, 2H, H7); 1.43 (s, 9H $C(CH_3)_3$); 1.35 (m, 2H, H8). Mass Spectrum (ES, +ve) *m/z* 686.4 (10%), 708.4 (100%) [MNa^+]. HRMS calcd for $C_{39}H_{48}N_3O_8$ 686.3441, found 686.3454.

Methyl (2*S*,5*R*)-2-(4-allyloxybenzyl)-3-aza-5-(9*H*-9-fluorenylmethylcarboxamido)-4-oxo-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]nonanoate (67)



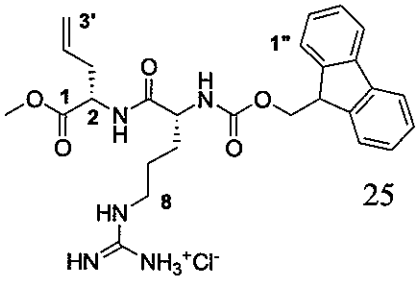
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **60** (200 mg, 0.74 mmol) and (2*R*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]pentanoic acid (411 mg, 0.62 mmol) to afford **67** (386 mg, 0.44 mmol, 71%) as a pale yellow solid. Mp 86°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, J = 7.5 Hz, 2H, ArH1''' and ArH8'''); 7.52 (d, J = 8.7 Hz, 2H, ArH4''' and ArH5'''); 7.33 (dd, J = 7.8, 7.8 Hz, 2H, ArH3''' and ArH6'''); 7.19 (m, 2H, ArH2''' and ArH7'''); 6.90 (d, J = 8.1 Hz, 2H, ArH2' and ArH6'); 6.68 (d, J = 8.1 Hz, 2H, ArH3' and ArH5'); 6.32 (bs, 2H, NH); 6.15 (d, J = 8.1 Hz, 1H , NH); 5.91 (m, 1H, H2''); 5.29 (d, J = 17.4, 1H, $H3_a$''); 5.18 (d, J = 10.5 Hz, 1H, $H3_b$''); 4.71 (dd, J = 7.8, 13.5 Hz, 1H, H2); 4.26 (m, 5H, H1'', $OC\underline{H_2}$-H9''' and H5); 4.06 (m, 1H, H9'''); 3.62 (s, 3H, OCH_3); 3.17 (m, 2H, H8); 2.98 (m, 2H, $ArCH_2$); 2.58 (s, 3H, 7''''-CH_3); 2.56 (m, 2H, H4''''); 2.55 (s, 3H, 5''''-CH_3); 2.06 (s, 3H, 8''''-CH_3); 1.71 (t, J = 6.6 Hz, 2H, H3''''); 1.60 (m, 2H, H6); 1.48 (m, 2H, H7); 1.24 (s, 6H, 2 x 2''''-CH_3). Mass Spectrum (ES, +ve) *m/z* 880 (100%), [MH^+]. HRMS calcd for $C_{48}H_{58}N_5O_9S$ 880.3955, found 880.3944.

Methyl (2*S*, 5*S*)-2-(4-allyloxybenzyl)-3-aza-5-(9*H*-9-fluorenylmethylcarboxamido)-4-oxo-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]nonanoate (67)



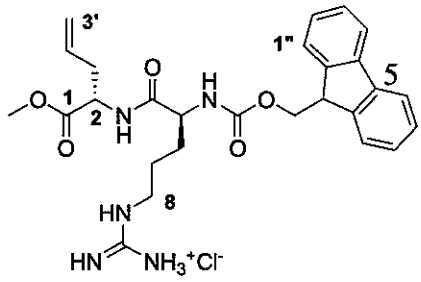
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **60** (200 mg, 0.74 mmol) and (2*S*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]pentanoic acid (411 mg, 0.62 mmol) to afford **67** (460 mg, 0.52 mmol, 84%) as a pale yellow solid. Mp 88-90°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, J = 7.8 Hz, 2H, ArH1''' and ArH8'''); 7.53 (d, J = 6.6 Hz, 2H, ArH4''' and ArH5'''); 7.33 (m, 2H, ArH3''' and ArH6'''); 7.18 (m, 2H, ArH2''' and ArH7'''); 6.98 (d, J = 8.1 Hz, 2H, ArH2' and ArH6'); 6.70 (d, J = 8.1 Hz, 2H, ArH3' and ArH5'); 6.34 (bs, 2H, NH); 6.13 (bs, 1H , NH); 5.93 (m, 1H, H2"); 5.30 (dd, J = 1.5, 17.1, 1H, $H3_a$"); 5.19 (d, J = 1.5, 10.5 Hz, 1H, $H3_b$"); 4.68 (m, 1H, H2); 4.30 (m, 5H, H1", $OC\underline{H}_2$-H9"'and H5); 4.08 (m, 1H, H9"'); 3.60 (s, 3H, OCH_3); 3.21 (m, 2H, H8); 2.97 (m, 2H, $ArCH_2$); 2.58 (s, 3H, 7""-CH_3); 2.56 (m, 2H, H4""); 2.54 (s, 3H, 5""-CH_3); 2.07 (s, 3H, 8""-CH_3); 1.84 (m, 2H, H6); 1.72 (t, J = 6.9 Hz, 2H, H3""); 1.55 (m, 2H, H7); 1.25 (s, 6H, 2 x 2""-CH_3). Mass Spectrum (ES, +ve) *m/z* 880 (30%), 902 (100%) [MNa^+]. HRMS calcd for $C_{48}H_{58}N_5O_9S$ 880.3955, found 880.3943.

Methyl (2*S*,5*R*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (69)



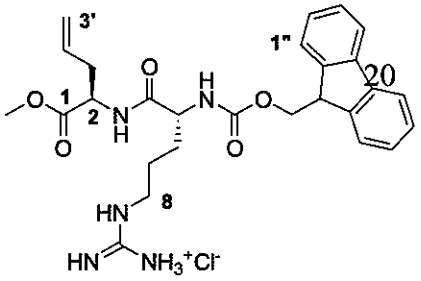
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **28** (81 mg, 0.105 mmol) giving **69** as a highly hydroscopic solid (43 mg, 0.079 mmol, 75%). Mp 203-208°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.88 (m, 2H, ArH1" and ArH8"); 7.62 (m, 2H, ArH4" and ArH5"); 7.36 (m, 4H, ArH3" and ArH6" and ArH2" and ArH7"); 5.72 (m, 1H, H2'); 5.06 (m, 2H, H3); 4.46 (dd, J = 5.4, 8.4 Hz, 1H, H2); 4.39 (d, J = 6.3 Hz, 2H, $OC\underline{H}_2$-H9"); 4.31 (m, 1H, H5); 4.19 (m, 1H, H9"); 3.68 (s, 3H, OCH_3); 3.17 (bs, 2H, H8); 2.51 (m, Hz, 2H, H1'); 1.79 (m, 2H, H7); 1.64 (m, 2H, H6). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.1, C4; 172.9, C1; 158.4, 5-NCO_2; 146.3, ArC8a" and ArC9a"; 142.4, ArC4a and ArC4b; 134.1, C2'; 129.1, ArCH3" and ArCH6"; 128.0, ArCH2" and ArCH7"; 126.6, ArCH4" and ArCH5"; 120.8, ArCH1" and ArCH8"; 118.9, C3'; 67.9, $\underline{C}H_2$-C9"; 55.8, C9"; 53.4, C2; 52.8, OCH_3; 51.1, C5; 42.0, C8; 36.8, C1'; 30.5, H7; 26.3, H6. Mass Spectrum (ES, +ve) *m/z* 508 (100%) [M^+]. HRMS calcd for $C_{27}H_{34}N_5O_5$ 508.2526, found 508.2570.

Methyl (2*S*,5*S*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (70)



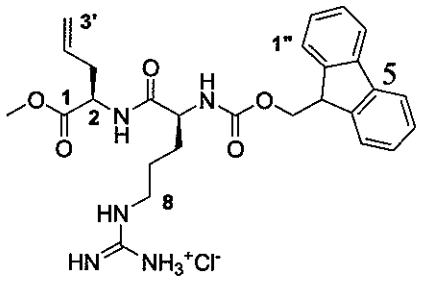
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **33** (81 mg, 0.105 mmol) giving **70** (27 mg, 0.05 mmol, 47%) as a highly hydroscopic solid. Mp 176-182°C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.79 (d, J = 7.5 Hz, 2H, ArH1" and ArH8"); 7.62 (m, 2H, ArH4" and ArH5"); 7.34 (m, 4H, ArH3" and ArH6" and ArH2" and ArH7"); 5.77 (m, 1H, H2'); 5.10 (m, 2H, H3'); 4.46 (dd, J = 6.0, 8.1 Hz, 1H, H2); 4.34 (d, J = 7.2 Hz, 2H, OC<u>H</u>$_2$-H9"); 4.32 (m, 1H, H5); 4.19 (m, 1H, H9"); 3.69 (s, 3H, OCH_3); 3.20 (m, 2H, H8); 2.52 (m, 2H, H1'); 1.83 (m, 2H, H7); 1.68 (m, 2H, H6). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.4, C4; 173.2, C1; 158.4, CN_3; 158.3, 5-NCO_2; 144.2, ArC8a" and ArC9a"; 142.4, ArC4a" and ArC4b"; 134.1, C2'; 129.1, ArCH3" and ArCH6"; 128.7, ArCH2" and ArCH7"; 126.7, ArCH4" and ArCH5"; 120.9, ArCH1" and ArCH8"; 119.0, C3'; 67.9, <u>C</u>H$_2$-C9"; 55.6, C9"; 53.5, C2; 52.8, OCH_3; 48.1, C5; 42.0, C8; 36.6, C1'; 30.3, H7; 26.2, H6. Mass Spectrum (ES, +ve) *m/z* 508 (100%) [M$^+$]. HRMS calcd for $C_{37}H_{34}N_5O_5$ 508.2560, found 508.2574.

Methyl (2*R*,5*R*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (71)



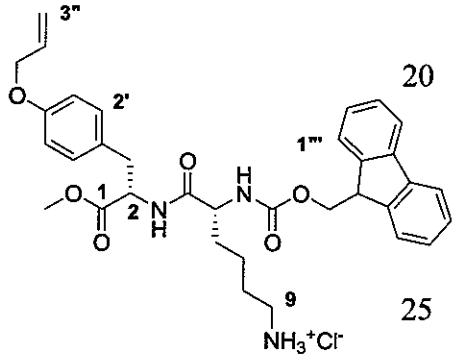
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **39** (80 mg, 0.10 mmol) to yield **71** as a highly hydroscopic white solid (45 mg, 0.083 mmol, 80%). ^{1}H NMR (CD_3OD, 500 MHz): δ 7.61 (d, J = 7.5 Hz, 2H, ArH1" and ArH8"); 7.47 (d, J = 8.5 Hz, 2H, ArH4" and ArH5"); 7.20 (t, J = 7.5 Hz, 2H, ArH3" and ArH6"); 7.12 (t, J = 7.5 Hz, 2H, ArH2" and ArH7"); 5.58 (m, 1H, H2'); 4.93 (d, J = 17.0 Hz, 1H, H3$_a$'); 4.87 (d, J = 10.0 Hz, 1H, H3$_b$'); 4.28 (dd, J = 6.0, 8.0 Hz, 1H, H2); 4.20 (d, J = 7.0 Hz, 2H, OC<u>H</u>$_2$-H9"); 4.03 (t, J = 7.0 Hz, 1H, H5); 3.99 (t, J = 7.0 Hz, 1H, H9"); 3.51 (s, 3H, OCH_3); 3.01 (bs, 2H, H8); 2.34 (m, 2H, H1'); 1.64 (bs, 2H, H7); 1.47 (bs, 2H, H6). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.1, C4; 173.1, C1; 158.4, CN_3; 158.2, 5-NCO_2; 145.1, ArC8a" and ArC9a"; 142.4, ArC4a and ArC4b; 133.9, C2'; 128.6, ArCH3" and ArCH6"; 128.0, ArCH2" and ArCH7"; 126.0, ArCH4" and ArCH5"; 120.8, ArCH1" and ArCH8"; 118.8, C3'; 67.9, <u>C</u>H$_2$-C9"; 55.6, C9"; 53.6, C2; 52.7, OCH_3; 49.3, C5; 42.1, C8; 36.7, C1'; 30.4, C7; 26.2, C6. Mass Spectrum (ES, +ve) *m/z* 508 (45%) [M$^+$]. HRMS calcd for $C_{27}H_{34}N_5O_5$ 508.2560, found 508.2592.

Methyl (2*R*,5*S*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (72)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **44** (94 mg, 0.12 mmol) to yield **72** as a highly hydroscopic white solid (33 mg, 0.061 mmol, 51%). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.79 (d, J = 7.5 Hz, 2H, ArH1" and ArH8"); 7.65 (m, 2H, ArH4" and ArH5"); 7.39 (t, J = 7.2 Hz, 2H, ArH3" and ArH6"); 7.30 (t, J = 7.2 Hz, 2H, ArH2" and ArH7"); 5.72 (m, 1H, H2'); 5.09 (d, J = 16.5 Hz, 1H, $H3_a$'); 5.04 (d, J = 9.6 Hz, 1H, $H3_b$'); 4.46 (dd, J = 5.7, 8.4 Hz, 1H, H2); 4.40 (d, J = 6.3 Hz, 2H, $OC\underline{H}_2$-H9"); 4.22 (t, J = 6.6 Hz, 1H, H5); 4.16 (m, 1H, H9"); 3.69 (s, 3H, OCH_3); 3.17 (t, J = 6.6 Hz, 2H, H8); 2.51 (m, 2H, H1'); 1.80 (m, 2H, H7); 1.62 (m, 2H, H6). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.0, C4; 172.9, C1; 158.4, CN_3; 158.2, 5-NCO_2; 145.1, ArC8a" and ArC9a"; 142.4, ArC4a" and ArC4b"; 134.1, C2'; 128.7, ArCH3" and ArCH6"; 128.0, ArCH2" and ArCH7"; 126.0, ArCH4" and ArCH5"; 120.8, ArCH1" and ArcH8"; 118.9, C3'; 67.9, $C\underline{H}_2$-C9"; 55.8, C9"; 53.4, C2; 52.8, OCH_3; 49.3, C5; 42.0, C8; 36.8, C1'; 30.5, C7; 26.3, C6. Mass Spectrum (ES, +ve) *m/z* 508 (25%) [M^+], 179 (100%) [Sodium allylglycinamide]. HRMS calcd for $C_{27}H_{34}N_5O_5$ 508.2560, found 508.2555.

Methyl (2*S*,5*R*)-2-(4-allyloxybenzyl)-9-amino-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxononanoate hydrochloride (73)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **61** (132 mg, 0.19 mmol) to yield **73** (92 mg, 0.15 mmol, 79%) as a white solid. Mp 162-170°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.02 (d, J = 8.0 Hz, 1H, NH); 7.79 (d, J = 7.6 Hz, 2H, ArH1"' and ArH8"'); 7.64 (t, J = 8.4 Hz, 2H, ArH4"' and ArH5"'); 7.38 (t, J = 7.2 Hz, 2H, ArH3"' and ArH6"'); 7.29 (m, 2H, ArH2"' and ArH7"'); 7.04 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.73 (d, J = 8.4 Hz, 2H, ArH3' and ArH5'); 5.94 (m, 1H, H2"); 5.28 (d, J = 17.3 Hz, 1H, $H3_a$"); 5.16 (d, J = 10.5 Hz, 1H, $H3_b$"); 4.62 (dt, J = 5.0, 8.8 Hz, 1H, H5); 4.33 (m, 4H, H1' and $OC\underline{H}_2$-H9"'); 4.19 (t, J = 6.7 Hz, 1H, H9"'); 4.07 (dd, J = 5.1, 8.0 Hz, 1H, H2); 3.70 (s, 3H, OCH_3); 3.11 (m, 2H, H9); 2.90 (m, 2H, $ArCH_2$); 1.60 (m, 4H, H6 and H7); 1.33 (m, 2H, H8). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.2, C4; 173.2, C1; 158.1, NCO_2; 145.1, ArC4'; 145.0, ArC8a"' and ArC9a"'; 142.4, ArC4a"' and ArC4b"'; 134.7, C2"; 131.1, ArCH2' and ArCH6'; 129.8, ArCH3"' and ArCH6"'; 128.7, ArCH2"' and ArCH7"'; 128.7, ArCH1"' and ArCH8"'; 128.1, ArCH4"' and ArCH5"'; 120.8, ArC1'; 117.3, C3'; 115.6, ArCH3' and ArCH5'; 69.6, $C\underline{H}_2$-C9"'; 68.0, C1"; 56.1, C5; 55.2, C2; 55.1, OCH_3; 52.8, C9"'; 40.5, C9; 37.3, $ArCH_2$; 32.6, C6; 28.1, C8; 23.6, C7. Mass Spectrum (ES, +ve) *m/z* 586.3 (100%) [M^+]. HRMS calcd for $C_{34}H_{40}N_3O_6$ 586.2917, found 586.2935.

Methyl (2*S*,5*S*)-2-(4-allyloxybenzyl)-9-amino-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxononanoate hydrochloride (74)

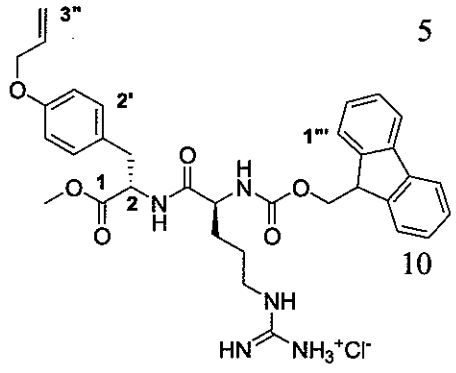
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **66** (73 mg, 0.106 mmol) to yield **74** (48 mg, 0.07 mmol, 68%) as a white solid. Mp 160-168°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.79 (d, J = 7.2 Hz, 2H, ArH1"' and ArH8"'); 7.65 (d, J = 7.2 Hz, 2H, ArH4"' and ArH5"'); 7.39 (t, J = 7.2 Hz, 2H, ArH3"' and ArH6"'); 7.29 (t, J = 7.2 Hz, 2H, ArH2"' and ArH7"'); 7.07 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.77 (d, J = 8.4 Hz, 2H, ArH3' and ArH5'); 5.96 (m, 1H, H2"); 5.29 (dd, J = 1.2, 18.3 Hz, 1H, $H3_a$"); 5.16 (dd, J = 1.2, 10.5 Hz, 1H, $H3_b$"); 4.63 (m, 1H, H5); 4.37 (m, 4H, H1' and $OC\underline{H}_2$-H9"'); 4.20 (m, 1H, H9"'); 4.09 (m, 1H, H2); 3.67 (s, 3H, OCH_3); 3.00 (m, 2H, H9); 2.90 (m, 2H, $ArCH_2$); 1.65 (m, 4H, H6 and H7); 1.39 (m, 2H, H8). ^{13}C NMR (CD_3OD, 125 MHz): δ 174.4, C4; 173.3, C1; 158.1, NCO_2; 145.2, ArC4'; 145.0, ArC8a"' and ArC9a"'; 142.4, ArC4a"' and ArC4b"'; 134.7, C2"; 131.2, ArCH2' and ArCH6'; 129.8, ArCH3"' and ArCH6"'; 128.8, ArCH2"' and ArCH7"'; 128.1, ArCH1"' and ArCH8"'; 126.2, ArCH4"' and ArCH5"'; 120.9, ArC1'; 117.4, C3'; 115.6, ArCH3' and ArCH5'; 69.6, $\underline{C}H_2$-C9"'; 68.0, C1"; 55.9, C5; 55.2, C2; 55.1, OCH_3; 52.8, C9"'; 40.4, C9; 37.3, $ArCH_2$; 32.4, C6; 27.9, C8; 23.6, C7. Mass Spectrum (ES, +ve) *m/z* 586.7 (100%) [M^+]. HRMS calcd for $C_{34}H_{40}N_3O_6$ 586.2917, found 586.2925.

Methyl (2*S*,5*R*)-2-(4-allyloxybenzyl)-3-aza-5-(9*H*-9-fluorenylmethylcarboxamido)-8-guanidino-4-oxononanoate hydrochloride (75)

The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **67** (62 mg, 0.068 mmol) to yield **75** (35 mg, 0.054 mmol, 79%) as a white solid. Mp 158-162°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.78 (d, J = 7.5 Hz, 2H, ArH1"' and ArH8"'); 7.64 (d, J = 8.1 Hz, 2H, ArH4"' and ArH5"'); 7.38 (t, J = 6.9 Hz, 2H, ArH3"' and ArH6"'); 7.37 (m, 2H, ArH2"' and ArH7"'); 7.04 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.72 (d, J = 8.4 Hz, 2H, ArH3' and ArH5'); 5.92 (m, 1H, H2"); 5.28 (d, J = 17.1, 1H, $H3_a$"); 5.16 (d, J = 10.8 Hz, 1H, $H3_b$"); 4.61 (dd, J = 5.1, 9.0 Hz, 1H, H2); 4.32 (m, 4H, H1" and $OC\underline{H}_2$-H9"'); 4.18 (m, 1H, H5); 4.09 (m, 1H, H9"'); 3.69 (s, 3H, OCH_3); 3.09 (m, 2H, H8); 2.91 (m, 2H, $ArCH_2$); 1.62 (m, 2H, H6); 1.51 (m, 2H, H7). ^{13}C NMR (CD_3OD, 75 MHz): δ 172.0, C4; 171.8, C1 156.8, CN_3; 156.6, ArC4'; 155.9, NCO_2; 143.8, ArC8a"' and ArC9a"'; 140.8, ArC4a"' and ArC4b"'; 135.5, C2"; 130.1, ArC1'; 129.6, ArCH4"' and ArCH5"'; 127.7, ArCH2"' and ArCH7"'; 127.2, ArCH1"' and ArCH8"'; 125.4, ArCH3"' and ArCH6"'; 120.2, ArCH2' and ArCH6'; 117.3, C3"; 114.3, ArCH3' and ArCH5'; 68.0, C1"; 65.8, $\underline{C}H_2$-C9"'; 59.3, C9"'; 54.0, C5; 52.0, OCH_3; 46.7, C2;

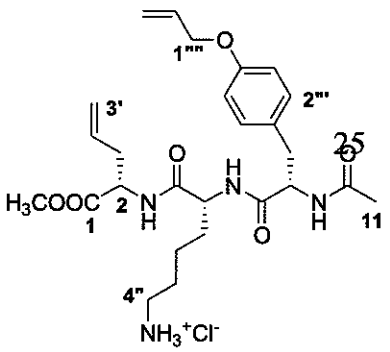
40.3, C8; 36.1, $ArCH_2$; 29.1, C6; 24.9, C7. Mass Spectrum (ES, +ve) *m/z* 614.6 (100%) [M^+]. HRMS calcd for $C_{34}H_{40}N_5O_6$ 614.2979, found 614.3007.

Methyl (2*S*,5*S*)-2-(4-allyloxybenzyl)-3-aza-5-(9*H*-9-fluorenylmethylcarboxamido)-8-guanidino-4-oxononanoate hydrochloride (76)



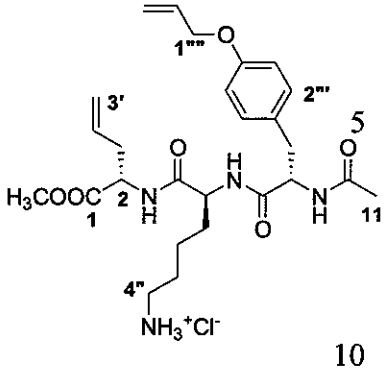
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **68** (93 mg, 0.10 mmol) to yield **76** (54 mg, 0.083 mmol, 83%) as a white solid. Mp 170-175°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.90 (d, *J* = 7.2 Hz, 2H, ArH1''' and ArH8'''); 7.75 (m, 2H, ArH4''' and ArH5'''); 7.38 (m, 4H, ArH3''', ArH6''', ArH2''' and ArH7'''); 7.14 (d, *J* = 8.1 Hz, 2H, ArH2' and ArH6'); 6.82 (d, *J* = 8.1 Hz, 2H, ArH3' and ArH5'); 5.98 (m, 1H, H2''); 5.34 (d, *J* = 17.1, 1H, $H3_a$''); 5.21 (d, *J* = 10.8 Hz, 1H, $H3_b$''); 4.46 (m, 2H, H2 and H5); 4.26 (m, 4H, H1'' and $OC\underline{H}_2$-H9'''); 4.08 (m, 1H, H9'''); 3.59 (s, 3H, OCH_3); 3.12 (m, 2H, H8); 2.94 (m, 2H, $ArCH_2$); 1.69 (m, 2H, H6); 1.52 (m, 2H, H7). ^{13}C NMR (CD_3OD, 75 MHz): δ 171.9, C4; 171.8, C1 157.0, CN_3; 156.6, ArC4'; 155.9, NCO_2; 143.9, ArC8a''' and ArC9a'''; 140.7, ArC4a''' and ArC4b'''; 133.8, C2''; 130.1, ArC1'; 129.0, ArCH4''' and ArCH5'''; 127.7, ArCH2''' and ArCH7'''; 127.1, ArCH1''' and ArCH8'''; 125.4, ArCH3''' and ArCH6'''; 120.1, ArCH2' and ArCH6'; 117.3, C3''; 114.4, ArCH3' and ArCH5'; 68.1, C1''; 65.7, $\underline{C}H_2$-C9'''; 59.3, C9'''; 53.9, C5; 51.8, OCH_3; 46.7, C2; 40.3, C8; 35.7, $ArCH_2$; 29.0, C6; 25.1, C7. Mass Spectrum (ES, +ve) *m/z* 614.8 (100%) [M^+]. HRMS calcd for $C_{34}H_{40}N_5O_6$ 614.2979, found 614.2972.

Methyl (2*S*,5*R*,8*S*)-2-allyl-8-(4-allyloxyphenyl)-5-(4-aminobutyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (77)



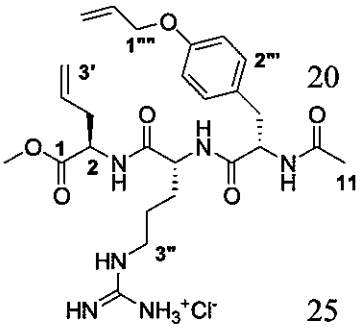
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **21** (64 mg, 0.11 mmol) to yield **77** (22 mg, 0.041 mmol, 37%) as a cream highly hydroscopic solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.15 (d, *J* = 8.0 Hz, 2H, ArH2''' and ArH6'''); 6.87 (d, *J* = 8.0 Hz, 2H, ArH3''' and ArH5'''); 6.05 (m, 1H, H2''''); 5.73 (m, 1H, H2'); 5.39 (d, *J* = 17.0 Hz, 1H, H3''''); 5.24 (d, *J* = 10.5 Hz, 1H, H3''''); 5.08 (d, *J* = 17.0 Hz, 1H, H3'); 5.04 (d, *J* = 10.0 Hz, 1H, H3'); 4.52 (d, *J* = 5.5 Hz, 2H, H1''''); 4.44 (m, 2H, H2 and H5); 4.15 (d, *J* = 6.5 Hz, 1H, H8); 3.69 (s, 3H, OCH_3); 2.92 (m, 2H, H1'); 2.83 (bs, 2H, H4''); 2.54 (m, 2H, $ArCH_2$); 1.93 (s, 3H, H11); 1.74 (bs, 2H, H1''); 1.50 (bs, 2H, H2''); 1.00 (bs, 2H, H3''). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.3, C7; 173.7, C1; 173.2, C4; 173.1, C10; 158.8, ArC4'''; 134.8, C2'; 134.5, C2''''; 131.3, ArCH2''' and ArCH6'''; 129.9, ArC1'''; 118.4, C3'; 117.5, C3''''; 115.8, ArCH3''' and ArCH5'''; 69.8, C1''''; 57.6, C5; 54.2, OCH_3; 53.8, C8; 52.7, C2; 40.3, C4'; 37.4, $ArCH_2$; 36.4, C1'; 31.7, C1''; 28.0, C3''; 23.5, C11; 22.4, C2''. Mass Spectrum (ES, +ve) *m/z* 503.7 (100%) [M^+]. HRMS calcd for $C_{26}H_{39}N_4O_6$ 503.2870, found 503.2881.

Methyl (2*S*,5*S*,8*S*)-8-acetamido-2-allyl-9-(4-allyloxyphenyl)-5-(4-aminobutyl)-3,6-diaza-4,7-dioxononanoate hydrochloride (78)



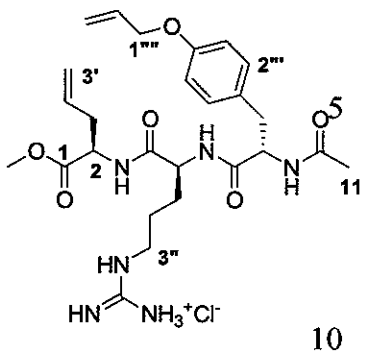
The title compound was synthesized using the general procedure (Procedure A), by deprotection of **25** (104 mg, 0.170 mmol) to yield **78** as a 1:1 mixture of epimers (55 mg, 0.10 mmol, 60%) as a highly hydroscopic yellow solid. Mp 150-154°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.14 (d, J = 8.0 Hz, 2H, ArH2"' and ArH6"'); 6.84 (t, J = 8.0 Hz, 2H, ArH3"' and ArH5"'); 6.03 (m, 1H, H2""); 5.76 (m, 1H, H2'); 5.37 (d, J = 17.3 Hz, 1H, $H3_a$""); 5.22 (d, J = 9.7 Hz, 1H, $H3_b$""); 5.10 (m, 2H, H3'); 4.53 (m, 5H, H2, H5, H8 and H1""); 3.69/3.67 (s, 3H, OCH_3); 2.87 (m, 4H, H1' and H4"); 2.54 (m, 2H, $ArCH_2$); 1.93/1.91 (s, 3H, H11); 1.50 (s, 6H, H1", H2" and H3"). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.7/173.6, C7; 173.4, C1; 173.1, C4; 173.0/172.9, C10; 158.7, ArCH4"'; 134.8, C2'; 134.3/134.0, C2""; 131.2/131.1, ArCH2"' and ArCH6"'; 130.2/130.1, ArC1"'; 118.8/118.5, C3'; 117.4/117.3, C3""; 115.7/115.6, ArCH3"' and ArCH5"'; 69.8/69.7, C1""; 57.2, C5; 54.0, OCH_3; 53.8/53.7, C8; 52.8/52.7, C2; 40.6/40.5, C4'; 37.8/37.7, $ArCH_2$; 36.6/36.5, C1'; 31.9, C1"; 28.0, C3"; 23.4, C11; 22.5, C2". Mass Spectrum (ES, +ve) *m/z* 503.3 (100%) [M^+]. HRMS calcd for $C_{26}H_{39}N_4O_6$ 503.2870, found 503.2894.

Methyl (2*R*,5*R*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino)-4,7,10-oxoundecanoate hydrochloride (79)



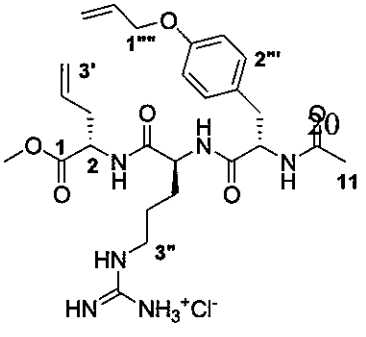
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **41** (48 mg, 0.60 mmol) to yield **79** as a highly hydroscopic solid (32 mg, 0.060 mmol, 100%). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.15 (d, J = 8.4 Hz, 2H, ArH2"' and ArH6"'); 6.86 (d, J = 8.7 Hz, 2H, ArH3"' and ArC5"'); 6.04 (m, 1H, H2""); 5.77 (m, 1H, H2'); 5.38 (dd, J = 1.5, 17.4 Hz, 1H, $H3_a$""); 5.23 (dd, J = 1.2, 10.5 Hz, 1H, $H3_b$""); 5.09 (dd, J = 1.2, 16.8 Hz, 1H, $H3_a$'); 5.06 (d, J = 10.6 Hz, 1H, $H3_b$'); 4.50 (m, 4H, H2"" and H2); 4.39 (dd, J = 5.7, 8.1 Hz, 1H, H5); 4.26 (dd, J = 4.5, 8.7 Hz, 1H, H8); 3.68 (s, 3H, OCH_3); 3.07 (t, J = 7.2 Hz, 2H, H3"); 2.94 (m, 2H, $ArCH_2$); 2.54 (m, 2H, H1'); 1.95 (s, 3H, H11); 1.62 (m, 2H, H1"); 1.32 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.7, C4; 173.6, C11; 173.4, C1; 172.9, C7; 158.8, ArC4"'; 158.4, CN_3; 134.8, C2""; 134.3, C2'; 131.2, ArC1"'; 130.0, ArCH2"' and ArCH6"'; 118.6, C3'; 117.4, C3""; 115.7, ArCH3"' and ArCH5"';69.8, C1""; 57.2, C2; 53.8, C5; 53.8, C8; 52.8, OCH_3; 50.1, C3"; 37.7, $ArCH_2$; 36.5, C1'; 29.7, C2"; 22.9, C11; 22.3, C1". Mass Spectrum (ES, +ve) *m/z* 531.5 (80%) [M^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2936.

Methyl (2*R*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino)-4,7,10-oxoundecanoate hydrochloride (80)



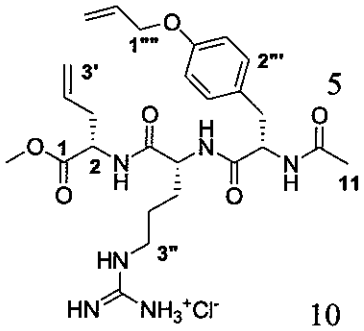
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **46** (87 mg, 0.11 mmol) to yield **80** as a highly hydroscopic solid (35 mg, 0.062 mmol, 56%). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.16 (d, J = 8.5 Hz, 2H, ArH2''' and ArH6'''); 6.83 (d, J = 8.0 Hz, 2H, ArH3''' and ArH5'''); 6.04 (m, 1H, H2''''); 5.74 (m, 1H, H2'); 5.38 (dd, J = 1.5, 17.5 Hz, 1H, $H3_a$''''); 5.23 (dd, J = 1.0, 10.5 Hz, 1H, $H3_b$''''); 5.12 (d, J = 17.0 Hz, 1H, $H3_a$'); 5.08 (d, J = 10.5 Hz, 1H, $H3_b$'); 4.50 (d, J = 5.0 Hz, 2H, H1''''); 4.43 (m, H2, H5 and H8); 3.71 (s, 3H, OCH_3); 2.97 (t, J = 7.5 Hz, 2H, H3''); 2.94 (m, 2H, $ArCH_2$); 2.52 (m, 2H, H1'); 1.93 (s, 3H, CH_3, H11); 1.78 (m, 2H, H1''); 1.61 (m, 2H, H2''). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.9, C4; 173.4, C11; 173.1, C1; 172.9, C7; 158.8, ArC4'''; 158.4, CN_3; 134.8, C2''''; 134.1, C2'; 131.1, ArC1'''; 130.2, ArCH2''' and ArCH6'''; 118.9, C3'; 117.2, C3''''; 115.6, ArCH3''' and ArCH5''';69.7, C1''''; 56.9, C2; 53.8, C5; 53.6, C8; 52.8, OCH_3; 50.1, C3''; 37.7, $ArCH_2$; 36.9, C1'; 26.1, C2''; 22.5, C11; 20.7, C1''. Mass Spectrum (ES, +ve) *m/z* 531.1 (85%) [M^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2952.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino]propyl)-4,7,10-oxoundecanoate hydrochloride (81)



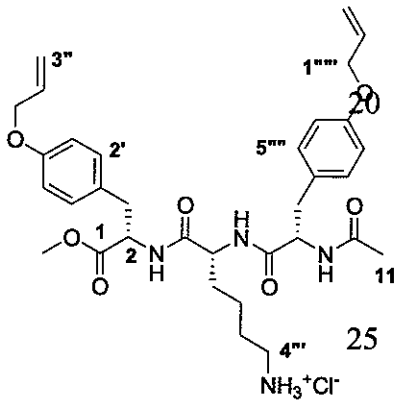
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **36** (63 mg, 0.079 mmol) to yield **81** as a highly hydroscopic solid (38 mg, 0.036 mmol, 85%). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.13 (d, J = 8.7 Hz, 2H, ArH2''' and ArH6'''); 6.82 (d, J = 8.7 Hz, 2H, ArH3''' and ArH5'''); 6.03 (m, 1H, H2''''); 5.77 (m, 1H, H2'); 5.36 (dd, J = 1.5, 17.4 Hz, 1H, $H3_a$''''); 5.22 (dd, J = 1.5, 10.5 Hz, 1H, $H3_b$''''); 5.13 (d, J = 18.3 Hz, 1H, $H3_a$'); 5.08 (d, J = 9.6 Hz, 1H, $H3_b$'); 4.49 (m, 3H, H1'''' and H5); 4.40 (m, 2H, H2 and H8); 3.69 (s, 3H, OCH_3); 3.18 (m, 2H, H3''); 3.02 (dd, J = 5.7, 13.8 Hz, 1H, ArCHH); 2.82 (dd, J = 9.0, 14.1 Hz, 1H, ArCHH); 2.51 (m, 2H, H1'); 1.92 (s, 3H, H11); 1.83 (m, 2H, H1''); 1.64 (m, 2H, H2''). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.9, C4; 173.5, C11; 173.4, C1; 173.2, C7; 158.8, ArC4'''; 158.4, CN_3; 134.9, C2''''; 134.2, C2'; 131.2, ArC1'''; 130.3, ArCH2''' and ArCH6'''; 117.4, C3'; 116.2, C3''''; 115.6, ArCH3''' and ArCH5'''; 69.7, C1''''; 56.6, C2; 53.8, C5; 53.6, C8; 52.8, OCH_3; 50.1, C3''; 36.6, $ArCH_2$; 36.5, C1'; 30.3, C2''; 23.0, C11; 22.5, C1''. Mass Spectrum (ES, +ve) *m/z* 531.1 (100%) [M^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2916.

Methyl (2*S*,5*R*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino]propyl)-4,7,10-oxoundecanoate hydrochloride (82)



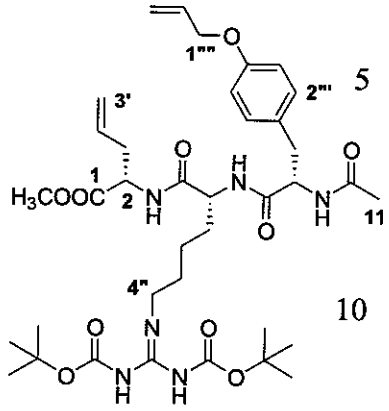
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **30** (70 mg, 0.088 mmol) to yield **82** as a highly hydroscopic solid (37 mg, 0.065 mmol, 74%). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.12 (d, J = 7.5 Hz, 2H, ArH2"' and ArH6"'); 6.83 (d, J = 7.5 Hz, 2H, ArH3"' and ArC5"'); 6.01 (m, 1H, H2""); 5.69 (m, 1H, H2'); 5.35 (d, J = 17.4 Hz, 1H, $H3_a$""); 5.19 (d, J = 9.9 Hz, 1H, $H3_b$""); 5.09 (m, 2H, H3'); 4.47 (m, 2H, H2""); 4.40 (m, 2H, H2 and H5); 4.16 (m, 1H, H8); 3.65 (s, 3H, OCH_3); 3.31 (m, 2H, H3"); 2.95 (m, 2H, $ArCH_2$); 2.50 (m, 2H, H1'); 1.92 (s, 3H, H11); 1.74 (m, 2H, H1"); 1.23 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.0, C4; 173.4, C11; 172.9, C1; 169.0, C7; 158.8, ArC4"'; 158.2, CN_3; 134.7, C2""; 134.3, C2'; 131.2, ArC1"'; 129.8, ArCH2"' and ArCH6"'; 118.4, C3'; 117.4, C3""; 115.7, ArCH3"' and ArCH5"'; 69.8, C1""; 57.7, C2; 54.0, C5; 53.7, C8; 52.8, OCH_3; 50.1, C3"; 37.5, $ArCH_2$; 36.4, C1'; 29.5, C2"; 24.0, C11; 22.3, C1". Mass Spectrum (ES, +ve) *m/z* 531 (100%) [M^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2939.

Methyl (2*S*,5*R*,8*S*)-2,8-di(4-allyloxybenzyl)-5-(4-aminobutyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (83)



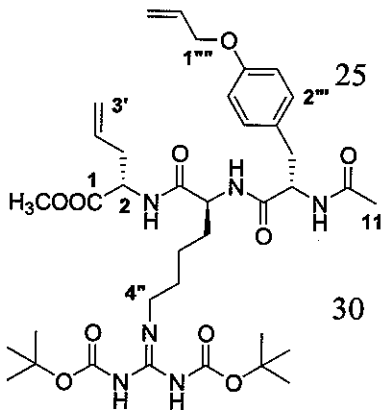
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **63** (33 mg, 0.051 mmol) to yield **83** (18 mg, 0.028 mmol, 55%) as a yellow solid. Mp 186-190°C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.50 (bs, 1H, NH); 7.41 (m, 4H, ArH); 7.17 (m, 4H, ArH); 6.38 (m, 2H, H2" and H2""'); 5.64 (m, 4H, H3" and H3""'); 4.83 (m, 6H, H2, H8, H1" and H1""'); 4.51 (m, 1H, H5); 3.70 (s, 3H, OCH_3); 3.28 (m, 6H, H4"', Ar'-CH_2 and Ar""-CH_2); 2.27 (s, 3H, H11); 1.87 (m, 4H, H1" and H3"); 1.33 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 125 MHz): δ 173.9, C7; 173.7, C4; 173.1, C1; 172.0, C10; 158.5, ArC4"" and ArC4'; 134.7, C2" and C2""'; 131.3, ArCH2' and ArCH6'; 131.1, ArCH2"" and ArCH6""; 130.0, ArC1""; 129.8, ArC1'; 117.8, C3"; 117.5, C3""'; 115.8, ArCH3' and ArCH5'; 115.6, ArCH3"" and ArCH5""; 70.0, C1"; 69.8, C1""'; 57.2, C2; 55.2, C5; 53.8, OCH_3; 52.4, C8; 40.7, C4"'; 37.4, Ar'-CH_2; 37.1, Ar""-CH_2; 31.7, C1"'; 27.9, C3"'; 23.2, C11; 22.2, C2"'. Mass Spectrum (ES, +ve) *m/z* 609.7 (100%) [M^+]. HRMS calcd for $C_{33}H_{45}N_4O_7$ 609.3288, found 609.3301.

Methyl (2*S*,5*R*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4[{*N*,*N*-di-*tert*-butoxycarbonyl}guanidino]butyl)-4,7,10-trioxoundecanoate (84)



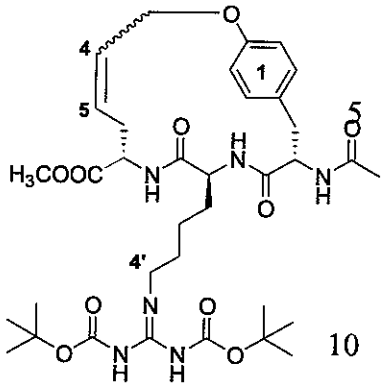
To a solution of **21** (56 mg, 0.093 mmol) in DCM (2 mL) was added TFA (2 mL) and the resulting mixture was allowed to stir for 3 h. The solvent was concentrated and the intermediate trifluoroacetate salt was precipitated by addition of diethyl ether and collected as a solid by vacuum filtration. To this solid was added *N-tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (65 mg, 0.17 mmol), triethylamine (0.2 mL) and DCM (2 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/ MeOH) to yield the title compound as a 1:1 mixture of epimers (70 mg, 0.093 mmole, 100%) as an orange/yellow solid. Mp 112-114°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.31 (bs, 1H, NH); 7.20 (d, J = 8.0 Hz, 1H, NH); 7.08 (m, 2H, ArH2"' and ArH6"'); 6.94 (d, J = 7.6 Hz, 1H, NH); 6.84 (m, 2H, ArH3"' and ArH5"'); 6.72 (d, J = 7.2 Hz, 1H, NH); 6.60 (d, J = 7.6 Hz, 1H, NH); 6.02 (m, 1H, H2""); 5.65 (m, 1H, H2'); 5.38 (d, J = 17.3 Hz, 1H, $H3_a$""); 5.26 (d, J = 10.5 Hz, 1H, $H3_b$""); 5.11 (m, 2H, H3'); 4.52 (m, 5H, H2, H5, H8 and H2""); 3.74/3.70 (s, 3H, OCH_3); 3.32 (d, J = 6.7 Hz, 2H, H4"); 2.95 (m, 2H, $ArCH_2$); 2.50 (m, 2H, H1'); 1.97./1.96 (s, 3H, H11); 1.37 (m, 6H, H1", H2" and H3"); 1.49 (s, 18H, 2 x $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 745.4 (100%) [MH^+]. HRMS calcd for $C_{37}H_{57}N_6O_{10}$ 745.4136, found 745.4138.

Methyl (2*S*,5*S*,8*S*) -2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4[{*N*,*N*-di-*tert*-butoxycarbonyl}guanidino]butyl)-4,7,10-trioxoundecanoate (85)



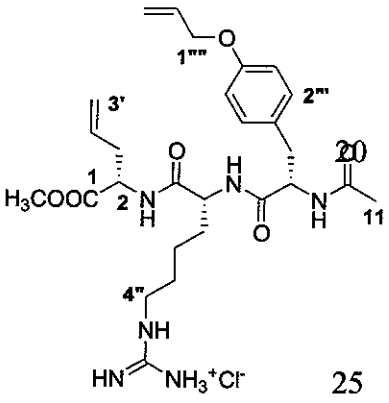
To a solution of **25** (41 mg, 0.081 mmol) in DCM (2 mL) was added *N-tert*-butoxycarboxamido (trifluoromethylsulfonylimino)methyl propanamide (35 mg, 0.089 mmol), triethylamine (0.1 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/ MeOH) to yield the title compound as a 1:1 mixture of epimers (45 mg, 0.060 mmole, 74%) as an orange/yellow solid. Mp 114-118°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (bs, 1H, NH); 7.08 (t, J = 8.4 Hz, 2H, ArH2"' and ArH6"'); 6.97 (m, 1H, NH); 6.83 (t, J = 8.4 Hz, 2H, ArH3"' and ArH5"'); 6.73 (d, J = 8.0 Hz, 1H, NH); 6.57 (t, J = 9.3 Hz, 1H, NH); 6.03 (m, 1H, H2""); 5.66 (m, 1H, H2'); 5.39 (d, J = 17.3 Hz, 1H, $H3_a$""); 5.26 (d, J = 10.1 Hz, 1H, $H3_b$""); 5.10 (m, 2H, H3'); 4.51 (m, 5H, H2, H5, H8 and H1""); 3.74/3.71 (s, 3H, OCH_3); 3.33 (bs, 2H, H4"); 2.96 (m, 2H, H1'); 2.52 (m, 2H, $ArCH_2$); 1.97 (s, 3H, H11); 1.47 (m, 6H, H1", H2" and H3");1.49 (s, 18H, $C(C\underline{H}_3)_3$). Mass Spectrum (ES, +ve) *m/z* 745.2 (100%) [MH^+]. HRMS calcd for $C_{37}H_{57}N_6O_{10}$ 745.4136, found 745.4105.

(7*S*,10*S*,13*S*,4*E/Z*)-13-Acetamido-8,11-diaza-10-(4-[{*N*,*N*-di-*tert*-butoxycarbonyl}guanidino]butyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (86)



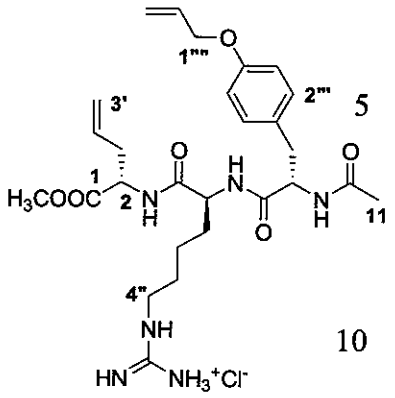
To a solution of **26** (75 mg, 0.15 mmol) in DCM (2 mL) was added *N*-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (115 mg, 0.29 mmol), triethylamine (0.1 mL) and DCM (2 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield **86** as a 1:1 mixture of epimers (96 mg, 0.13 mmole, 87%) as an orange/yellow solid. Mp 104-102°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (m, 1H, NH); 6.89 (m, 4H, ArH); 5.63 (m, 2H, H4 and H5); 4.65 (m, 5H, H2, H7, H10 and H13); 3.79/3.78 (s, 3H, OCH_3); 3.30 (m, 2H, H4'); 2.92 (m, 2H, H6); 2.67 (m, 2H, H14); 2.09/2.07 (s, 3H, $NCOCH_3$); 1.55 (m, 6H, H1', H2' and H3'); 1.49/1.48 (s, 18H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 717.4 (100%) [MH^+]. HRMS calcd for $C_{35}H_{53}N_6O_{10}$ 717.3823, found 717.3806.

Methyl (2*S*,5*R*,8*S*) -2-allyl-9-(4-allyloxybenzyl)-5-(4-[guanidino]butyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (87)



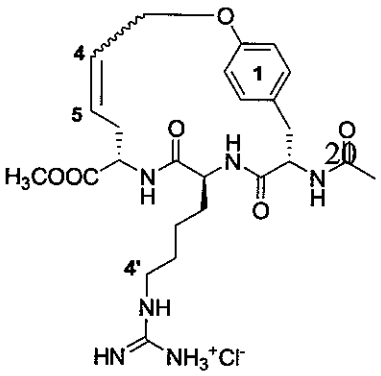
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **84** (71 mg, 0.095 mmol) to yield **87** (43 mg, 0.074mmol, 78%) as a yellow hydroscopic solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.20 (m, 2H, NH x 2); 7.15 (d, J = 8.4 Hz, 2H, ArH2''' and ArH6'''); 6.87 (d, J = 8.4 Hz, 2H, ArH3''' and ArH5'''); 6.03 (m, 1H, H2''''); 5.73 (m, 1H, H2'); 5.39 (d, J = 17.3 Hz, 1H, $H3_a$''''); 5.24 (d, J = 10.5 Hz, 1H, $H3_b$''''); 5.12 (d, J = 6.0 Hz, 1H, $H3_a$'); 5.05 (d, J = 9.9 Hz, 1H, $H3_b$'); 4.45 (m, 4H, H2, H5 and H1''''); 4.17 (dd, J = 4.0, 8.7 Hz, 1H, H8); 3.72 (s, 3H, OCH_3); 2.99 (m, 4H, H1' and H4"); 2.53 (m, 2H, $ArCH_2$); 1.94 (s, 3H, H11); 1.59 (m, 4H, H2" and H3"); 1.00 (m, 2H, H1"). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.3, C4; 174.0, C11; 173.3, C1; 173.2, C7; 159.0, ArC4'''; 158.5, CN_3; 134.9, C2''''; 134.5, C2'; 131.4, ArC1'''; 130.4, ArCH2''' and ArCH6'''; 118.6, C3'; 117.5, C3''''; 115.9, ArCH3''' and ArCH5'''; 69.8, C1''''; 57.5, C2; 54.3, C5; 53.8, C8; 52.7, OCH_3; 42.1, C4"; 37.5, $ArCH_2$; 36.4, C1'; 31.9, C2"; 29.2, C3"; 23.6, C11; 22.4, C1". Mass Spectrum (ES, +ve) *m/z* 545.4 (100%) [M^+]. HRMS calcd for $C_{27}H_{41}N_6O_6$ 545.3088, found 545.3073.

Methyl (2*S*,5*S*,8*S*)-2-allyl-9-(4-allyloxyphenyl)-5-(4-[guanidino]butyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (88)



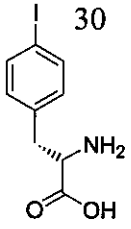
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **85** (40 mg, 0.054 mmol) to yield **88** (11 mg, 0.019 mmol, 35%) as a highly hydroscopic yellow solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.10 (bs, 2H, ArH2''' and ArH6'''); 6.79 (bs, 2H, ArH3''' and ArH5'''); 6.00 (m, 1H, H2''''); 5.72 (m, 1H, H2'); 5.16 (m, 4H, H3'''' and H3'); 4.40 (m, 5H, H2, H5, H8 and H1''''); 3.65 (s, 3H, OCH_3); 3.00 (m, 4H, H1' and H4"); 2.49 (bs, 2H, $ArCH_2$); 1.87 (s, 3H, H11); 1.36 (m, 6H, H1", H2" and H3"). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.2, C4; 174.1, C11; 173.6, C1; 173.2, C7; 159.4, ArC4'''; 158.4, CN_3; 134.6, C2''''; 134.2, C2'; 131.2, ArC1'''; 130.3, ArCH2''' and ArCH6'''; 119.6, C3'; 118.2, C3''''; 116.3, ArCH3''' and ArCH5'''; 70.0, C1''''; 57.4, C2; 54.4, C5; 53.9, C8; 52.4, OCH_3; 42.2, C4"; 37.6, $ArCH_2$; 36.6, C1'; 32.5, C2"; 29.5, C3"; 23.6, C11; 22.8, C1". Mass Spectrum (ES, +ve) *m/z* 545.3 (100%) [M^+]. HRMS calcd for $C_{27}H_{41}N_6O_6$ 545.3088, found 545.3066.

(7*S*,10*S*,13*S*,4*E/Z*)-13-Acetamido-10-(4-[guanidino]butyl)-8,11-diaza-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (89)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **86** (86 mg, 0.12 mmol) to yield **89** (50 mg, 0.097 mmol, 81%) as a highly hydroscopic yellow solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 10.34 (bs, 1H, NH); .42 (m, 2H, ArH); 7.08 (m, 2H, ArH); 5.97 (m, 2H, H4 and H5); 4.80 (m, 5H, H2, H7, H10 and H13); 3.65 (s, 3H, OCH_3); 3.32 (m, 2H, H4'); 3.09 (m, 2H, H6); 2.42 (m, 2H, H14); 2.10 (s, 3H, $NCOC\underline{H}_3$); 2.04 (m, 2H, H3'); 1.86 (m, 2H, H1'); 1.50 (m, 2H, H2'). ^{13}C NMR (CD_3OD, 125 MHz): δ 173.3/173.2, C9; 172.7/173.6, 7-CO; 172.5, 13-NCO; 169.4, C12; 158.5/158.4, 1-ArC1; 131.4/131.3, 1-ArCH2 and 1-ArCH6; 131.0, C4; 129.3, C5; 129.0, 1-ArC4; 116.5, 1-ArCH3 and 1-ArCH5; 67.0, C3; 58.2, C7; 57.5, C13; 57.4, C10; 53.9, OCH_3; 42.1, C4'; 33.9, C14; 29.0, C6; 23.5, C3'; 22.7, C1'; 22.5, $NCO\underline{C}H_3$; 22.5, C2'. Mass Spectrum (ES, +ve) *m/z* 517.4 (100%) [M^+]. HRMS calcd for $C_{25}H_{37}N_6O_6$ 517.2775, found 517.2765.

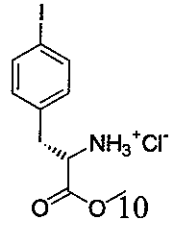
(*S*)-2-Amino-3-(4-iodophenyl)propanoic acid (92)



To a solution (*S*)-2-amino-3-phenylpropanoic acid **91** (4.01 g, 24.3 mmol) in acetic acid (22 mL) was added sulfuric acid (2.9 mL, 5.14 mmol), iodine (2.47 g, 4.7 mmol) and sodium iodate (1.02 g, 5.14 mmol). The mixture was heated to 70°C and allowed to stir at this temperature for 16 h before an additional portion of sodium iodate (1.02 g, 5.14 mmol) was added. The reaction was left for a further 2 h before being concentrated, dissolved in methanol (20 mL) and treated with NaOH (60 mL). The mixture was left to precipitate out of the basic solution overnight and the resulting solid was filtered by vacuum filtration to yield the title compound (7.07 g, 24.3 mmol, 100%) as a pink solid, which had spectral data in

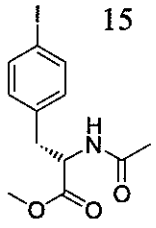
agreement with that reported.[93] $[\alpha]_D^{21}$ –10.6 (*c.* 0.3, HCl). Mp 258-260°C (lit. 261-262°C)[93] ^{1}H NMR (CD_3OD, 300 MHz): δ 7.71 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 7.10 (d, *J* = 8.4 Hz, 2H, ArH3' and ArH5'); 4.26 (dd, *J* = 6.3, 7.2 Hz, H2); 3.26 (dd, *J* = 5.4, 14.1 Hz, 1H, $H3_a$); 3.04 (dd, *J* = 7.2, 14.4 Hz, 1H, $H3_b$). Mass Spectrum (CI, +ve) *m/z* 279 (100%), 292 (70%) [MH^+]. HRMS calcd for $C_9H_{11}INO_2$ 291.9834 found 291.9568.

Methyl (*2S*)-2-amino-3-(4-iodophenyl)propanoate hydrochloride (93)



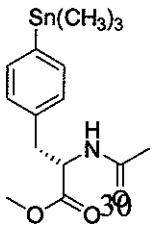
To a solution of **92** (2.00 g, 6.87 mmol) in MeOH (10 mL) at 0°C was added thionyl chloride (2 mL) and the resulting solution was allowed to stir for 16 h whilst equilibrating to RT. The reaction was evaporated to dryness *in vacuo* to yield the title compound (2.25 g, 6.80 mmol, 99%) as a white solid, which had spectral data in agreement with that reported.[93] $[\alpha]_D^{21}$ -9.3 (*c.* 0.15, HCl). Mp 195-198°C (lit. 199.5-200.5°C)[93] ^{1}H NMR (CD_3OD, 300 MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 7.06 (d, *J* = 8.4 Hz, 2H, ArH3' and ArH5'); 4.33 (dd, *J* = 6.3, 6.9 Hz, 1H, H2); 3.80 (s, 3H, OCH_3); 3.23 (dd, *J* = 6.6, 14.4 Hz, 1H, $H3_a$); 3.15 (dd, *J* = 7.2, 14.4 Hz, 1H, $H3_b$). Mass Spectrum (ES, +ve) *m/z* 306 (100%) [M^+]. HRMS calcd for $C_{10}H_{13}INO_2$ 305.9986 found 305.9980.

Methyl (*2S*)-2-acetamido-3-(4-iodophenyl)propanoate (94)



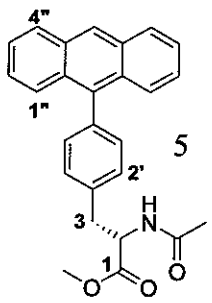
To a solution of **93** (2.25 g, 6.80 mmol) in 10% HCl (10 mL) at 0°C was added 4M sodium acetate (115 mL) and the resulting reaction was allowed to stir whilst equilibrating to 0°C. Acetic anhydride (50 mL) was added and the reaction allowed to proceed with vigorous stirring. After 1 h the product was collected by vacuum filtration, dissolved in ethyl acetate (30 mL) and washed with 2M sodium bicarbonate (2 x 30 mL). The organic layer was dried and evaporated to yield the title compound (1.31 g, 3.79 mmol, 56%) as a white solid. Mp 118-120°C. $[\alpha]_D^{27}$ +93.8 (*c.* 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 6.84 (d, *J* = 8.1 Hz, 2H, ArH3' and ArH5'); 5.92 (d, *J* = 7.2 Hz, 1H, NH); 4.87 (m, 1H, H2); 3.73 (s, 3H, OCH_3); 3.11 (dd, *J* = 6.0, 13.8, Hz, 1H, $H3_a$); 3.03 (dd, *J* = 5.4, 13.8 Hz, 1H, $H3_b$); 1.99 (s, 3H, $NCOCH_3$). Mass Spectrum (CI, +ve) *m/z* 348 (100%) [MH^+]. HRMS calcd for $C_{12}H_{15}NO_3I$ 348.0097, found 348.0104.

Methyl (*2S*)-2-acetamido-3-(4-trimethylstannylphenyl)propanoate (95)



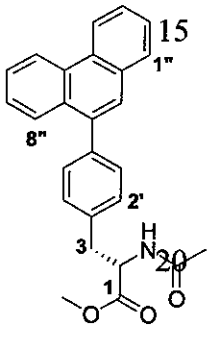
A solution of **94** (590 mg, 1.7 mmol), hexamethyldistannane (781 mg, 2.38 mmol), palladium acetate (20 mg, 0.085 mmol), and triphenylphosphine (45 mg, 0.17 mmol) in toluene (7 mL) was flushed with nitrogen for 15 minutes and then heated at 100°C for 30 min under N_2. The brown mixture was filtered through a short pad of silica, diluted with diethyl ether (40 mL) and washed twice with water. The organic layer was dried and evaporated to yield the title compound (497 mg, 1.29 mmol, 76%) as a clear oil. $[\alpha]_D^{27}$ +13.7 (*c.* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (d, *J* = 7.5 Hz, 2H, ArH2' and ArH6'); 7.07 (d, *J* = 7.8 Hz, 2H, ArH3' and ArH5'); 6.25 (d, *J* = 7.8 Hz, 1H, NH); 4.87 (m, 1H H2); 3.72 (s, 3H, OCH_3); 3.12 (dd, *J* = 5.7, 14.1 Hz, 1H, $H3_a$); 3.04 (dd, *J* = 6.0, 13.9 Hz, 1H, $H3_b$); 1.98 (s, 3H, $NCOCH_3$); 0.27 (t, *J* = 27.6 Hz, 9H, $Sn(CH_3)_3$). Mass Spectrum (CI, +ve) *m/z* 386 (50%) [MH^+], 382 (10%) [MH^+] (Sn 112), 85 (100%). HRMS calcd for $C_{15}H_{24}NO_3Sn$ (Sn 112) 382.075357 found 382.075603.

Methyl (*2S*)-2-acetamido-3-(4-[9-anthracenyl]phenyl)-propanoate (96)



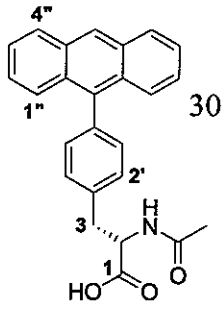
A solution of **95** (192 mg, 0.50 mmol), 9-bromoanthracene (141 mg, 0.55 mmol), palladium acetate (6 mg, 0.025 mmol), and tri-*o*-tolylphosphine (15 mg, 0.05 mmol) in DMF (2 mL) was flushed with N_2 for 15 min then heated to 70°C and allowed to stir for 16 h. The reaction was diluted with diethyl ether (20 mL) and washed with water (5 x 20 mL), dried and evaporated. The crude product was purified by flash column chromatography (15% EtOAc/hexane then 5% MeOH/DCM) to yield the title compound (133 mg, 0.33 mmol, 67%) as an orange oil. $[\alpha]_D^{27}$ +66.9 (*c.* 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.48 (s, 1H, ArH10"); 8.03 (dd, *J* = 0.9, 8.7 Hz, 2H, ArH3" and ArH6"); 7.63 (dd, *J* = 0.6, 9.0 Hz, 2H, ArH8" and ArH1"); 7.45 (m, 2H, ArH4" and ArH5"); 7.36 (m, 6H, ArH2" and ArH7", 4 x ArH'); 5.40 (d, *J* = 7.8 Hz, 1H, NH); 5.04 (m, 1H, H2); 3.79 (s, 3H, OCH_3); 3.32 (dd, *J* = 5.7, 13.8 Hz, 1H, $H3_a$); 3.25 (dd, *J* = 6.3, 13.8 Hz, 1H, $H3_b$); 2.08 (s, 3H, $COCH_3$). Mass Spectrum (CI, +ve) *m/z* 398 (100%) [MH^+]. HRMS calcd for $C_{26}H_{23}NO_3$ 397.1678, found 397.1675.

Methyl (*2S*)-2-acetamido-3-(4-[9-phenanthrenyl]phenyl)propanoate (98)



A solution of **95** (259 mg, 0.67 mmol), 9-bromophenanthrene (190 mg, 0.74 mmol), palladium acetate (8 mg, 0.034 mmol), and tri-*o*-tolylphosphine (20 mg, 0.067 mmol) in DMF (2 mL) was flushed with N_2 for 15 min then heated to 70°C and allowed to stir for 16 h. The reaction was diluted with diethyl ether (20 mL) and washed with water (5x 20 mL), dried and evaporated. The crude product was purified by flash column chromatography (15% EtOAc/hexane then 5% MeOH/DCM) to yield the title compound (157 mg, 0.40 mmol, 59%) as a clear oil. $[\alpha]_D^{27}$ +94.6 (*c.* 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.77 (d, *J* = 9.0 Hz, 1H, ArH4"); 8.71 (d, *J* = 8.1 Hz, 1H, ArH3"); 7.89 (m, 2H, ArH1" and ArH10"); 7.61 (m, 5H, ArH7", ArH6", ArH5", ArH2" and ArH1"); 7.48 (d, *J* = 8.4 Hz, 2H, ArH2' and ArH6'); 7.26 (d, *J* = 8.1 Hz, 2H, ArH3' and ArH5'); 6.25 (d, *J* = 7.5 Hz, 1H, NH); 5.00 (m, 1H, H2); 3.79 (s, 3H, OCH_3); 3.30 (dd, *J* = 5.7, 13.8 Hz, 1H, $H3_a$); 3.20 (dd, *J* = 6.0, 13.8 Hz, 1H, $H3_b$); 2.05 (s, 3H, $COCH_3$). Mass Spectrum (CI, +ve) *m/z* 398 (100%) [MH^+]. HRMS (EI) calcd for $C_{26}H_{23}NO_3$ 397.1678, found 397.1680.

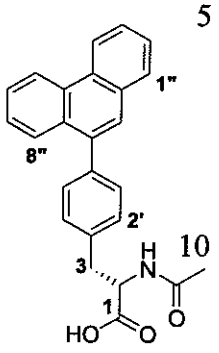
(*2S*)-2-Acetamido-3-(4-[9-anthracenyl]phenyl) propanoic acid (97)



To a solution of **96** (80 mg, 0.20 mmol) in THF/water, 2:1 (3 mL) was added lithium hydroxide monohydrate (17 mg, 0.40 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation. The aqueous layer was washed with DCM (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with DCM (3 x 40 mL). The combined organics were dried and evaporated to yield the title compound (69 mg, 0.18 mmol, 90%) as a white solid. Mp 76°C. $[\alpha]_D^{20}$ +29.7 (*c.* 0.1, EtOH). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.47 (s, 1H, ArH10"); 8.02 (d, *J* = 8.4 Hz, 2H, ArH3" and ArH6"); 7.59 (d, *J* = 8.7 Hz, 2H, ArH8" and ArH1"); 7.45 (m, 2H, ArH4" and ArH5"); 7.35 (m, 6H,

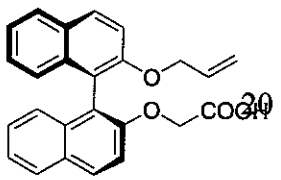
ArH2" and ArH7", 4 x ArH'); 6.27 (d, J = 6.6 Hz, 1H, NH); 5.00 (m, 1H, H2); 3.39 (dd, J = 4.8, 12.9 Hz, 1H, $H3_a$); 3.26 (dd, J = 6.3, 14.4 Hz, 1H, $H3_b$); 2.07 (s, 3H, $COCH_3$). Mass Spectrum (ES, +ve) *m/z* 383 (70%) [MH^+]. HRMS calcd for $C_{25}H_{22}NO_3$ 384.1600, found 384.1610.

(2*S*)-2-Acetamido-3-(4-[9-phenanthrenyl]phenyl)propanoic acid (99)



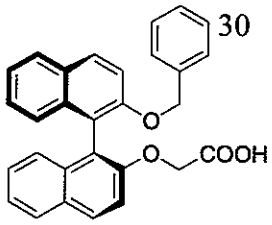
To a solution of **98** (124 mg, 0.31 mmol) in THF/water, 2:1 (9 mL) was added lithium hydroxide monohydrate (26 mg, 0.62 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation. The aqueous layer was washed with DCM (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with DCM (3 x 40 mL). The combined organics were dried and evaporated to yield the title compound (65 mg, 0.17 mmol, 55%) as a white solid. Mp 128-132°C. $[\alpha]_D^{20}$ +36.8 (*c*. 0.1, EtOH). ^1H NMR (CD_3OD, 300 MHz): δ 8.71 (d, J = 8.1 Hz, 1H, ArH4"); 8.66 (d, J = 8.4 Hz, 1H, ArH3"); 7.79 (s, 1H, ArH1"); 7.76 (s, 1H, ArH10"); 7.51 (m, 5H, ArH7", ArH6", ArH5", ArH2" and ArH1"); 7.32 (m, 2H, Ar'H); 4.76 (dd, J = 5.1, 9.0 Hz, 1H, H2); 3.29 (dd, J = 4.8, 13.5 Hz, 1H, $H3_a$); 3.03 (dd, J = 8.7, 13.5 Hz, 1H, $H3_b$); 1.95 (s, 3H, $COCH_3$). Mass Spectrum (ES, +ve) *m/z* 384 (50%) [MH^+]. HRMS calcd for $C_{25}H_{22}NO_3$ 384.1600, found 384.1628.

(2'-Allyloxy-[1,1']-(*S*)-binaphthalen-2-yloxy)-acetic acid (101)



To a solution of 1,1'-(*S*)-binapthol (1.00 g, 3.50 mmol) and K_2CO_3 (600 mg, 4.35 mmol) in acetone (12 mL) was added dropwise, allyl bromide (0.26 mL, 3.68 mmol). The resulting mixture was heated at reflux with stirring for 16 h before being filtered, concentrated and dissolved in anhydrous MeOH (40 mL). To this solution was added K_2CO_3 (2.4 g, 17.4 mmol) and bromoacetic acid (1.21 g, 8.75 mmol). This mixture was heated at reflux for a further 3 h before evaporation to dryness and dissolution in water (50 mL). The aqueous layer was then washed with diethyl ether (3 x 30 mL) before acidification with 3M HCl. The acidified solution was extracted with DCM, dried before being evaporated to dryness to yield the title compound (825 mg, 2.15 mmol, 61%) as a viscous yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.96 (m, 2H, ArH); 7.86 (m, 2H, ArH); 7.26 (m, 8H, ArH); 5.66 (m, 1H, H2"); 4.94 (m, 2H, H3"); 4.61 (AB_q, J = 16.8 Hz, 2H, $C\underline{H}_2$-COOH); 4.48 (m, 2H, H1"). Mass Spectrum (CI, +ve) *m/z* 339 (40%) [-COOH], 385 (100%) [MH^+]. HRMS calcd for $C_{25}H_{21}O_4$ 385.143984, found 385.142526.

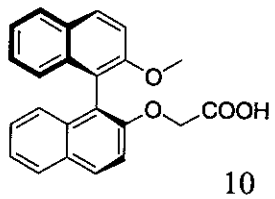
(2'-Benzyloxy-[1,1']-(*S*)-binaphthalen-2-yloxy)-acetic acid (102)



To a solution of 1,1'-(*S*)-binapthol (500 mg, 1.75 mmol) and K_2CO_3 (300 mg, 2.18 mmol) in acetone (6 mL) was added dropwise, benzyl bromide (0.21 mL, 1.75 mmol). The resulting mixture was heated at reflux with stirring for 16 h before being filtered, concentrated and dissolved in anhydrous MeOH (5 mL). To this solution was added K_2CO_3 (2.4 g, 17.4 mmol) and bromoacetic acid (740 g, 5.25 mmol). This mixture was heated at reflux for a further 3 h before evaporation to dryness and dissolution in water (50 mL). The aqueous layer was then washed with diethyl ether (3 x 30 mL) before acidification with 3M HCl. The acidified solution was

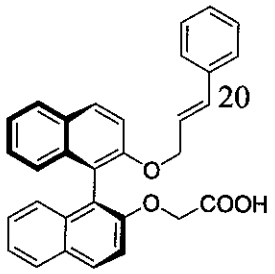
extracted with DCM, dried before being evaporated to dryness to yield the title compound (218 mg, 0.50 mmol, 29%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.30 (bs, 1H, COOH); 7.85 (m, 4H, ArH); 7.16 (m, 13H, ArH); 4.99 (AB_q, J = 12.6 Hz, 2H, C<u>H</u>$_2$-COOH); 4.48 (AB_q, J = 17.1 Hz, 2H, H1"). Mass Spectrum (CI, +ve) *m/z* 435 (100%) [MH^+]. HRMS calcd for $C_{29}H_{23}O_4$ 435.159634, found 435.158151.

(2'-Methyloxy-[1,1']-(*S*)-binaphthalen-2-yloxy)-acetic acid (103)



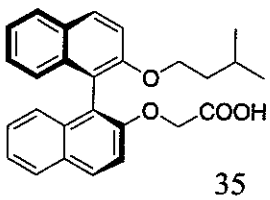
To a solution of 1,1'-(*S*)-binapthol (500 mg, 1.75 mmol) and K_2CO_3 (300 mg, 2.18 mmol) in acetone (6 mL) was added dropwise, methyl iodide (0.11 mL, 1.75 mmol). The resulting mixture was heated at reflux with stirring for 16 h before being filtered, concentrated and dissolved in anhydrous MeOH (5 mL). To this solution was added K_2CO_3 (2.4 g, 17.4 mmol) and bromoacetic acid (740 g, 5.25 mmol). This mixture was heated at reflux for a further 3 h before evaporation to dryness and dissolution in water (50 mL). The aqueous layer was then washed with diethyl ether (3 x 30 mL) before acidification with 3M HCl. The acidified solution was extracted with DCM, and dried before being evaporated to dryness to yield the title compound (236 mg, 0.66 mmol, 38%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.22, COOH; 7.84 (m, 4H, ArH); 7.22 (m, 8H, ArH); 4.49 (AB_q, J = 16.8 Hz, 2H, C<u>H</u>$_2$-COOH); 3.65 (s, 3H, OCH_3). Mass Spectrum (CI, +ve) *m/z* 359 (100%) [MH^+]. HRMS (EI) calcd for $C_{23}H_{18}O_4$ 358.120509, found 358.120418.

(2'-(3-Phenylallyloxy)-[1,1']-(*S*)-binaphthalen-2-yloxy)-acetic acid (104)



To a solution of 1,1'-(*S*)-binapthol (500 mg, 1.75 mmol) and K_2CO_3 (300 mg, 2.18 mmol) in acetone (6 mL) was added dropwise, cinnamyl bromide (362 mg, 1.84 mmol). The resulting mixture was heated at reflux with stirring for 16 h before being filtered, concentrated and dissolved in anhydrous MeOH (5 mL). To this solution was added K_2CO_3 (2.4 g, 17.4 mmol) and bromoacetic acid (740 g, 5.25 mmol). This mixture was heated at reflux for a further 3 h before evaporation to dryness and dissolution in water (50 mL). The aqueous layer was then washed with diethyl ether (3 x 30 mL) before acidification with 3M HCl. The acidified solution was extracted with DCM, dried, then evaporated to dryness to yield the title compound (544 mg, 1.18 mmol, 67%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.20, COOH; 7.84 (m, 4H, ArH); 7.29 (m, 4H, ArH); 7.09 (m, 8H, ArH); 6.12 (d, J = 15.9 Hz, 1H, H3"); 5.90 (dt, J = 5.7, 15.9 Hz, 1H, H2"); 5.58 (m, 2H, H1"); 4.49 (AB_q, J = 16.8 Hz, 2H, C<u>H</u>$_2$-COOH). Mass Spectrum (CI, +ve) *m/z* 117 (100%), 461 (50%) [MH^+]. HRMS calcd for $C_{31}H_{24}O_4$ 460.167460, found 460.167568.

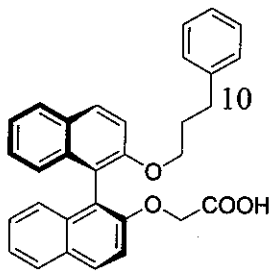
[2'-(3-Methylbutoxy-[1,1']-(*S*)-binaphthalen-2-yloxy]-acetic acid (105)



To a solution of 1,1'-(*S*)-binapthol (500 mg, 1.75 mmol) and K_2CO_3 (300 mg, 2.18 mmol) in acetone (6 mL) was added dropwise, 1-bromo-3-methylbutane (0.22 mL, 1.75 mmol). The resulting mixture heated at reflux with stirring for 16 h before being filtered, concentrated and dissolved in anhydrous MeOH (5 mL). To this solution was added K_2CO_3 (2.4 g, 17.4 mmol) and bromoacetic acid (740 g, 5.25 mmol). This mixture was heated at reflux for a further 3 h before evaporation to dryness and dissolution in water (50 mL). The aqueous layer

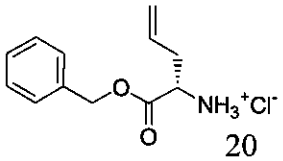
was then washed with diethyl ether (3 x 30 mL) before acidification with 3M HCl. The acidified solution was extracted with DCM, dried before being evaporated to dryness to yield the title compound (604 mg, 1.46 mmol, 83%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.93, COOH; 7.95 (m, 4H, ArH); 7.40 (m, 8H, ArH); 4.65 (m, 2H, C$\underline{H}_2$-COOH); 4.09 (m, 2H, H1"); 1.38 (m, 2H, H2"); 1.26 (m, 1H, H3"); 0.71 (d, J = 6.3 Hz, 3H, H4a"); 0.61 (d, J = 6.3 Hz, 3H, H4b"). Mass Spectrum (CI, +ve) *m/z* 415 (100%) [MH^+]. HRMS calcd for $C_{27}H_{27}O_4$ 415.1090, found 415.1913.

(2'-(3-Phenylpropyloxy)-[1,1']-(*S*)-binaphthalen-2-yloxy)-acetic acid (107)



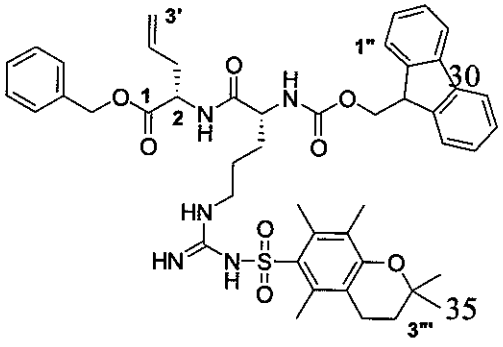
To a solution **104** (213 mg, 0.46 mmol) in THF (15 mL) was added palladium on activated carbon (5 mol%). The resulting mixture was allowed to stir for 16 h under a hydrogen atmosphere (balloon) before being filtered and evaporated to dryness to yield the title compound (188 mg, 0.4 mmol, 87%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.97 (m, 4H, ArH); 7.24 (m, 11H, ArH); 6.68 (m, 2H, ArH); 4.65 (AB_q, J = 16.8 Hz, 2H, C$\underline{H}_2$-COOH); 3.96 (m, 2H, H1"); 2.09 (m, 2H, H3"); 1.69 (m, 2H, H2"). Mass Spectrum (CI, +ve) *m/z* 463 (100%) [MH^+]. HRMS calcd for $C_{31}H_{27}O_4$ 463.1909, found 463.1915.

Benzyl (2*S*)-2-amino-4-pentenoate hydrochloride (108)



To a solution of (2*S*)-2-amino-4-pentenoic acid **17** (225 mg, 1.96 mmol) in benzyl alcohol (5 mL) was added thionyl chloride (2 mL) and the resulting mixture was allowed to stir for 16 h before addition of diethyl ether (30 mL) and extraction with water (3 x 30 mL). The aqueous layer was concentrated, diluted with 2M sodium bicarbonate (20 mL), and extracted with DCM (3 x 30 mL). The combined organic fractions were dried and acidified with 1M HCl/diethyl ether (2 mL) and evaporated. The crude product dissolved in a minimal volume of MeOH and precipitated with diethyl ether to yield the title compound (322 mg, 1.34 mmol, 68%) as a white solid. $[\alpha]_D^{20}$ – 40.6 (*c*. 0.1, H_2O). Mp 186-191°C. ^{1}H NMR (D_2O, 300 MHz): δ 7.28 (m, 5H, ArH); 5.51 (m, 1H, H4); 5.11 (m, 4H, H5 and ArCH_2); 4.08 (t, J = 5.4 Hz, 1H, H2); 2.55 (m, 2H, H3). Mass Spectrum (CI, +ve) *m/z* 205 (25%) [MH^+]. HRMS calcd for $C_{12}H_{16}NO_2$ 206.1181, found 206.1169.

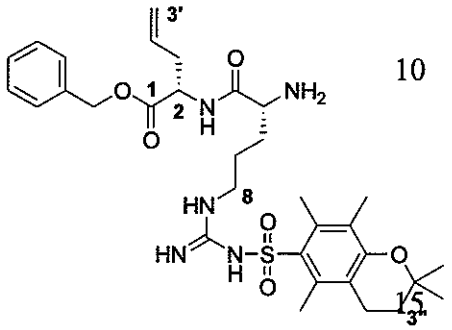
Benzyl (2*S*,5*R*)-2-allyl-3-aza-5-(9*H*-9-fluorenylmethyloxycarboxamido)-4-oxo-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]octanoate (109)



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **108** (155 mg, 0.65 mmol) and (2*R*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidine]pentanoic acid (431 mg, 0.65 mmol) to afford **109** (280 mg, 0.33 mmol, 51%) as a white solid. Mp 78-74°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (d, J = 7.5 Hz, 2H,

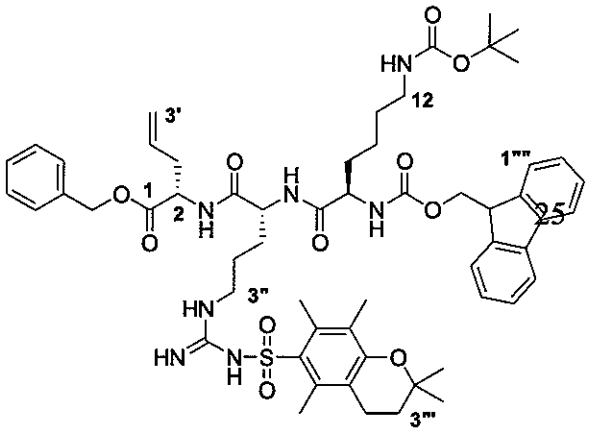
ArH1" and ArH8"); 7.51 (d, J = 7.5 Hz, 2H, ArH4" and ArH5"); 7.28 (m, 9H, ArH); 6.33 (m, 3H, NH); 5.68 (m, 1H, H2'); 5.61 (m, 1H, NH); 4.99 (m, 4H, $ArCH_2$ and H3'); 4.58 (m, 1H, H2); 4.24 (m, 3H, $OC\underline{H}_2$-H9"and H5); 4.05 (t, J = 7.2 Hz, 1H, H9"); 3.20 (m, 2H, H8); 2.57 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.52 (m, 4H, H3"' and H1'); 2.05 (s, 3H, 8"'-CH_3); 1.85 (m, 2H, H6); 1.69 (t, J = 6.3 Hz, H4"'); 1.58 (m, 2H, H7); 1.22 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 850 (100%) [MH^+]. HRMS calcd for $C_{47}H_{56}N_5O_8S$ 850.3850, found 850.3855.

Benzyl (2*S*,5*R*)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonamido)guanidino]-4-oxooctanoate (110)



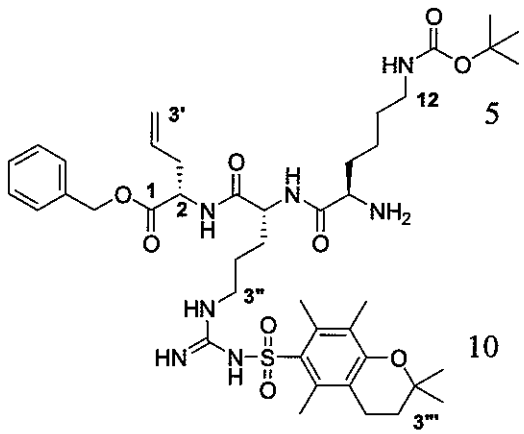
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **109** (278 mg, 0.33 mmol) to yield **110** (144 mg, 0.23 mmole, 70%) as a cream semi-solid. Mp 66-68°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.85 (d, J = 7.8 Hz, 1H, NH); 7.60 (d, J = 7.8 Hz, 1H, NH); 7.32 (m, 5H, ArH); 6.33 (m, 2H, NH_2); 5.63 (s, 1H, H2'); 5.14 (m, 4H, $ArCH_2$ and H3'); 4.56 (m, 1H, H2); 3.40 (m, 1H, H5); 3.16 (m, 2H, H8); 3.09 (m, 2H, H1'); 2.61 (t, J = 6.9 Hz, 2H, H4"); 2.56 (s, 3H, 7"-CH_3); 2.55 (s, 3H, 5"-CH_3); 2.09 (s, 3H, 8"-CH_3); 1.78 (t, J = 7.2 Hz, 2H, H3"); 1.68 (m, 4H, H6 and NH_2); 1.54 (m, 2H, H7); 1.29 (s, 6H, 2 x 2"-CH_3). Mass Spectrum (ES, +ve) *m/z* 628 (100%) [MH^+]. HRMS calcd for $C_{32}H_{46}N_5O_6S$ 628.3169, found 628.3157.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6-diaza-12-(*tert*-butoxycarboxamido)-8-(9*H*-9-fluorenylmethyloxycarboxamido)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonamido}guanidino]propyl)-4,7dioxododecanoate (111)



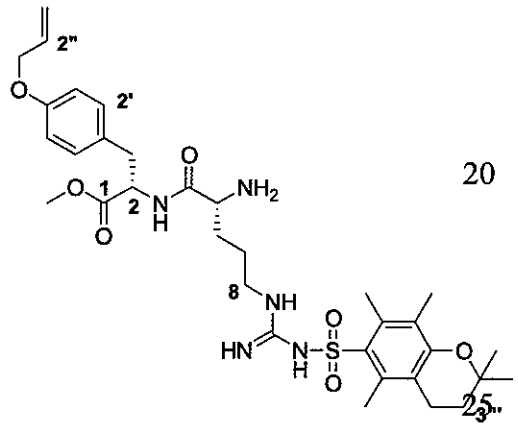
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **110** (200 mg, 0.32 mmol) and (2*R*)-6-*tert*-butoxycarboxamido-2-(9*H*-9-fluorenylmethyloxycarboxamido)hexanoic acid (151 mg, 0.32 mmol) to afford **111** (202 mg, 0.19 mmol, 59%) as a white solid. Mp 116°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, J = 7.8 Hz, 2H, ArH1"" and ArH8""); 7.55 (d, J = 7.8 Hz, 2H, ArH4"" and ArH5""); 7.45 (m, 1H, NH); 7.29 (m, 11H, ArH); 6.25 (m, 3H, NH); 5.64 (m, 1H, H2'); 5.03 (m, 4H, $ArCH_2$, H3'); 4.59 (m, 1H, H2); 4.51 (m, 1H, H5); 4.29 (m, 1H, H8); 4.20 (m, 2H, $OC\underline{H}_2$-H9""); 3.98 (m, 1H, H9""); 3.18 (m, 2H, H3"); 3.05 (m, 2H, H12); 2.55 (s, 3H, 7"'-CH_3); 2.52 (s, 3H, 5"'-CH_3); 2.50 (m, 4H, H4"' and H1'); 2.03 (s, 3H, 8"'-CH_3); 1.95 (m, 4H, H1" and H9); 1.74 (m, 2H, H3"'); 1.67 (m, 4H, H2" and H10); 1.59 (m, 2H, H11); 1.41 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 1078 (10%) [MH^+]; 288 (100%). HRMS calcd for $C_{58}H_{76}N_7O_{11}S$ 1078.5324, found 1078.5333.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-8-amino-3,6-diaza-12-(*tert*-butoxycarboxamido)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonamido}guanidino]propyl)-4,7dioxododecanoate (112)



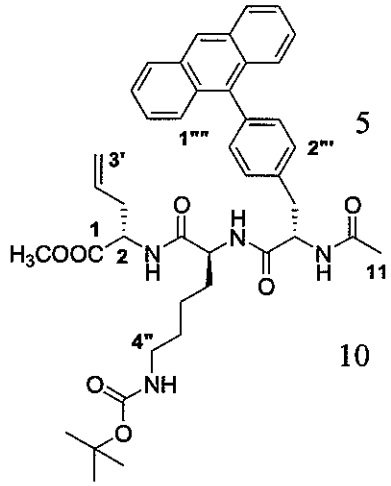
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **111** (202 mg, 0.19 mmol) to yield **112** (157 mg, 0.18 mmole, 93%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, J = 7.2 Hz, 1H, NH); 7.58 (d, J = 7.2 Hz, 1H, NH); 7.32 (m, 5H, ArH); 6.44 (m, 3H, NH); 5.63 (m, 1H, H2'); 5.09 (m, 4H, $ArCH_2$ and H3'); 4.61 (m, 2H, H2 and H5); 3.36 (m, 1H, H8); 3.22 (m, 2H, H3"); 3.05 (m, 2H, H12); 2.62 (m, 2H, H4"'); 2.58 (s, 3H, 7"'-CH_3); 2.56 (s, 3H, 5"'-CH_3); 2.47 (m, 2H, H1'); 2.15 (m, 2H, H1"); 2.10 (s, 3H, 8"'-CH_3); 1.89 (m, 2H, H9); 1.80 (t, J = 6.3 Hz, H3"'); 1.72 (m, 4H, H2" and H10); 1.58 (m, 4H, H11 and NH_2); 1.42 (s, 9H, $C(CH_3)_3$); 1.31 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 856 (100%) [MH^+]. HRMS calcd for $C_{43}H_{66}N_7O_9S$ 856.4643, found 856.4655.

Methyl (2*S*,5*R*)-2-(4-allyloxybenzyl)-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl)guanidino]-4-oxononanoate (113)



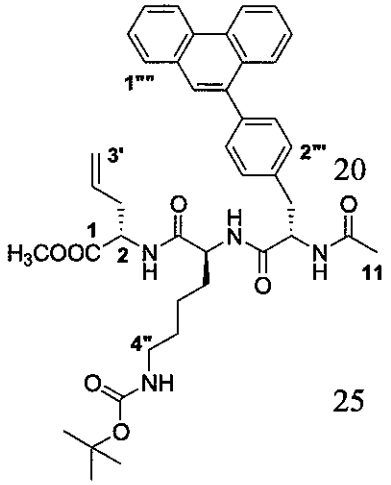
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **67** (295 mg, 0.32 mmol) to yield **113** (145 mg, 0.21 mmol, 66%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83 (d, J = 7.5 Hz, 1H, NH); 7.04 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.81 (d, J = 8.4 Hz, 2H , ArH3' and ArH5'); 6.37 (bs, 2H, NH); 6.01 (m, 1H, H2"); 5.30 (m, 2H, H3"); 4.68 (dd, J = 7.5, 13.2 Hz, 1H, H2); 4.47 (m, 2H, H1"); 4.22 (m, 1H, H5); 3.67 (s, 3H, OCH_3); 3.07 (m, 4H, H8 and $ArCH_2$); 2.61 (t, J = 6.6 Hz, 2H, H4"'); 2.56 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.10 (s, 3H, 8"'-CH_3); 1.87 (m, 2H, NH_2); 1.79 (m, 2H, H3"'); 1.68 (m, 2H, H6); 1.50 (m, 2H, H7); 1.29 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 658 (100%) [MH^+]. HRMS calcd for $C_{33}H_{48}N_5O_2S$ 658.3274 found 658.3282.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-[9-anthrecenyl]benzyl)-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate (114)



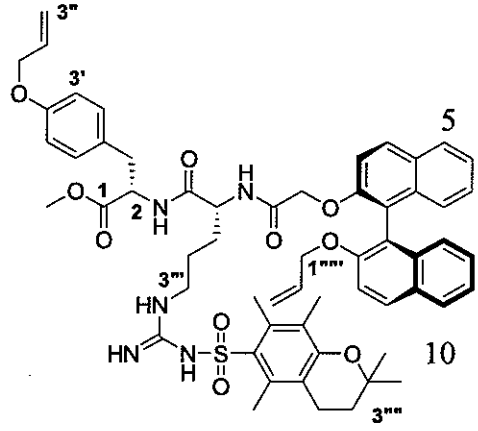
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **24** (35 mg, 0.098 mmol) and **97** (20 mg, 0.052 mmol) to afford the title compound (22 mg, 0.030 mmol, 59%) as a cream solid. Mp 128°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.49 (s, 1H, ArH10''''); 8.04 (d, J = 8.7 Hz, 2H, ArH2''' and ArH6'''); 7.64 (d, J = 8.4 Hz, 2H, ArH3''' and ArH5'''); 7.38 (m, 8H, ArH''''); 6.72 (d, J = 7.2 Hz, 1H, NH); 6.48 (d, J = 7.2 Hz, 1H, NH); 6.37 (bs, 1H, NH); 5.59 (m, 1H, H2'); 5.06 (m, 2H, H3'); 4.82 (m, 1H, H8); 4.60 (dd, J = 6.9, 14.1 Hz, 1H, H2); 4.45 (m, 1H, H5); 3.73 (s, 3H, OCH_3); 3.24 (m, 2H, $ArCH_2$); 3.08 (m, 2H, H4''); 2.47 (m, 2H, H1'); 2.07 (s, 3H, H11); 1.93 (m, 2H, H1''); 1.68 (m, 2H, H3''); 1.50 (m, 2H, H2''); 1.44 (s, 9H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 745 (50%) [MNa^+], 723 (20%) [MH^+], 623 (100%) [M less Boc]. HRMS calcd for $C_{44}H_{49}N_4O_7$ 745.3601, found 745.3590.

Methyl (2*S*,5*S*,8*S*)-2-allyl-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]butyl)-4,7,10-trioxo-8-(4-[9-phenanthrenyl]benzyl)undecanoate (115)



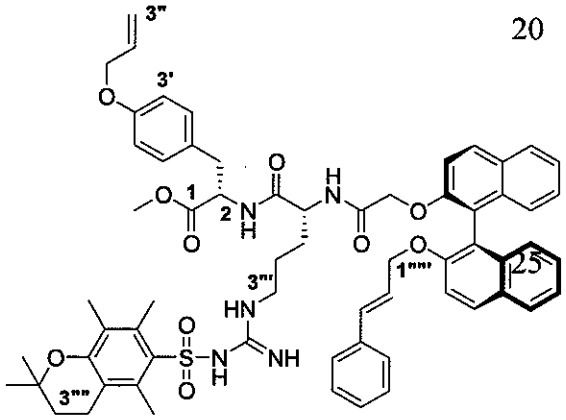
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **24** (28 mg, 0.078 mmol) and **99** (15 mg, 0.039 mmol) to afford **115** (14 mg, 0.019 mmol, 50%) as a cream solid. Mp 132-134°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76 (d, J = 8.1 Hz, 1H, ArH4''''); 8.71 (d, J = 8.4 Hz, 1H, ArH3''''); 7.88 (m, 2H, ArH1'''' and ArH10''''); 7.60 (m, 5H, ArH7'''', ArH6'''', ArH5'''', ArH2'''' and ArH1''''); 7.45 (d, J = 7.8 Hz, 2H, ArH2''' and ArH6'''); 7.33 (d, J = 7.8 Hz, 2H, ArH3''' and ArH5'''); 7.10 (d, J = 8.4 Hz, 1H, NH); 6.94 (d, J = 8.7 Hz, 1H, NH); 6.74 (d, J = 8.1 Hz, 1H, NH); 5.61 (m, 1H, H2'); 5.06 (m, 2H, H3'); 4.90 (m, 1H, H8); 4.57 (m, 2H, H2 and H5); 3.72 (s, 3H, OCH_3); 3.20 (m, 2H, $ArCH_2$); 3.08 (m, 2H, H4''); 2.47 (m, 2H, H1'); 2.04 (s, 3H, H11); 1.92 (m, 2H, H1''); 1.68 (m, 2H, H3''); 1.48 (m, 2H, H2''); 1.42 (s, 9H, $C(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 745 (60%) [MNa^+], 723 (20%) [MH^+], 623 (100%) [M less Boc]. HRMS calcd for $C_{42}H_{51}N_4O_7$ 723.3758, found 723.3767.

Methyl (2*S*,5*R*)-2-allyloxybenzyl-8-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3,6-diaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7-dioxooctanoate (116)



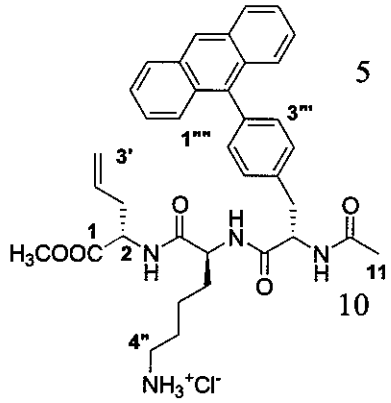
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **113** (81 mg, 0.11 mmol) and **101** (49 mg, 0.13 mmol) to afford **116** (70 mg, 0.065 mmol, 59%) as a white solid. Mp 110°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (m, 4H, ArH); 7.75 (d, J = 8.4 Hz, 1H, NH); 7.22, (m, 8H, ArH); 6.99 (d, J = 8.7 Hz, 2H, ArH2' and ArH6'); 6.79 (d, J = 8.7 Hz, 2H, ArH3' and ArH5'); 6.31 (d, J = 8.1 Hz, 1H, NH); 6.15 (bs, 2H, NH); 5.98 (m, 1H, H2"); 5.77 (bs, 1H, NH); 5.63 (m, 1H, H2""'); 5.35 (dd, J = 1.5, 18.9 Hz, 1H, $H3_a$"); 5.23 (dd, J = 1.5, 10.5 Hz, 1H, $H3_b$"); 4.88 (m, 2H, H3""'); 4.64 (m, 1H, H2); 4.40 (m, 6H, H1", H1""' and H8); 4.13 (m, 1H, H5); 3.61 (s, 3H, OCH_3); 2.91 (m, 4H, $ArCH_2$ and H3"'); 2.60 (s, 3H, 7""-CH_3); 2.78 (s, 3H, 5""-CH_3); 2.54 (m, 2H, H4""); 2.10 (s, 3H, 8""-CH_3); 1.75 (t, J = 6.6 Hz, 2H, H3""); 1.36 (m, 2H, H2"'); 1.26 (s, 6H, 2 x 2""-CH_3); 0.84 (m, 2H, H1"'). Mass Spectrum (ES, +ve) *m/z* 1024 (100%) [MH^+]. HRMS calcd for $C_{58}H_{66}N_5O_{10}S$ 1024.4530, found 1024.4513.

Methyl (2*S*,5*R*)-2-allyloxybenzyl-3,6-diaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7-dioxo-8-(2-[2'-{3-phenyl-allyloxy}-{1,1'}-(*S*)-binaphthalen-2-yloxy])octanoate (117)



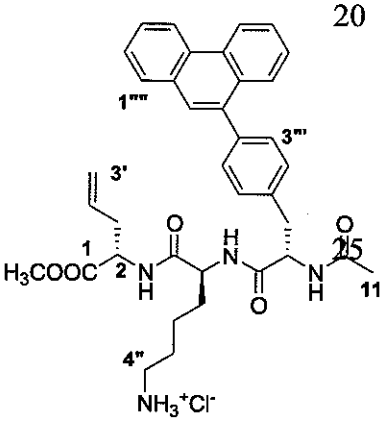
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **113** (64 mg, 0.09 mmol) and **104** (42 mg, 0.09 mmol) to afford **117** (61 mg, 0.055 mmol, 62%) as a cream solid. Mp 100°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (m, 4H, ArH); 7.76 (d, J = 8.1 Hz, 1H, NH); 7.46 (d, J = 9.0 Hz, 1H, NH); 7.17, (m, 13H, ArH); 6.99 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.79 (d, J = 8.4 Hz, 2H, ArH3' and ArH5'); 6.39 (d, J = 8.1 Hz, 1H, NH); 6.13 (m, 2H, H2""' and H3""'); 5.98 (m, 1H, H2"); 5.30 (m, 2H, H3"); 4.64 (m, 1H, H2); 4.39 (m, 6H, H1", H1""' and H8); 4.15 (m, 1H, H5); 3.60 (s, 3H, OCH_3); 2.95 (m, 4H, $ArCH_2$ and H3"'); 2.60 (s, 3H, 7""-CH_3); 2.58 (s, 3H, 5""-CH_3); 2.52 (m, 2H, H4""); 2.10 (s, 3H, 8""-CH_3); 1.74 (t, J = 6.7 Hz, 2H, H3""); 1.36 (m, 2H, H2"'); 1.25 (s, 6H, 2 x 2""-CH_3); 0.85 (m, 2H, H1"'). Mass Spectrum (ES, +ve) *m/z* 1100 (100%) [MH^+]. HRMS calcd for $C_{64}H_{70}N_5O_{10}S$ 1100.4843, found 1100.4833.

Methyl (2*S*,5*S*,8*S*)-2-allyl-5-(4-aminobutyl)-8-(4-[9-anthrecenyl]benzyl)-3,6,9-triaza-5-butylamino-4,7,10-trioxoundecanoate hydrochloride(118)



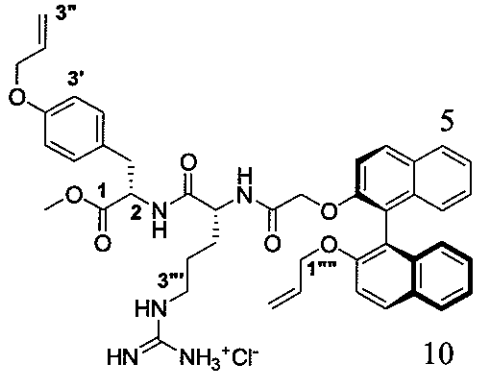
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **114** (20 mg, 0.028 mmol) to yield **118** (13 mg, 0.017 mmol, 61%) as a light yellow solid. Mp 194-202°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.53 (s, 1H, ArH10""); 8.26 (m, 3H, exchanging NH's); 8.06 (d, J = 8.1 Hz, 2H, ArH2"' and ArH6"'); 7.64 (d, J = 9.0 Hz, 2H, ArH3"' and ArH5"'); 7.38 (m, 8H, ArH""); 5.68 (m, 1H, H2'); 5.02 (m, 2H, H3'); 4.67 (m, 1H, H8); 4.45 (m, 2H, H2 and H5); 3.69 (s, 3H, OCH_3); 2.93 (m, 4H, H4" and $ArCH_2$); 2.44 (m, 2H, H1'); 2.00 (s, 3H, H11); 1.69 (m, 4H, H1" and H3"); 1.50 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.4, C7; 173.7, C1; 173.6, C4; 173.5, C10; 138.7, ArC4"'; 137.8, ArC1"'; 137.7, ArC9""; 134.1, C2'; 132.9, ArCH2"' and ArCH6"'; 132.4, ArC4a"" and ArC10a""; 131.5, ArC8a"" and ArC9a""; 130.4, ArCH4"" and ArCH5""; 130.1, ArCH3"' and ArCH5"'; 129.5, ArCH10""; 127.7, ArCH8"" and ArCH1""; 126.5, ArCH2"" and ArCH7""; 126.2, ArCH3"" and ArCH6""; 118.8, C3'; 56.7, C5; 53.8, OCH_3; 53.6, C8; 52.7, C2; 40.5, C4"; 38.6, $ArCH_2$; 36.6, C1'; 32.8, C1"; 28.1, C3"; 23.4, C11; 22.4, C2". Mass Spectrum (ES, +ve) *m/z* 623 (100%) [M^+]. HRMS calcd for $C_{37}H_{43}N_4O_5$ 623.3233, found 623.3215.

Methyl (2*S*,5*S*,8*S*)-2-allyl-5-(4-aminobutyl)-3,6,9-triaza-5-butylamino-4,7,10-trioxo-8-(4-[9-[phenanthrenyl]benzyl)undecanoate hydrochloride (119)



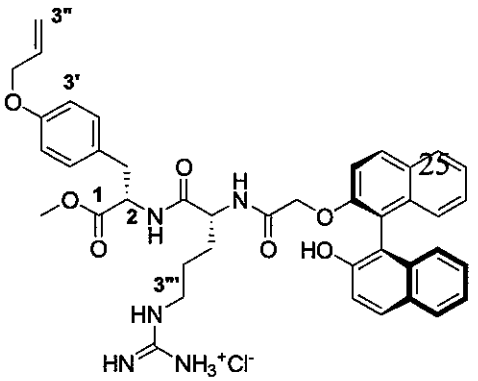
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **115** (24 mg, 0.033 mmol) to yield **119** (15 mg, 0.023 mmol, 69%) as a light yellow solid. Mp 198°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.84 (d, J = 7.8 Hz, 1H, ArH4""); 8.78 (d, J = 8.1 Hz, 1H, ArH5""); 8.30 (d, J = 7.2 Hz, 1H, exchanging NH); 8.15 (d, J = 8.1 Hz, 1H, exchanging NH); 7.90 (m, 2H, ArH1"" and ArH10""); 7.60 (m, 5H, ArH7"", ArH6"", ArH5"", ArH2"" and ArH1""); 7.45 (d, J = 8.4 Hz, 2H, ArH2"' and ArH6"'); 7.40 (d, J = 8.7 Hz, 2H, ArH3"' and ArH5"'); 5.68 (m, 1H, H2'); 4.98 (m, 2H, H3'); 4.61 (m, 1H, H8); 4.40 (m, 2H, H2 and H5); 3.67 (s, 3H, OCH_3); 2.93 (t, J = 7.5 Hz, 2H, H4"); 2.40 (m, 2H, H1'); 1.99 (s, 3H, H11); 1.83 (m, 4H, H1" and $ArCH_2$); 1.69 (m, 2H, H3"); 1.49 (m, 2H, H2").). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.7, C7; 173.6, C1; 173.5, C4; 173.4, C10; 140.7, ArC4"'; 139.8, ArC1"'; 137.5, ArC9""; 134.0, C2'; 133.0, ArC8a""; 132.3, ArC4b""; 132.0, ArC4a""; 131.3, ArCH2"' and ArCH6"'; 131.2, ArC10a""; 130.3, ArCH3"' and ArCH5"'; 129.7, ArCH1""; 128.5, ArCH7""; 128.0, ArCH6""; 127.9, ArCH1""; 127.8, ArCH5""; 127.7, ArCH10""; 127.6, ArCH2""; 124.2, ArC4""; 124.1, ArCH3""; 118.8, C3'; 56.7, C5; 53.7, OCH_3; 53.6, C8; 52.7, C2; 40.5, C4"; 38.5, $ArCH_2$; 36.5, C1'; 32.8, C1"; 28.0, C3"; 23.3, C11; 22.4, C2". Mass Spectrum (ES, +ve) *m/z* 623 (100%) [M^+]. HRMS calcd for $C_{37}H_{43}N_4O_5$ 623.3233, found 623.3262.

Methyl (2*S*,5*R*)-2-allyloxybenzyl-8-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3,6-diaza-5-(3-[guanidino)-4,7-dioxooctanoate hydrochloride (120)



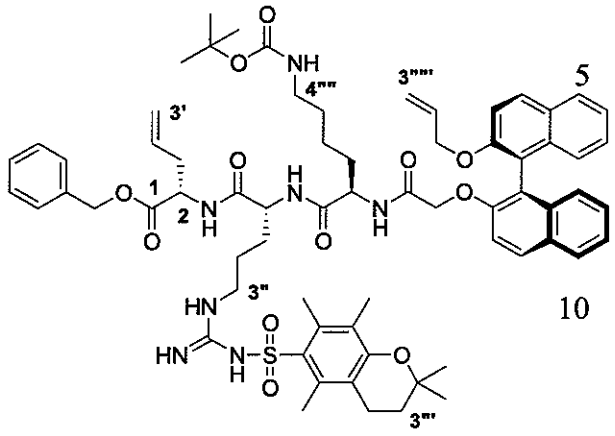
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **116** (70 mg, 0.068 mmol) to yield **120** (31 mg, 0.039 mmol, 58%) as a cream solid. Mp 104-110°C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.62 (m, 4H, ArH); 6.95, (m, 8H, ArH); 6.82 (d, J = 7.0 Hz, 2H, ArH2' and ArH6'); 6.58 (d, J = 7.0 Hz, 2H, ArH3' and ArH5'; 5.74 (m, 1H, H2"); 5.40 (m, 1H, H2""'); 5.09 (d, J = 17.0 Hz, 1H, $H3_a$"); 4.93 (d, J = 10.0 Hz, 1H, $H3_b$"); 4.62 (m, 2H, H3""'); 4.37 (m, 1H, H2); 4.18 (m, 6H, H1", H1""' and H8); 3.98 (m, 1H, H5); 3.36 (s, 3H, OCH_3); 2.75 (m, 4H, $ArCH_2$ and H3"'; 1.40 (m, 2H, H1'"); 0.68 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 125 MHz): δ 173.1, C1; 172.3, C7; 170.5, C4; 158.8, CN_3; 158.2, ArC; 155.1, ArC; 153.8, ArC; 134.9, ArC4'; 134.8, ArC; 134.7, C2"; 134.7, C2""'; 131.3, ArCH; 131.2, ArCH; 130.8, ArCH; 130.7, ArCH; 130.5, ArCH2' and ArCH6'; 130.0, ArCH; 129.1, ArCH; 129.1, ArC; 129.1, ArC; 127.5, ArCH; 127.4, ArCH; 126.4, ArC1'; 125.7, ArCH; 125.2, ArCH; 124.8, ArC; 121.6, ArCH; 120.1, ArCH; 117.5, C3"; 117.0, C3""'; 116.1, ArC; 115.6, ArCH3' and ArCH5'; 70.7, C8; 69.6, C1"; 69.2, C1""'; 55.0, C2; 52.8, OCH_3; 52.6, C5; 41.6, C3"'; 37.4, $ArCH_2$; 30.4, C1'"; 25.6, C2"'. Mass Spectrum (ES, +ve) *m/z* 758 (100%) [M^+]. HRMS calcd for $C_{44}H_{49}N_5O_7$ 759.3632, found 759.3555.

Methyl (2*S*,5*R*)-2-allyloxybenzyl-3,6-diaza-8-(2-[2'-hydroxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-5-(3-[guanidino]propyl)-4,7-dioxooctanoate (121)



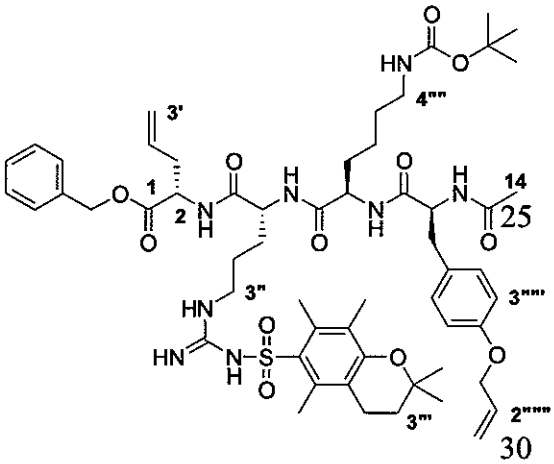
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **117** (58 mg, 0.053 mmol) to yield **121** (28 mg, 0.037 mmol, 70%) as a cream solid. Mp 132°C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.91 (m, 4H, ArH); 7.20, (m, 8H, ArH); 7.06 (d, J = 8.4 Hz, 2H, ArH2' and ArH6'); 6.83 (d, J = 8.4 Hz, 2H, ArH3' and ArH5'); 6.01 (m, 1H, H2"); 5.29 (m, 2H, H3"); 4.62 (m, 2H, H8); 4.55 (dd, J = 4.5, 9.6 Hz, 1H, H2); 4.46 (m, 2H, H1"); 4.22 (dd, J = 5.4, 8.7 Hz,1H, H5); 3.67 (s, 3H, OCH_3); 3.00 (m, 4H, $ArCH_2$ and H3"'); 1.58 (m, 2H, H1'"); 1.06 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 125 MHz): δ 173.2, C1; 172.7, C7; 171.0, C4; 159.5, CN_3; 159.1, ArC; 158.4, ArC; 153.7, ArC4'; 135.4, ArC; 135.3, ArC; 134.9, C2"; 132.5, ArCH; 131.5, ArCH; 131.4, ArCH; 131.2, ArCH; 130.6, ArCH2' and ArCH6'; 130.3, ArCH; 130.1, ArCH; 129.2, ArCH; 128.2, ArCH; 127.7, ArCH; 127.4, ArCH; 126.4, ArC1'; 125.3, ArC; 124.1, ArC; 121.1, ArC; 119.6, ArC; 117.5, C3"; 116.7, ArCH; 115.9, ArCH; 115.8, ArCH3' and ArCH5'; 69.7, C8; 69.0, C1"; 55.2, C2; 53.1, OCH_3; 52.8, C5; 42.0, C3"'; 37.4, $ArCH_2$; 30.1, C1'"; 25.5, C2"'. Mass Spectrum (ES, +ve) *m/z* 718 (100%) [M^+]. HRMS calcd for $C_{41}H_{44}N_5O_7$ 718.3241, found 718.3209.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-11-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3,6,9-triaza-8-(*tert*-butoxycarboxamidobutyl)-5-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (122)



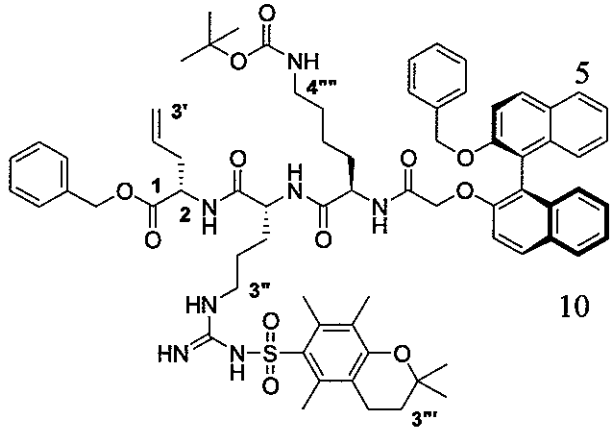
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (63 mg, 0.073 mmol) and **101** (28 mg, 0.073 mmol) to afford **122** (71 mg, 0.058 mmol, 79%) as a white solid. Mp 72-74°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (m, 2H, ArH); 7.85 (m, 2H, ArH); 7.27 (m, 13H, ArH); 6.20 (m, 2H, NH); 5.63 (m, 2H, H2' and H2''''); 5.13 (AB_q, J = 12.3 Hz, 2H, PhC<u>H</u>$_2$O); 4.94 (m, 6H, H11, H3' and H3''''); 4.50 (m, 4H, H1'''', H2 and H5); 4.06 (m, 1H, H8); 3.08 (m, 2H, H3''); 2.89 (m, 2H, H4''''); 2.57 (m, 2H, H4'''); 2.55 (s, 3H, 7'''-CH_3); 2.53 (s, 3H, 5'''-CH_3); 2.49 (m, 2H, H1'); 2.08 (s, 3H, 8'''-CH_3); 1.75 (t, J = 6.3 Hz, H3'''); 1.52 (m, 2H, H1''); 1.40 (s, 9H, $C(CH_3)_3$); 1.34 (m, 2H, H1''''); 1.27 (s, 6H, 2 x 2'''-CH_3); 1.21 (m, 2H, H3''''); 0.95 (m, 2H, H2''); 0.77 (m, 2H, H2''''). Mass Spectrum (ES, +ve) *m/z* 1222 (10%) [MH^+], 1172 (100%). HRMS calcd for $C_{68}H_{84}N_7O_{12}S$ 1222.5899, found 1222.5889.

Benzyl (2*S*,5*R*,8*R*,11*S*)-2-allyl-11-(4-allyloxybenzyl)-3,6,9,12-tetraaza-8-(4-[*tert*-butoxycarboxamido]butyl)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonamido}guanidino]propyl)-4,7,10,13-tetraoxotetradecanoate (123)



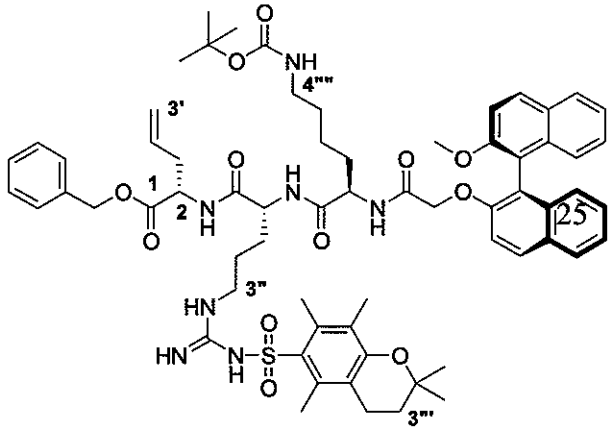
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (60 mg, 0.069 mmol) and **16** (18 mg, 0.068 mmol) to afford the **123** (65 mg, 0.058 mmol, 85%) as a white solid. Mp 94-102°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (bs, 1H, NH); 7.54 (bs, 1H, NH); 7.41 (bs, 1H, NH); 7.31 (m, 5H, ArH); 7.09 (d, J = 8.7 Hz, 2H, ArH2'''' and ArH6''''); 6.77 (d, J = 8.4 Hz, 2H, ArH3'''' and ArH5''''); 6.39 (bs, 3H, 3 x NH's); 6.02 (m, 1H, H2''''); 5.70 (m, 1H, H2'); 5.39 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$''''); 5.26 (dd, J = 1.2, 10.5 Hz, 1H, $H3_b$''''); 5.06 (m, 2H, H3'); 5.05 (m, 2H, PhC<u>H</u>$_2$O); 4.65 (dd, J = 6.9, 13.5 Hz, 1H, H11); 4.57 (dd, J = 8.1, 13.5 Hz, 1H, H2); 4.50 (m, 1H, H5); 4.45 (d, J = 5.4 Hz, 2H, H1''''); 4.41 (m, 1H, H8); 4.14 (bs, 1H, NH); 3.15 (m, 2H, H3''); 2.92 (m, 4H, H4'''' and 11-CH_2); 2.58 (m, 4H, H1' and H4'''); 2.53 (s, 3H, 7'''-CH_3); 2.52 (s, 3H, 5'''-CH_3); 2.08 (s, 3H, H14); 1.94 (m, 4H, H1'' and H1''''); 1.84 (s, 3H, 8'''-CH_3); 1.78 (m, 2H, H3'''); 1.69 (m, 4H, H2'' and H2''''); 1.55 (m, 2H, H3''''); 1.40 (s, 9H, $C(CH_3)_3$); 1.30 (s, 6H, 2 x 2'''-CH_3). Mass Spectrum (ES, +ve) *m/z* 1101 (30%) [MH^+]; 288 (100%). HRMS calcd for $C_{57}H_{81}N_8O_{12}S$ 1101.5695, found 1101.5731.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-11-(2-[2'-benzyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-8-(*tert*-butoxycarboxamidobutyl)-5-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (124)



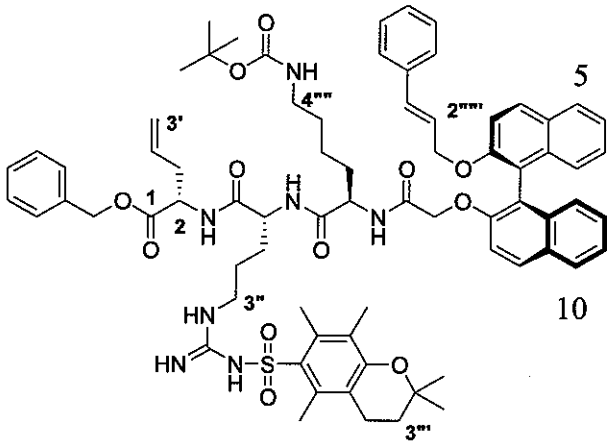
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (58 mg, 0.067 mmol) and **102** (29 mg, 0.067 mmol) to afford **124** (61 mg, 0.048 mmol, 71%) as a white solid. Mp 114-119°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (m, 4H, ArH); 7.26 (m, 18H, ArH); 6.80 (d, J = 6.9 Hz, 1H, NH); 6.23 (m, 3H, NH); 5.65 (m, 1H, H2'); 5.07 (m, 6H, H11, PhC$\underline{H}_2$O-ester and H3'); 4.81 (m, 1H, H2); 4.60 (m, 1H, H5); 4.40 (m, 2H, H11); 4.08 (m, 1H, H8); 3.01 (m, 2H, H3"); 2.89 (m, 2H, H4""); 2.59 (m, 2H, H4"'); 2.57 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.50 (m, 2H, H1'); 2.08 (s, 3H, 8"'-CH_3); 1.75 (t, J = 6.6 Hz, H3"'); 1.52 (m, 2H, H1"); 1.41 (s, 9H, C(CH_3)$_3$); 1.35 (m, 2H, H1"" and H3""); 1.27 (s, 6H, 2 x 2"'-CH_3); 1.15 (m, 4H, H2" and H2""). Mass Spectrum (ES, +ve) *m/z* 1272 (100%) [MH^+]. HRMS calcd for $C_{72}H_{86}N_7O_{12}S$ 1272.6055, found 1272.6061.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(*tert*-butoxycarboxamidobutyl)-11-(2-[2'-methoxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-5-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (125)



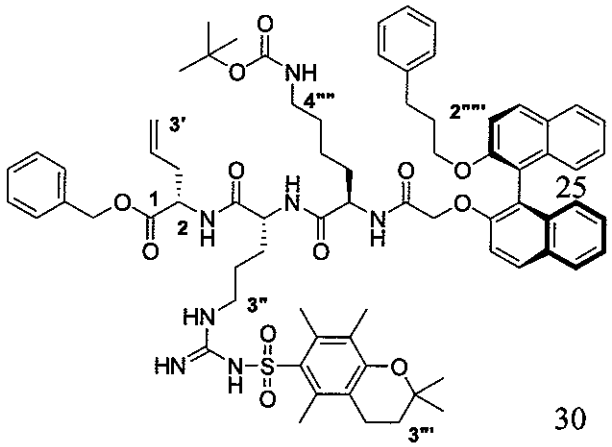
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (55 mg, 0.064 mmol) and **103** (23 mg, 0.064 mmol) to afford **125** (51 mg, 0.042 mmol, 66%) as a white solid. Mp 104°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (m, 4H, ArH); 7.30 (m, 13H, ArH); 6.23 (m, 3H, NH); 5.63 (m, 1H, H2'); 5.10 (m, 4H, PhC$\underline{H}_2$O and H3'); 4.80 (m, 1H, H2); 4.58 (m, 2H, H11); 4.41 (m, 1H, H5); 4.11 (m, 1H, H8); 3.71 (s, 3H, OCH_3); 3.09 (m, 2H, H3"); 2.89 (m, 2H, H4""); 2.56 (m, 2H, H4"'); 2.54 (s, 3H, 7"'-CH_3); 2.51 (s, 3H, 5"'-CH_3); 2.48 (m, 2H, H1'); 2.07 (s, 3H, 8"'-CH_3); 1.86 (m, 2H, H1"); 1.75 (t, J = 5.7 Hz, H3"'); 1.56 (m, 2H, H1""); 1.41 (s, 9H, C(CH_3)$_3$); 1.34 (m, 4H, H1"" and H3""); 1.27 (s, 6H, 2 x 2"'-CH_3); 1.54 (m, 4H, H2" and H2""). Mass Spectrum (ES, +ve) *m/z* 1196 (30%) [MH^+], 346 (100%). HRMS calcd for $C_{66}H_{82}N_7O_{12}S$ 1196.5742, found 1196.5757.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(*tert*-butoxycarboxamidobutyl)-5-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-11-(2-[2'-{3-phenylallyloxy}-[1,1']-(*S*)-binaphthalen-2-yloxy])-4,7,10-trioxoundecanoate (126)



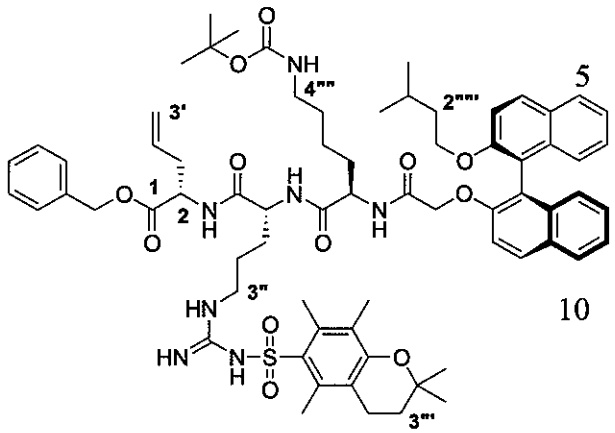
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (63 mg, 0.073 mmol) and **104** (34 mg, 0.073 mmol) to afford **126** (64 mg, 0.049 mmol, 67%) as a white solid. Mp 110-112°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (m, 4H, ArH); 7.28 (m, 18H, ArH); 6.22 (m, 3H, NH); 6.11 (d, J = 16.2 Hz, 1H, H3''''); 5.91 (dt, J = 5.1, 16.2 Hz, 1H, H2''''); 5.64 (m, 1H, H2'); 5.10 (m, 6H, PhC$\underline{H_2}$O, H1'''' and H3'); 4.81 (m, 1H, H2); 4.67 (m, 2H, H11); 4.59 (dd, J = 7.5, 12.9 Hz, 1H, H5); 4.09 (m, 1H, H8); 3.05 (m, 2H, H3''); 2.88 (m, 2H, H4''''); 2.56 (m, 2H, H4'''); 2.56 (s, 3H, 7'''-CH_3); 2.53 (s, 3H, 5'''-CH_3); 2.49 (m, 2H, H1'); 2.08 (s, 3H, 8'''-CH_3); 1.74 (m, 2H, H3'''); 1.55 (m, 4H, H1'' and H1''''); 1.41 (s, 9H, C(CH_3)$_3$); 1.32 (m, 2H, H3''''); 1.26 (s, 6H, 2 x 2'''-CH_3); 1.15 (m, 4H, H2'' and H2''''). Mass Spectrum (ES, +ve) *m/z* 1298 (5%) [MH^+], 1172 (100%). HRMS calcd for $C_{74}H_{88}N_7O_{12}S$ 1298.6212, found 1298.6185.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(*tert*-butoxycarboxamidobutyl)-5-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-11-(2-[2'-{3-phenylpropyloxy}-[1,1']-(*S*)-binaphthalen-2-yloxy])-4,7,10-trioxoundecanoate (127)



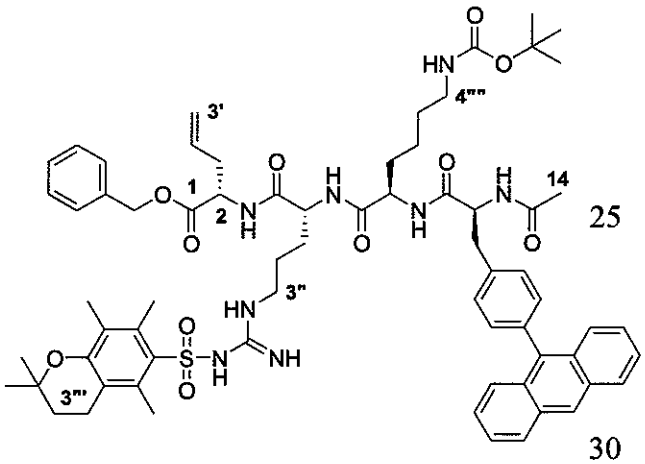
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (124 mg, 0.14 mmol) and **107** (68 mg, 0.14 mmol) to afford **127** (146 mg, 0.11 mmol, 80%) as a white solid. Mp 92-98°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (m, 4H, ArH); 7.23 (m, 18H, ArH); 6.68 (d, J = 9.0 Hz, 1H, NH); 6.27 (bs, 1H, NH); 6.21 (d, J = 7.2 Hz, 1H, NH); 5.65 (m, 1H, H2'); 5.12 (AB_q, J = 12.3 Hz, 2H, PhC$\underline{H_2}$O); 5.03 (m, 2H, H3'); 4.55 (m, 2H, H5 and H2); 4.40 (AB_q, J = 14.4 Hz, 2H, H11); 4.07 (m, 1H, H8); 3.85 (m, 2H, H1''''); 3.08 (m, 2H, H3''); 2.90 (m, 4H, H4'''' and H3''''); 2.58 (m, 2H, H4'''); 2.55 (s, 3H, 7'''-CH_3); 2.53 (s, 3H, 5'''-CH_3); 2.47 (m, 2H, H1'); 2.08 (s, 3H, 8'''-CH_3); 1.99 (m, 2H, H1'); 1.74 (t, J = 6.6 Hz, 2H, H3'''); 1.62 (m, 2H, H2''''); 1.40 (s, 9H, C(CH_3)$_3$); 1.23 (s, 6H, 2 x 2'''-CH_3); 1.14 (m, 2H, H3''''); 0.95 (m, 2H, H2''); 0.77 (m, 2H, H2''''). Mass Spectrum (ES, +ve) *m/z* 1321 (100%) [MNH_4^+]. HRMS calcd for $C_{74}H_{90}N_7O_{12}S$ 1300.6368, found 1300.6356.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(*tert*-butoxycarboxamidobutyl-11-(2-[2'-(3-methylbutoxy)-{1,1'}-(*S*)-binaphthalen-2-yloxy])-5-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (128)



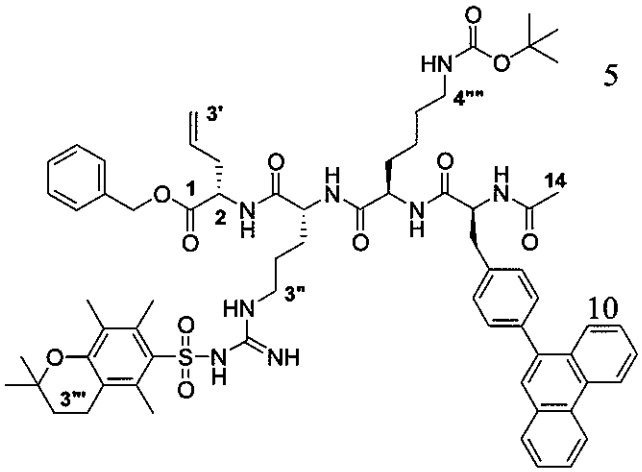
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (121 mg, 0.14 mmol) and **105** (58 mg, 0.14 mmol) to afford **128** (114 mg, 0.091 mmol, 65%) as a white solid. Mp 90-94°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (m, 4H, ArH); 7.30 (m, 13H, ArH); 6.47 (m, 1H, NH); 6.29 (bs, 2H, NH); 6.18 (d, J = 6.9 Hz, 1H, NH); 5.65 (m, 1H, H2'); 5.13 (AB_q, J = 12.3 Hz, 2H, PhC$\underline{H_2}$O); 5.05 (m, 2H, H3'); 4.80 (m, 5H, H2, H5, H8 and H11); 3.95 (m, 2H, H1''''); 3.14 (m, 2H, H3"); 2.92 (m, 2H, H4''''); 2.64 (m, 2H, H4"'); 2.56 (s, 3H, 7"'-CH_3); 2.55 (s, 3H, 5"'-CH_3); 2.49 (m, 2H, H1'); 2.09 (s, 3H, 8"'-CH_3); 1.76 (t, J = 5.7 Hz, H3"'); 1.52 (m, 4H, H1" and H1''''); 1.41 (s, 9H, $C(CH_3)_3$); 1.26 (s, 6H, 2 x 2"'-CH_3); 1.12 (m, 2H, H3''''); 0.92 (m, 2H, H2''''); 0.79 (m, 4H, H3'''' and H2"); 0.52 (d, J = 6.3 Hz, 3H, $H4_a$''''); 0.46 (d, J = 6.3 Hz, 3H, $H4_b$''''). Mass Spectrum (ES, +ve) *m/z* 1274 (100%) [MNH_4^+]. HRMS calcd for $C_{70}H_{90}N_7O_{12}S$ 1252.6368, found 1252.6388.

Benzyl (2*S*,5*R*,8*R*,11*S*)-2-allyl-11-(4-[9-anthracenyl]benzyl)-3,6,9,12-tetraaza-8-(4-[*tert*-butoxycarboxamido]butyl)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10,13-tetraoxotetradecanoate (129)



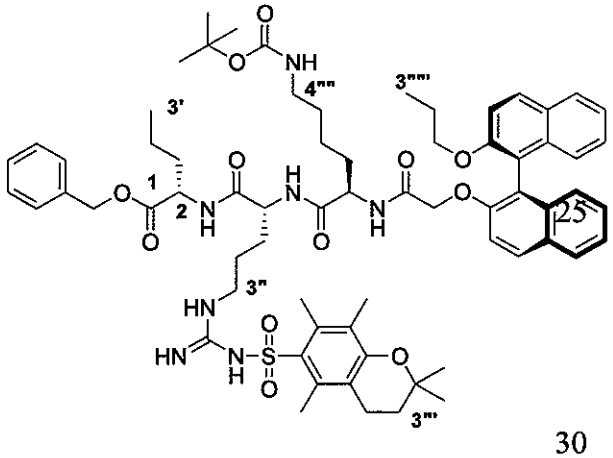
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (40 mg, 0.045 mmol) and **97** (17 mg, 0.045 mmol) to afford **129** (20 mg, 0.016 mmol, 36%) as a white solid. Mp 108-110°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (s, 1H, ArH10''''); 8.03 (m, 2H, ArH); 7.58 (m, 2H, ArH); 7.44 (m, 2H, ArH); 7.30 (m, 11H, ArH); 6.82 (bs, 1H, NH); 6.36 (bs, 2H,n 2 x NH's); 5.77 (m, 1H, H2'); 5.12 (m, 4H, H3' and PhC$\underline{H_2}$O); 4.85 (m, 1H, H11); 4.59 (m, 1H, H2); 4.44 (m, 1H, H5); 4.31 (m, 1H, H8); 3.19 (m, 2H, 11-CH_2); 2.95 (m, 4H, H4'''' and H3"); 2.56 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.52 (m, 4H, H4"' and H1'); 2.06 (s, 3H, 8"'-CH_3); 1.97 (m, 2H, H3''''); 1.94 (s, 3H, H14); 1.74 (m, 4H, H1" and H1''''); 1.71 (m, 2H, H3"'); 1.62 (m, 2H, H2"); 1.38 (m, 2H, H2''''); 1.36 (s, 9H, $C(CH_3)_3$); 1.23 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 1221 (10%) [MH^+]; 282 (100%). HRMS calcd for $C_{68}H_{85}N_8O_{11}S$ 1221.6059, found 1221.6089.

Benzyl (2*S*,5*R*,8*R*,11*S*)-2-allyl-3,6,9,12-tetraaza-8-(4-[*tert*-butoxycarboxamido]butyl)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10,13-tetraoxo-11-(4-[9-phenanthrenyl]benzyl)tetradecanoate (130)



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **112** (38 mg, 0.044 mmol) and **99** (16 mg, 0.042 mmol) to afford **130** (41 mg, 0.034 mmol, 80%) as a white solid. Mp 108°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.72 (m, 2H, ArH); 7.58 (m, 16H, ArH); 6.40 (bs, 2H, NH); 5.71 (m, 1H, H2'); 5.13 (m, 2H, PhC$\underline{H_2}$O); 5.03 (m, 2H, H3'); 4.83 (m, 1H, H11); 4.60 (m, 1H, H2); 4.59 (m, 1H, H5); 4.29 (m, 1H, H8); 3.12 (m, 2H, 11-CH_2); 2.94 (m, 4H, H4"" and H3"); 2.56 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.53 (m, 4H, H4"' and H1'); 2.07 (s, 3H, 8"'-CH_3); 1.91 (s, 3H, H14); 1.82 (m, 4H, H1" and H1""); 1.72 (t, J = 6.6 Hz, 2H, H3"'); 1.62 (m, 4H, H2" and H3""); 1.39 (m, 2H, H2""); 1.34 (s, 9H, C(CH_3)$_3$); 1.23 (s, 6H, 2 x 2"'-CH_3). Mass Spectrum (ES, +ve) *m/z* 1221 (100%) [MH^+]. HRMS calcd for $C_{68}H_{85}N_8O_{11}S$ 1221.6059, found 1221.6045.

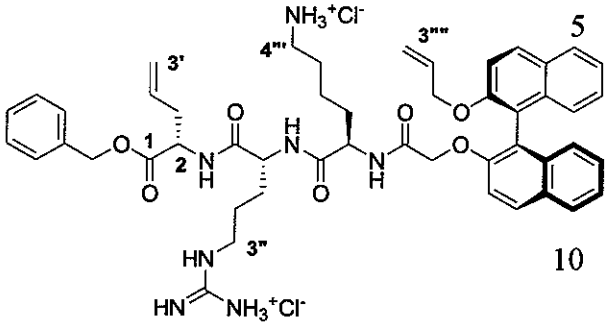
Benzyl (2*S*,5*R*,8*R*)-3,6,9-triaza-8-(*tert*-butoxycarboxamidobutyl)-5-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxo-2-propyl-11-(2-[2'-3-(propyloxy)-{1,1'}-(*S*)-binaphthalen-2-yloxy])undecanoate (131)



To a solution of **122** (170 mg, 0.145 mmol) in THF (5 mL) was added palladium on activated carbon. The reaction vessel was degassed under vacuum and regassed with hydrogen before being allowed to stir for 13 h. The solution was filtered, evaporated to dryness and dissolved in acetone (5 mL). To this solution was added K_2CO_3 (39 mg, 0.28 mmol) and benzyl bromide (24 mg, 0.14 mmol). After a further 13 h the reaction was concentrated by vacuum and the product isolated by flash column chromatography (5% MeOH/ DCM) to yield **131** (127 mg, 0.10 mmol, 71%) as a white solid. Mp 118-123°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (m, 4H, ArH); 7.30 (m, 13H, ArH); 6.26 (bs, 2H, NH); 6.20 (d, J = 7.2 Hz, 1H, NH); 5.13 (AB_q, J = 12.6 Hz, 2H, PhC$\underline{H_2}$O); 4.50 (m, 2H, H2 and H5) 4.43 (m, 2H, H11); 3.99 (m, 1H, H8); 3.69 (m, 2H, H1""'); 3.13 (m, 2H, H3"); 2.91 (m, 2H, H4""); 2.60 (m, 2H, H4"'); 2.56 (s, 3H, 7"'-CH_3); 2.54 (s, 3H, 5"'-CH_3); 2.08 (s, 3H, 8"'-CH_3); 1.90 (m, 2H, H1'); 1.88 (m, 2H, H2""'); 1.76 (m, 2H, H3"'); 1.58 (m, 2H, H2""); 1.41 (s, 9H, C(CH_3)$_3$); 1.38 (m, 4H, H1" and H1""); 1.34 (m, 2H, H2'); 1.27 (s, 6H, 2 x 2"'-CH_3); 1.20 (m, 2H, H2"); 0.87 (t, J = 6.9 Hz, 3H, H3""'); 0.43 (t, J = 7.2 Hz, 3H,

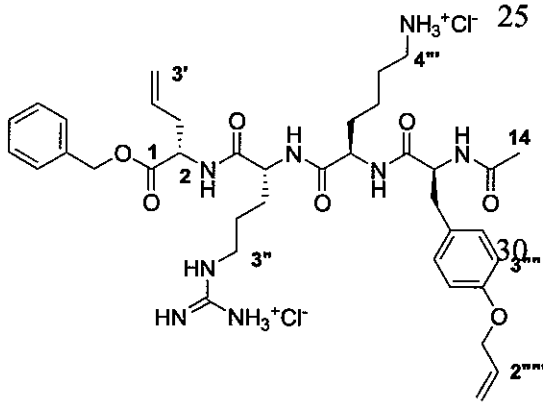
H3'). Mass Spectrum (ES, +ve) *m/z* 1226 (100%) [MH^+]. HRMS calcd for $C_{68}H_{88}N_7O_{12}S$ 1226.6212, found 1226.6240.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-11-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3,6,9-triaza-8-(butylamino)-5-(3-guanidinopropyl)-4,7,10-trioxoundecanoate dihydrochloride (132)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **122** (65 mg, 0.055 mmol) to yield **132** (29 mg, 0.034 mmol, 62%) as a highly hydroscopic cream solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.04 (d, *J* = 6.0 Hz, 1H, ArH); 8.01 (d, *J* = 6.0 Hz, 1H, ArH); 7.93 (s, 1H, ArH); 7.90 (s, 1H, ArH); 7.55 (d, *J* = 9.3 Hz, 1H, ArH); 7.48 (d, *J* = 9.3 Hz, 1H, ArH); 7.35 (m, 7H, ArH); 7.23 (m, 2H, ArH); 7.07 (m, 1H, ArH); 7.05 (m, 1H, ArH); 5.73 (m, 2H, H2' and H2""); 5.16 (AB_q, *J* = 3.6 Hz, 2H, PhC<u>H</u>$_2$O); 5.01 (m, 4H, H3' and H3""); 4.55 (m, 6H, H2, H5, H11 and H1""); 4.13 (m, 1H, H8); 3.13 (m, 2H, H3"); 2.77 (m, 2H, H4"'); 2.54 (ddd, *J* = 5.4, 14.4, 24.3 Hz, 2H, H1'); 1.77 (m, 2H, H1"); 1.62 (m, 2H, H1"'); 1.52 (m, 2H, H3"'); 1.44 (m, 2H, H2"); 0.95 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.8, C4; 173.2, C2; 172.5, C7; 170.9, C10; 158.5, CN_3; 155.4, ArC; 154.1, ArC; 137.1, ArC; 135.1, C2'; 135.1, C2""; 135.0, ArC; 134.2, ArC; 131.4, ArCH; 131.0, ArCH; 130.8, ArCH; 130.8, ArCH; 129.6, ArC; 129.4, ArC; 129.3, ArCH; 129.3, ArCH; 129.2, ArCH; 127.6, ArCH; 127.6, ArCH; 126.4, ArCH; 126.0, ArCH; 125.3, ArCH; 124.9, ArCH; 21.6, ArCH; 120.5, ArC; 119.1, ArC; 117.0, C3'; 116.9, C3""; 116.0, ArCH; 70.9, C11; 69.2, C1""; 68.1, $ArCH_2$; 53.9, C5; 53.7, C2; 53.6, C8; 41.9, C3"; 40.4, C4"'; 36.7, C1'; 32.2, C1"; 30.3, C1"'; 27.8, C2"; 26.2, C2"'; 23.2, C3"'. Mass Spectrum (ES, +ve) *m/z* 856 (100%) [M^{2+}]. HRMS calcd for $C_{49}H_{58}N_7O_7$ 856.4398, found 856.4367.

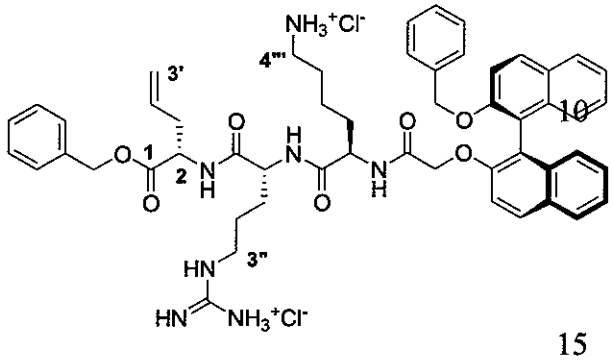
Benzyl (2*S*,5*R*,8*R*,11*S*)-2-allyl-11-(4-allyloxybenzyl)-8-(4-aminobutyl)-3,6,9,12-tetraaza-5-(3-[guanidino]propyl)-4,7,10,13-tetraoxotetradecanoate hydrochloride (133)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **123** (65 mg, 0.059 mmol) to yield **133** (39 mg, 0.048 mmol, 82%) as a cream solid. Mp 108°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (m, 5H, ArH); 7.16 (d, *J* = 8.7 Hz, 2H, ArH2"' and ArH6"'); 6.87 (d, *J* = 8.7 Hz, 2H, ArH3"' and ArH5"'); 6.02 (m, 1H, H2"'); 5.78 (m, 1H, H2'); 5.39 (dd, *J* = 1.8, 17.1 Hz, 1H, $H3_a$""'); 5.24 (dd, *J* = 1.8, 10.5 Hz, 1H, $H3_b$""'); 5.10 (m, 4H, H3' and PhC<u>H</u>$_2$O); 4.52 (m, 2H, H1""'); 4.39 (m, 2H, H13 and H2); 4.24 (dd, *J* = 4.8, 9.0 Hz, 1H, H5); 3.98 (dd, *J* = 3.9, 9.9 Hz, 1H, H8); 3.16 (m, 2H, H3"); 2.94 (m, 2H, 11-CH_2); 2.84 (m, 2H, H4"'); 2.55 (m, 2H, H1'); 1.94 (s, 3H, H14); 1.87 (m, 2H, H1"); 1.73 (m, 2H, H1"'); 1.54 (m, 4H, H2" and H2"'); 1.03 (m, 2H, H3"'). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.4, C1; 174.4, C4; 174.2, C7; 172.5, C10; 159.0, C13; 158.5,

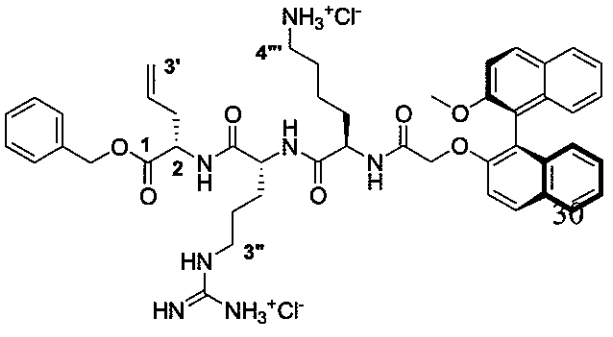
NCO; 137.2, ArC4""; 134.9, C2"""; 134.3, C2'; 131.5, ArC; 130.0, ArCH2"" and ArCH6""; 129.6, ArCH; 129.4, ArCH; 129.4, ArCH; 128.5, ArC1"; 119.0, C3'; 117.6, C3"""; 115.9, ArCH3"" and ArCH5""; 69.8, C1"""; 67.9, CH_2-ester); 57.8, C11; 55.3, C5; 54.8, C8; 54.0, C2; 41.9, C3"; 40.3, C4""; 37.4, 11-CH_2; 36.5, C1'; 31.2, C1""; 29.5, C2"; 28.0, C2""; 26.5, C14; 23.8, C3""; 22.5, C1". Mass Spectrum (ES, +ve) *m/z* 735 2 [M^{2+}] (70%), 368 (100%). HRMS calcd for $C_{38}H_{55}N_8O_7$ 735.4194, found 735.4200.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-11-(2-[2'-benzyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-8-(butylamino)-5-(3-guanidinopropyl)-4,7,10-trioxoundecanoate dihydrochloride (134)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from 124 (50 mg, 0.039 mmol) to yield 134 (29 mg, 0.030 mmol, 76%) as a cream solid. Mp 116-118°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.70 (m, 4H, ArH); 6.91 (m, 18H, ArH); 5.54 (m, 1H, H2'); 4.89 (m, 6H, PhC$\underline{H_2}$O, H1"" and H3'); 4.49 (m, 1H, H2); 4.30 (m, 1H, H5); 4.23 (m, 2H, H11); 4.05 (m, 1H, H8); 3.21 (m, 2H, H3"); 2.95 (m, 2H, H4"'); 2.50 (m, 2H, H1'); 1.62 (m, 2H, H1"); 1.43 (m, 4H, H1"' and H3"'); 1.15 (m, 2H, H2"); 0.89 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.6, C4; 173.4, C2; 172.4, C7; 171.1, C10; 158.2, CN_3; 154.3, ArC; 154.1, ArC; 153.4, ArC; 142.1, ArC; 141.8, ArC; 140.8, ArC; 136.8, ArCH; 135.9, ArCH; 135.2, C2'; 132.6, ArC; 131.1, ArCH; 130.6, ArCH; 130.1, ArCH; 129.7, ArC; 129.6, ArC; 129.5, ArCH; 129.3, ArCH; 129.2, ArCH; 129.1, ArCH; 128.8, ArCH; 127.4, ArCH; 126.9, ArCH; 126.7, ArCH; 126.3, ArCH; 125.5, ArCH; 125.1, ArCH; 120.6, ArCH; 120.2, ArCH; 119.2, ArC; 116.6, C3'; 68.7, C11; 68.7, C1""; 68.0, $ArCH_2$; 54.0, C5; 53.9, C2; 53.6, C8; 41.8, C3"; 40.4, C4"'; 36.5, C1'; 31.9, C1"; 30.0, C1"'; 27.6, C2"; 26.1, C2"'; 23.2, C3"'. Mass Spectrum (ES, +ve) *m/z* 906 (100%) [M^{2+}]. HRMS calcd for $C_{53}H_{60}N_7O_7$ 906.4554, found 906.4544.

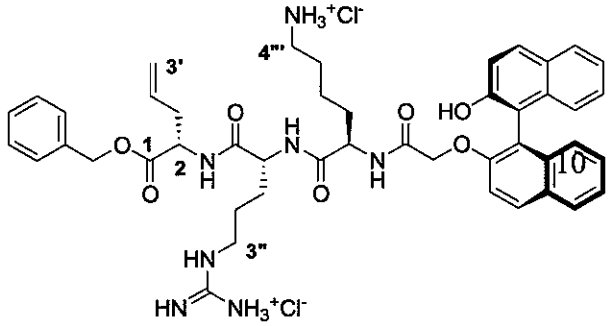
Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(butylamino)-5-(3-guanidinopropyl)-11-(2-[2'-methyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-4,7,10-trioxoundecanoate dihydrochloride (135)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from 125 (45 mg, 0.037 mmol) to yield 135 (24 mg, 0.027 mmol, 72%) as a highly hydroscopic cream solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.76 (m, 4H, ArH); 7.03 (m, 13H, ArH); 5.56 (m, 1H, H2'); 4.94 (m, 4H, PhC$\underline{H_2}$O and H3'); 4.31 (m, 4H, H2, H5 and H11); 4.03 (m, 1H, H8); 3.56 (s, 3H, OCH_3); 2.98 (m, 2H, H3"); 2.64 (m, 2H, H4"'); 2.36 (m, 2H, H1'); 1.42(m, 4H, H1" and H1"'); 0.99 (m, 2H, H2"); 0.78 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.7, C4; 173.1, C2; 172.4, C7; 170.8, C10; 158.4, CN_3; 156.2, ArC; 153.8, ArC; 136.9, ArC; 135.0, ArC; 134.8, C2'; 134.1, ArCH; 131.2, ArC; 131.0, ArCH; 130.9, ArCH; 130.5, ArC; 129.5, ArCH; 129.3, ArCH; 129.2, ArCH; 129.2, ArC; 129.1, ArCH; 127.6, ArC; 127.5, ArCH; 126.1, ArCH;

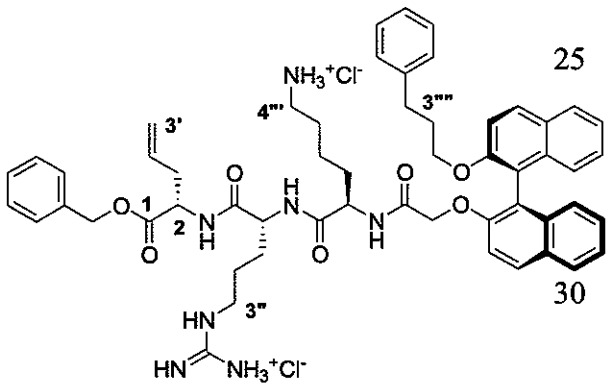
125.7, ArCH; 125.2, ArCH; 124.7, ArCH; 121.4, ArC; 119.5, ArCH; 119.2, C3'; 116.0, ArCH; 115.3, ArCH; 69.1, C11; 68.0, $ArCH_2$; 57.2, OCH_3; 54.0, C5; 53.6, C2; 53.6, C8; 41.9, C3"; 40.5, C4"'; 36.6, C1'; 32.2, C1"; 30.1, C1"'; 27.7, C2"; 26.2, C2"'; 23.1, C3"'. Mass Spectrum (ES, +ve) *m/z* 830 (100%) [M^{2+}]. HRMS calcd for $C_{47}H_{56}N_7O_7$ 830.4241, found 830.4219.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(butylamino)-5-(3-guanidinopropyl)-11-(2-[2'-hydroxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-4,7,10-trioxoundecanoate dihydrochloride (136)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from 126 (50 mg, 0.038 mmol) to yield 136 (35 mg, 0.036 mmol, 96%) as a highly hydroscopic cream solid. ^1H NMR (CD_3OD, 300 MHz): δ 7.62 (m, 4H, ArH); 6.90 (m, 13H, ArH); 5.44 (m, 1H, H2'); 4.82 (m, 4H, $PhC\underline{H_2}O$ and H3'); 4.40 (m, 1H, H5); 4.31 (m, 2H, H11); 4.21 (m, 1H, H2); 3.96 (m, 1H, H8); 2.86 (m, 2H, H3"); 2.54 (m, 2H, H4"'); 2.26 (m, 2H, H1'); 1.54 (m, 2H, H1"); 1.34 (m, 4H, H3"' and H1"'); 1.05 (m, 2H, H2"); 0.79 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.6, C4; 173.4, C2; 172.4, C7; 171.1, C10; 158.2, CN_3; 154.0, ArC; 153.3, ArC; 136.7, ArC; 135.2, ArC; 135.0, C2'; 133.9, ArCH; 131.0, ArCH; 130.8, ArC; 130.6, ArCH; 130.0, ArCH; 129.4, ArCH; 129.2, ArCH; 129.1, ArCH; 128.1, ArC; 127.8, ArCH; 127.5, ArC; 127.3, ArC; 126.2, ArCH; 125.5, ArCH; 125.1, ArCH; 124.1, ArCH; 120.5, ArC; 119.5, ArCH; 119.2, C3'; 116.5, ArCH; 115.5, ArCH; 68.6, C11; 67.9, $ArCH_2$; 54.0, C5; 53.9, C2; 53.5, C8; 41.7, C3"; 40.3, C4"'; 36.4, C1'; 32.0, C1"; 30.0, C1"'; 27.6, C2"; 26.0, C2"'; 23.2, C3"'. Mass Spectrum (ES, +ve) *m/z* 888 (5%) [M^{2+}], 831 (100%). HRMS calcd for $C_{46}H_{54}N_7O_7$ 816.4085, found 816.4086.

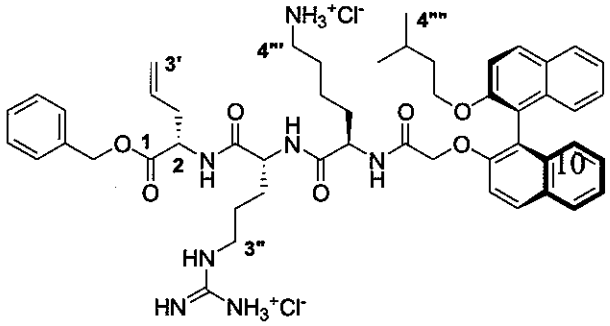
Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(butylamino)-5-(3-guanidinopropyl)- 4,7,10-trioxo-11-(2-[2'-(3-phenylpropyloxy)-{1,1'}-(*S*)-binaphthalen-2-yloxy])-undecanoate dihydrochloride (137)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from 127 (146 mg, 0.11 mmol) to yield 137 (91 mg, 0.090 mmol, 82%) as a highly hydroscopic cream solid. ^1H NMR (CD_3OD, 500 MHz): δ 7.95 (m, 4H, ArH); 7.15 (m, 18H, ArH); 5.73 (m, 1H, H2'); 5.10 (m, 4H, H3' and $PhC\underline{H_2}O$); 4.47 (m, 1H, H5); 4.35 (m, 2H, H11); 4.17 (m, 1H, H2); 4.08 (m, 1H, H8); 3.86 (m, 2H, H1""); 3.13 (m, 2H, H3"); 2.80 (m, 2H, H2""); 2.52 (m, 2H, H4"'); 2.10 (m, 2H, H1'); 1.61 (m, 4H, H3"" and H1"); 1.49 (m, 4H, H3' and H1"'); 1.12 (m, 2H, H2"); 0.96 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 125 MHz): δ 173.8, C4; 173.1, C2; 172.4, C7; 170.7, C10; 158.5, CN_3; 155.6, ArC; 154.0, ArC; 142.7, ArC; 137.0, C2'; 135.2, ArCH; 135.0, ArCH; 134.4, ArC; 134.1, ArCH; 131.3, ArC; 130.9, ArC; 130.6, ArCH; 129.6, ArCH; 129.3, ArCH; 129.3, ArCH; 129.2, ArCH; 129.2, ArCH; 129.0, ArCH; 127.9, ArC; 127.6, ArCH;

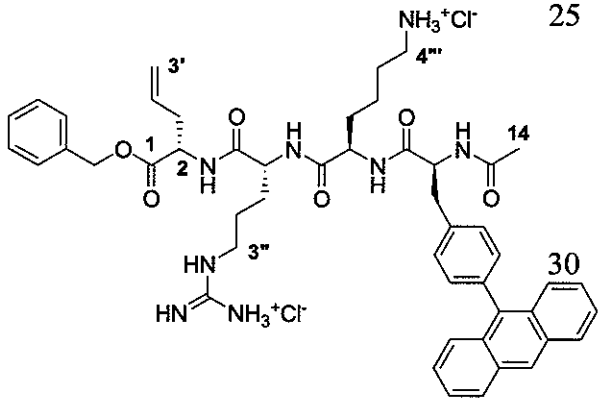
126.5, ArCH; 126.4, ArC; 125.9, ArC; 125.3, ArCH; 124.8, ArCH; 121.7, ArCH; 120.9, ArCH; 120.3, ArC; 119.1, C3'; 116.7, ArCH; 116.0, ArCH; 69.3, C11; 69.2, $ArCH_2$; 68.0, C1''''; 54.1, C5; 53.6, C2; 53.5, C8; 41.9, C3''; 40.3, C4'''; 36.6, C1'; 32.5, C1''; 32.2, C1'''; 32.1, C3''''; 30.1, C2''''; 27.7, C2''; 26.2, C2'''; 23.1, C3'''. Mass Spectrum (ES, +ve) *m/z* 934 (5%) [M^{2+}], 468 (100%). HRMS calcd for $C_{55}H_{64}N_7O_7$ 934.4867, found 934.4844.

Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6,9-triaza-8-(butylamino)-5-(3-guanidinopropyl) -11-(2-[2'-(3-methylbutoxy)-{1,1'}-(*S*)-binaphthalen-2-yloxy])- 4,7,10-trioxoundecanoate dihydrochloride (138)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **128** (114 mg, 0.091 mmol) to yield **138** (48 mg, 0.050 mmol, 55%) as a highly hydroscopic cream solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.968 (m, 4H, ArH); 5.32 (m, 13H, ArH); 5.74 (m, 1H, H2'); 5.11 (m, 4H, PhC$\underline{H_2}$O and H3'); 4.49 (m, 3H, H5 and H11); 4.35 (m, 1H, H2); 4.14 (m, 2H, H1''''); 3.95 (m, 1H, H8); 3.14 (m, 2H, H3''); 2.79 (m, 2H, H4''); 2.55 (m, 2H, H1'); 1.79 (m, 2H, H1''); 1.71 (m, 2H, H3'''); 1.55 (m, 4H, H2'''' and H1'''); 1.24 (m, 2H, H3''''); 1.17 (m, 2H, H2''); 0.96 (m, 2H, H2'''); 0.53 (d, J = 6.3 Hz, 3H, $H4_a$''''); 0.47 (d, J = 6.3 Hz, 3H, $H4_b$''''). ^{13}C NMR (CD_3OD, 125 MHz): δ 173.9, C4; 173.2, C2; 172.5, C7; 170.9, C10; 158.5, CN_3; 155.9, ArC; 154.0, ArC; 137.1, C2'; 135.2, ArC; 135.0, ArC; 134.3, ArCH; 134.2, ArCH; 131.4, ArC; 129.6, ArCH; 129.6, ArCH; 129.4, ArCH; 129.3, ArC; 129.1, ArCH; 128.2, ArC; 128.0, ArC; 127.6, ArCH; 127.5, ArCH; 126.4, ArCH; 126.0, ArCH; 125.2, ArC; 124.8, ArCH; 121.8, ArCH; 120.5, ArCH; 119.1, C3'; 117.0, ArCH; 116.0, ArCH; 69.0, $ArCH_2$; 68.0, C11; 65.2, C1''''; 54.2, C5; 53.7, C2; 53.6, C8; 41.9, C3''; 40.4, C4'''; 39.3, C2''''; 36.7, C1'; 32.2, C1''; 30.1, C2''; 27.7, C2'''; 26.2, C3'''; 25.6, C3''''; 22.8, $C4_a$''''; 22.6, $C4_b$''''. Mass Spectrum (ES, +ve) *m/z* 886 (5%) [M^{2+}], 444 (100%). HRMS calcd for $C_{51}H_{64}N_7O_7$ 886.4867, found 886.4869.

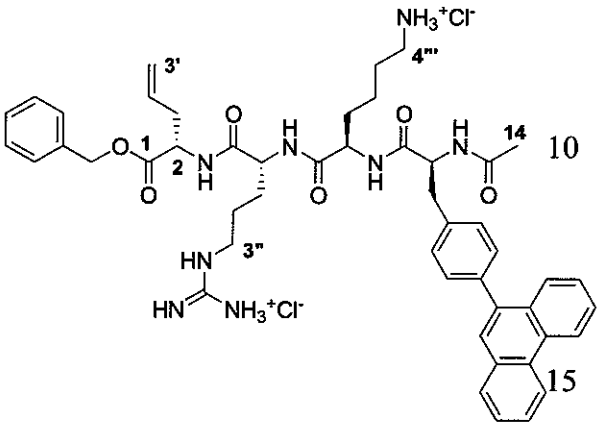
Benzyl (2*S*,5*R*,8*R*,11*S*)-2-allyl-8-(4-aminobutyl)-11-(4-[9-anthracenyl]benzyl)-3,6,9,12-tetraaza-5-(3-guanidinopropyl)-4,7,10,13-tetraoxotetradecanoate (139)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **129** (20 mg, 0.016 mmol) to yield **139** (13 mg, 0.014mmol, 88%) as a white solid. Mp 218-220°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.68 (m, 17H, ArH); 5.77 (m, 1H, H2'); 5.15 (m, 4H, H3' and PhC$\underline{H_2}$O); 4.82 (m, 1H, H11); 4.42 (m, 1H, H2); 4.25 (m, 1H, H5); 4.07 (m, 1H, H8); 3.18 (m, 2H, 11-CH_2); 2.88 (m, 4H, H4'''' and H3''); 2.55 (m, 2H, H1'); 1.95 (s, 3H, H14); 1.85 (m, 2H, H1''); 1.65 (m, 2H, H1'''); 1.53 (m, 2H, H2''); 0.94 (m, 2H, H2'''). ^{13}C NMR (CD_3OD, 75 MHz): δ 175.2, C13; 174.4, C1; 174.2, C4; 174.1, C10; 172.5, C7; 158.6, CN_3; 140.0, ArC; 139.9, ArC; 138.1, ArC; 137.4, ArC; 133.2, ArC; 134.3, C2'; 131.5, ArC; 131.3, ArCH; 130.1, ArCH; 129.2, ArC; 128.1, ArC;

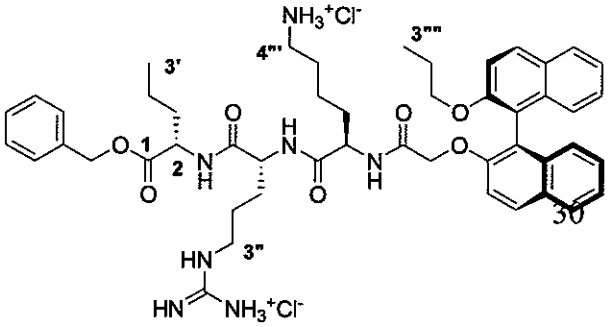
127.9, ArCH; 127.6, ArCH; 127.5, ArCH; 126.6, ArCH; 125.9, ArCH; 125.8, ArCH; 125.6, ArCH; 124.2, ArCH; 119.1, C3'; 68.1, CH_2-ester; 57.9, C11; 55.3, C8; 54.7, C5; 54.2, C2; 42.1, C3"; 40.3, C4"'; 38.1, 11-CH_2; 36.7, C1'; 31.4, C1": 29.4, C1"'; 27.3, C14; 26.5, C2"; 23.6, C3"'; 22.5, C2"'. (. Mass Spectrum (ES, +ve) *m/z* 855 (50%) [M^{2+}]; 428 (100%). HRMS calcd for $C_{49}H_{59}N_8O_6$ 855.4558, found 855.4539.

Benzyl (2*S*,5*R*,8*R*,11*S*)-2-allyl-8-(4-aminobutyl)-3,6,9,12-tetraaza-5-(3-guanidinopropyl)-4,7,10,13-tetraoxo-11-(4-[9-phenanthrenyl]benzyl)tetradecanoate (140)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **130** (42 mg, 0.034 mmol) to yield **140** (25 mg, 0.027 mmol, 79%) as a white solid. Mp 215-220°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.82 (m, 2H, ArH); 7.60 (m, 16H, ArH); 5.81 (m, 1H, H2'); 5.15 (m, 4H, PhC$\underline{H}_2$O and H3'); 4.58 (m, 1H, H11); 4.43 (m, 1H, H2); 4.35 (dd, *J* = 4.8, 9.0 Hz, 1H, H5); 4.17 (dd, *J* = 4.8, 9.6 Hz, 1H, H8); 3.17 (m, 4H, H4"" and H3"); 2.72 (m, 2H, 11-ArCH_2); 2.59 (m, 1H, H1'); 1.96 (s, 3H, H14); 1.80 (m, 4H, H1" and H1"'); 1.65 (m, 2H, H3"'); 1.51 (m, 2H, H2"); 1.22 (m, 2H, H2"'). ^{13}C NMR (CD_3OD, 75 MHz): δ 175.2, C13; 174.4, C1; 174.2, C4; 174.1, C10; 172.5, C7; 158.6, CN_3; 140.7, ArC; 139.6, ArC; 137.4, ArC; 137.2, ArC; 134.3, C2'; 132.9, ArC; 132.1, ArC; 131.3, ArCH; 130.5, ArCH; 129.7, ArC; 129.6, ArC; 129.4, ArCH; 129.4, ArCH; 128.5, ArCH; 128.1, ArCH; 127.9, ArCH; 127.8, ArCH; 127.6, ArCH; 124.2, ArCH; 123.7, ArCH; 12.4, ArCH; 122.1, ArCH; 121.8, ArCH; 119.0, C3'; 68.0, CH_2-ester; 57.7, C11; 55.2, C8; 54.7, C5; 54.0, C2; 42.0, C3"; 40.1, C4"'; 38.1, 11-CH_2; 36.6, C1'; 31.3, C1": 29.6, C1"'; 27.8, C14; 26.4, C2"; 23.8, C3"'; 22.6, C2"'. Mass Spectrum (ES, +ve) *m/z* 855 (30%) [M^{2+}], 428 (100%). HRMS calcd for $C_{49}H_{59}N_8O_6$ 855.4558, found 855.4528.

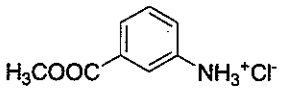
Benzyl (2*S*,5*R*,8*R*)- 3,6,9-triaza-8-(4-aminobutyl)-5-(3-guanidinopropyl)-4,7,10-trioxo-2-propyl-11-(2-[2'-3-(propyloxy)-{1,1'}-(*S*)-binaphthalen-2-yloxy])undecanoate (141)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **131** (115 mg, 0.094 mmol) to yield **141** (75 mg, 0.080 mmol, 85%) as a highly hydroscopic white solid. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.95 (m, 4H, ArH); 7.30 (m, 13H, ArH); 5.11 (m, 2H, PhC$\underline{H}_2$O); 4.58 (m, 2H, H11); 4.39 (m, 1H, H5); 4.15 (m, 1H, H2); 4.89 (m, 1H, H8); 3.68 (m, 2H, H1""); 3.17 (m, 2H, H3"); 2.55 (m, 2H, H4"'); 2.07 (m, 4H, H1' and H2""); 1.38 (m, 6H, H1", H3"' and H1"'); 1.34 (m, 2H, H2'); 1.13 (m, 2H, H2"'); 1.08 (m, 2H, H2"); 0.89 (m, 3H, H3""); 0.50 (m, 3H, H3'). ^{13}C NMR (CD_3OD, 125 MHz) δ 173.9, C4; 173.3, C2; 173.1, C7; 170.8, C10; 158.4, CN_3; 155.8, ArC; 153.9, ArC; 142.6, ArC; 137.1, ArC; 135.1, ArCH; 135.1, ArCH; 131.3, ArC; 130.9, ArC; 130.6, ArC; 129.6, ArCH; 129.3, ArCH; 129.3,

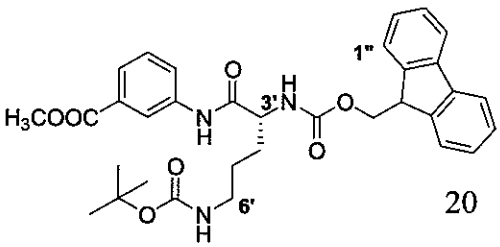
ArCH; 129.1, ArC; 128.2, ArC; 127.6, ArCH; 127.4, ArCH; 126.3, ArCH; 125.9, ArCH; 125.2, ArCH; 124.8, ArCH; 11.7, ArCH; 120.4, ArCH; 116.8, ArCH; 116.0, ArCH; 72.1, C1""; 69.2, C11; 67.9, $ArCH_2$; 54.1, C5; 53.7, C2; 53.6, C8; 41.9, C3"; 40.4, C4"'; 34.3, C1'; 32.2, C1"; 30.1, C1"'; 27.7, C2"; 26.2, C2""; 23.7, C2"'; 23.1, C3"'; 20.0, C2'; 13.9, C3'; 10.8, C3"". Mass Spectrum (ES, +ve) *m/z* 860 (30%) [M^{2+}], 431 (100%). HRMS calcd for $C_{49}H_{62}N_7O_7$ 860.4711, found 860.4730.

Methyl 3-amino-benzoate hydrochloride (143)



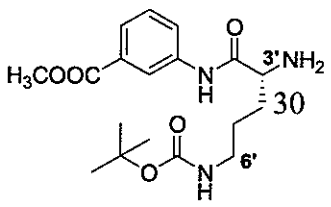
To a suspension of 3-aminobenzoic acid (1.03 g mg, 7.52 mmol) in MeOH (80 mL) at 0°C was added dropwise thionyl chloride (5 mL). The resulting solution was allowed to stir for 16 h before the solvent was removed by evaporation and the product precipitated with diethyl ether. The diethyl ether was removed by evaporation to yield the title compound (1.38 g, 7.38 mmol, 98%) as a white solid. Mp 176-178°C. ^{1}H NMR (D_2O, 300 MHz): δ 7.75 (dt, *J* = 1.8, 3.3, 7.2 Hz, 1H, ArH); 7.71 (m, 1H, ArH); 7.42 (m, 1H, ArH); 7.37 (m,1H, ArH); 3.66 (s, 3H, OCH_3). Mass Spectrum (CI) *m/z* 152 (100%) [M^+]. HRMS calcd for $C_8H_{10}NO_2$ 152.0712, found 152.0698.

Methyl (3'*R*)-3-(1-aza-6-*tert*-butoxycarboxamido-3'-[9H-9-flurorenylmethoxycarboxamido]-2-oxohexyl)benzoate (144)



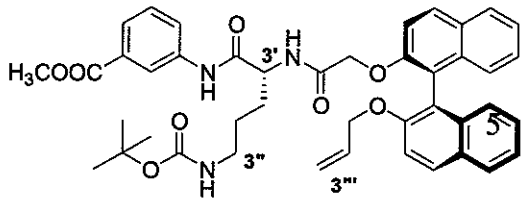
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **143** (220 mg, 2.27 mmol) and (*R*)-5-(*tert*-butoxycarboxamido)-2-(9H-9-fluorenylmethyloxycarboxamido)pentanoic acid (578 mg, 1.27 mmol) to afford **144** (277 mg, mmol, 36%) as a white solid. Mp 96-98°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.15 (s, 1H, ArH); 8.17 (s, 1H, NH); 7.88 (d, *J* = 8.1 Hz, 1H, ArH); 7.77 (m, 1H, ArH); 7.72 (d, *J* = 7.8 Hz, 2H, ArH1" and ArH8"); 7.56 (d, *J* = 7.2, Hz, 2H, ArH4" and ArH5"); 7.36 (m, 2H, ArH3" and ArH6"); 7.26 (m, 2H, ArH2" and ArH7"); 6.03 (d, *J* = 8.1 Hz, 2H, NH); 4.63 (m, 1H, H3'); 4.36 (d, *J* = 6.9 Hz, 2H, OCH_2-H9"); 4.17 (t, *J* = 6.9 Hz, 1H, H9"); 3.86 (s, 3H, OCH_3); 3.08 (m, 2H, H6'); 1.78 (m, 2H, H4'); 1.60 (m, 2H, H5'); 1.42 (s, 9H, $(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 610 (100%) [MNa^+], 588 (70%) [MH^+]. HRMS calcd for $C_{33}H_{38}N_3O_7$ 588.2710, found 588.2726.

Methyl (3*R*)-3-(3'-amino-1-aza-6-*tert*-butoxycarboxamido-2-oxohexyl)benzoate (145)



The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **144** (555 mg, 0.95 mmol) to yield **145** (285 mg, 0.78 mmole, 82%) as a clourless viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (m, 1H, ArH); 7.84 (t, *J* = 1.8 Hz, 1H, ArH); 7.51 (t, *J* = 7.8 Hz, 1H, ArH); 7.36 (m, 1H, ArH); 5.11 (m, 1H, NH); 3.91 (s, 3H, OCH_3); 3.69 (m, 1H, H3'); 3.19 (m, 2H, H6'); 2.08 (m, 2H, H4'); 1.65 (m, 4H, H5' and NH_2); 1.43 (s, 9H, $(CH_3)_3$). HRMS calcd for $C_{18}H_{28}N_3O_5$ 366.2029, found 366.2051.

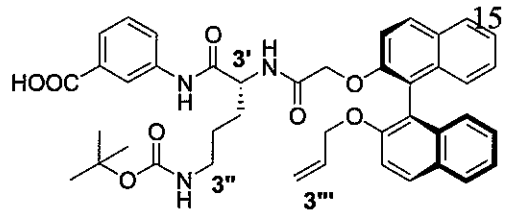
Methyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-[(3-*tert*-butoxycarboxamido)propyl]-2,5-dioxohexyl)benzoate (146)



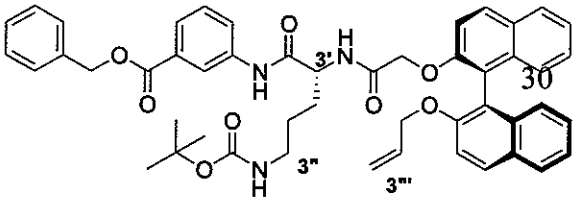
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **101** (288 mg, 0.75 mmol) and **145** (275 mg, 0.75 mmol) to afford **146** (434 mg, 0.59 mmol, 79%) as a white foam. Mp 70°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.08 (s, 1H, ArH); 7.91 (m, 7H, ArH); 7.85 (m, 8H, ArH); 6.45 (d, J = 8.1 Hz, 1H, NH); 5.69 (m, 1H, H2"'); 4.94 (m, 2H, H3"'); 4.55 (m, 5H, H6', H1"' and H3'); 3.87 (s, 3H, OCH_3); 2.96 (m, 2H, H3"); 1.62 (m, 2H, H1"); 1.44 (s, 9H, $(CH_3)_3$); 1.04 (m, 2H, H2")". Mass Spectrum (ES, +ve) *m/z* 732 (50%) [MH^+], 351 (100%). HRMS calcd for $C_{43}H_{46}N_3O_8$ 732.3285, found 732.3316.

(3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-[(3-*tert*-butoxycarboxamido)propyl]-2,5-dioxohexyl)benzoic acid (147)

To a solution of **146** (370 mg, 0.51 mmol) in THF/water, 3:1 (8 mL) was added lithium hydroxide monohydrate (43 mg, 0.51 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation before the remaining aqueous layer was wased with diethyl ether (40 mL) to remove unreacted starting material. The aqueous phase was acidified with dilute potassium bisulfate and the resulting precipitate was extracted with DCM (3 x 40 mL). The combined DCM fractions were dried and evaporated to yield the title compound (350 mg, 0.49 mmol, 96%) as a white solid. Mp 86-90°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.70 (bs, 1H, COOH); 9.26 (s, 1H, ArH); 7.97 (m, 7H, ArH); 7.34 (m, 8H, ArH); 6.63 (d, J = 9.0 Hz, 1H, NH); 5.71 (m, 1H, H2"'); 5.01 (m, 2H, H3"'); 4.59 (m, 5H, H6', H1"' and H3'); 3.03 (m, 2H, H3"); 1.65 (m, 2H, H1"); 1.49 (s, 9H, $(CH_3)_3$); 1.15 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 740 (100%) [MNa^+], 718 (20%) [MH^+]. HRMS calcd for $C_{42}H_{44}N_3O_8$ 718.3128, found 718.3152.



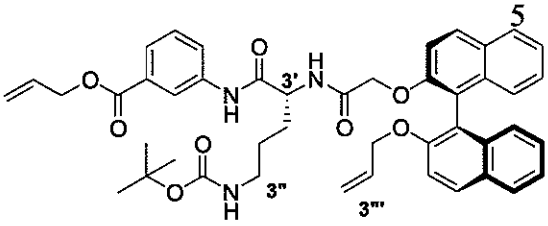
Benzyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-[(3-*tert*-butoxycarboxamido)propyl]-2,5-dioxohexyl)benzoate (148)



To a solution of **147** (40 mg, 0.056 mmol) in acetone (2 mL) was added K_2CO_3 (17 mg, 0.12 mmol) and benzyl bromide (21 mg, 0.12 mmol). The resulting suspension was allowed to stir for 16 h before concentration and purification by flash column chromatography (5% MeOH/DCM) to yield the title compound (36 mg, 0.045 mmol, 80%) as a white solid. Mp 145-152°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.63 (s, 1H, ArH); 7.90 (m, 7H, ArH); 7.30 (m, 11H, ArH); 6.27 (d, J = 8.4 Hz, 1H, NH); 5.68 (m, 1H, H2"'); 5.30 (s, 2H, $ArCH_2$); 4.87 (m, 2H, H3"'); 4.50 (m, 5H, H6', H1"' and

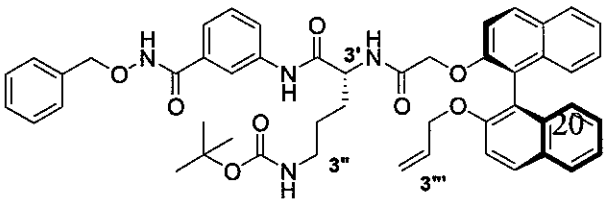
H3'); 3.00 (m, 2H, H3"); 1.52 (m, 2H, H1"); 1.42 (s, 9H, $(CH_3)_3$); 1.05 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 808 (30%) [MH^+]; 414 (100%). HRMS calcd for $C_{49}H_{50}N_3O_8$ 808.3598, found 808.3634.

Allyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-[(3-*tert*-butoxycarboxamido)propyl]-2,5-dioxohexyl)benzoate (149)



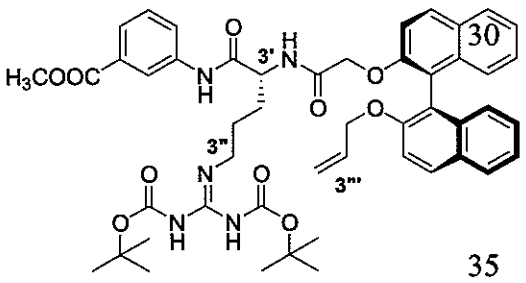
To a solution of **147** (43 mg, 0.060 mmol) in acetone (2 mL) was added K_2CO_3 (18 mg, 0.12 mmol) and allyl bromide (0.1 mL, 0.12 mmol). The resulting suspension was allowed to stir for 16 h before concentration and purification by flash column chromatography (5% MeOH/DCM) to yield the title compound (36 mg, 0.047 mmol, 79%) as a white solid. Mp 142-150°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.75 (s, 1H, ArH); 7.90 (m, 7H, ArH); 7.29 (m, 8H, ArH); 6.32 (d, *J* = 8.4 Hz, 1H, NH); 6.02 (m, 1H, C<u>H</u>-ester); 5.65 (m, 1H, H2"'); 5.39 (dd, *J* = 1.5, 17.4 Hz, 1H, $H3_a$-ester); 5.27 (dd, *J* = 1.5, 10.5 Hz, 1H, $H3_b$-ester); 4.89 (m, 2H, H3"'); 4.81 (m, 2H, H1-ester); 4.55 (AB_q, *J* = 14.7 Hz, 2H, H6'); 4.52 (m, 2H, H1"'); 4.23 (m, 1H, H3'); 3.00 (m, 2H, H3"); 1.91 (m, 2H, H1"); 1.44 (s, 9H, $(CH_3)_3$); 1.01 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 758 (10%) [MH^+]; 444 (100%). HRMS calcd for $C_{45}H_{47}N_3O_8Na$ 780.3261, found 780.3290.

(3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-[(3-*tert*-butoxycarboxamido)propyl]-2,5-dioxohexyl)-*N*-benzyloxybenzamide (150)



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **147** (91 mg, 0.127 mmol) and *O*-benzylhydroxylamine (20 mg, 1.27 mmol) to afford **150** (82 mg, 0.100mmol, 78%) as a white solid. Mp 141-144°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.14 (s, 1H, ArH); 7.97 (m, 2H, ArH); 7.88 (m, 2H, ArH); 7.31 (m, 10H, ArH); 6.41 (d, *J* = 7.5 Hz, 1H, NH); 5.66 (m, 1H, H2"'); 4.95 (m, 4H, H3"' and $ArCH_2$); 4.66 (t, *J* = 5.1 Hz, 1H, NH); 4.54 (m, 4H, H6', H1"'); 4.30 (m, 1H, H3'); 2.93 (m, 2H, H3"); 1.54 (m, 2H, H1"); 1.43 (s, 9H, $(CH_3)_3$); 1.06 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 823 (100%) [MH^+]. HRMS calcd for $C_{49}H_{51}N_4O_8$ 823.3707, found 823.3726.

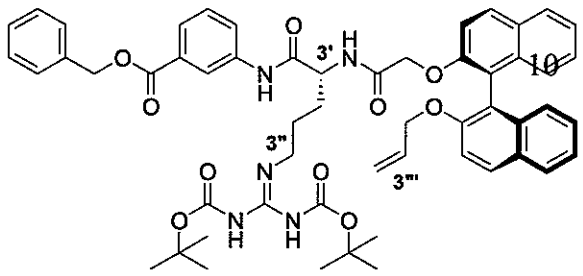
Methyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-(3[{di-*tert*-butoxycarbonyl}guanidino]propyl)-2,5-dioxohexyl)benzoate (151)



To a solution of **155** (32 mg, 0.048 mmol) in DCM (3 mL) was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (28 mg, 0.072 mmol), triethylamine (7.3 mg, 0.072 mmol). The resulting solution was allowed to stir for 16 h under a nitrogen atmosphere. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the title compound (41 mg, 0.047 mmole, 98%) as a white solid. Mp 74-76°C. ^{1}H NMR

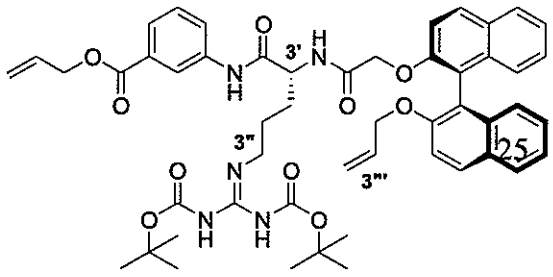
($CDCl_3$, 300 MHz): δ 8.55 (s, 1H, ArH); 8.27 (bs, 1H, NH); 7.77 (m, 7H, ArH); 7.26 (m, 8H, ArH); 6.34 (d, J = 8.4 Hz, 1H, NH); 5.59 (m, 1H, H2"'); 4.67 (m, 2H, H3"'); 4.57 (d, J = 3.3 Hz, 2H, H1"'); 4.48 (m, 2H, C6'); 4.34 (m, 1H, H3'); 3.91 (s, 3H, OCH_3); 3.26 (m, 2H, H3"); 1.65 (m, 2H, H1"); 1.51 (s, 9H, $(CH_3)_3$); 1.46 (s, 9H, $(CH_3)_3$); 1.14 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 896 (100%) [MNa^+], 875 (95%) [MH^+]. HRMS calcd for $C_{49}H_{56}N_5O_{10}$ 874.4027, found 874.4043.

Benzyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-(3[{di-*tert*-butoxycarbonyl}guanidino]propyl)-2,5-dioxohexyl)benzoate (152)



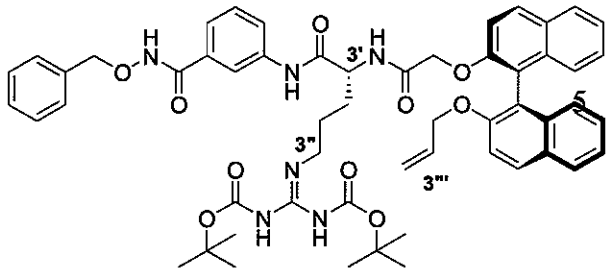
To a solution of **157** (20 mg, 0.027 mmol) in DCM (2 mL) was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (16 mg, 0.041 mmol), and triethylamine (4 mg, 0.041 mmol). The resulting solution was allowed to stir for 16 h under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the title compound (15 mg, 0.016 mmole, 58%) as a white solid. Mp 122-126°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.41 (s, 1H, ArH); 8.26 (bs, 1H, NH); 7.85 (m, 7H, ArH); 7.32 (m, 8H, ArH); 6.31 (d, J = 8.1 Hz, 1H, NH); 5.56 (m, 1H, H2"'); 5.37 (s, 2H, $ArCH_2$); 4.85 (m, 2H, H3"'); 4.56 (m, 2H, H1"'); 4.45 (m, 2H, H6'); 4.32 (m, 1H, H3'); 3.25 (m, 2H, H3"); 1.63 (m, 2H, H1"); 1.50 (s, 9H, $(CH_3)_3$); 1.46 (s, 9H, $(CH_3)_3$); 1.15 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 950 (100%) [MH^+]. HRMS calcd for $C_{55}H_{60}N_5O_{10}$ 950.4340, found 950.4339.

Allyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-(3[{di-*tert*-butoxycarbonyl}guanidino]propyl)-2,5-dioxohexyl)benzoate (153)



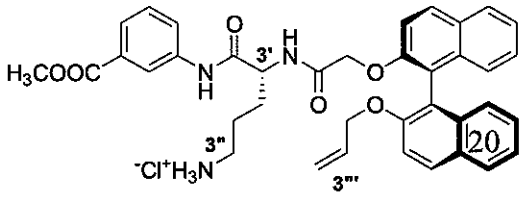
To a solution of **159** (25 mg, 0.036 mmol) in DCM (2 mL) was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (21 mg, 0.054 mmol), and triethylamine (0.1 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the title compound (31 mg, 0.034 mmole, 97%) as a white solid. Mp 70°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.57 (s, 1H, ArH); 8.26 (bs, 1H, NH); 7.88 (m, 7H, ArH); 7.28 (m, 8H, ArH); 6.34 (d, J = 8.1 Hz, 1H, NH); 6.03 (m, 1H, CH-ester); 5.58 (m, 1H, H2"'); 5.40 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$-ester); 5.28 (dd, J = 1.5, 10.5 Hz, 1H, $H3_b$-ester); 4.85 (m, 4H, H1-ester and H3"'); 4.50 (m, 4H, H6' and H1"'); 4.34 (m, 1H, H3'); 3.26 (m, 2H, H3"); 1.62 (m, 2H, H1"); 1.50 (s, 9H, $(CH_3)_3$); 1.46 (s, 9H, $(CH_3)_3$); 1.10 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 900 (10%) [MH^+], 700 (100%). HRMS calcd for $C_{51}H_{58}N_5O_{10}$ 900.4184, found 900.4179.

(3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-(3[{di-*tert*-butoxycarbonyl}guanidino]propyl)-2,5-dioxohexyl)-*N*-benzyloxybenzamide (154)



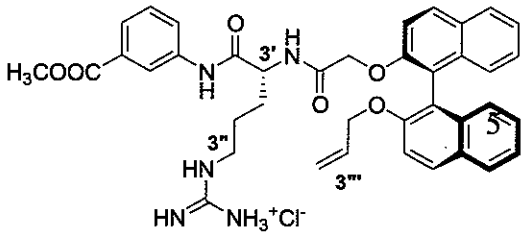
To a solution of **161** (51 mg, 0.067 mmol) in DCM (3 mL) was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (39 mg, 0.10 mmol), and triethylamine (0.1 mL). The resulting solution was allowed to stir for 16 hr under N_2. The solvent was evaporated and the crude product was purified by flash column chromatography (15:1, DCM/MeOH) to yield the title compound (58 mg, 0.060 mmole, 90%) as a white solid. Mp 112°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.05 (s, 1H, ArH); 8.25 (bs, 1H, NH); 7.90 (m, 4H, ArH); 7.31 (m, 16H, ArH); 6.34 (d, J = 7.5 Hz, 1H, NH); 5.63 (m, 1H, H2"'); 5.00 (s, 2H, $ArCH_2$); 4.89 (m, 2H, H3"'); 4.51 (m, 4H, H6' and H1"'); 4.25 (m, 1H, H3'); 3.23 (m, 2H, H3"); 1.65 (m, 2H, H1"); 1.50 (s, 9H, $(CH_3)_3$); 1.44 (s, 9H, $(CH_3)_3$); 1.10 (m, 2H, H2"). Mass Spectrum (ES, +ve) *m/z* 987 (100%) [MNa^+], 965 (90%) [MH^+]. HRMS calcd for $C_{55}H_{61}N_6O_{10}$ 965.4449, found 965.4422.

Methyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3-(3-aminopropyl)-1,4-diaza-2,5-dioxohexyl)benzoate hydrochloride(155)



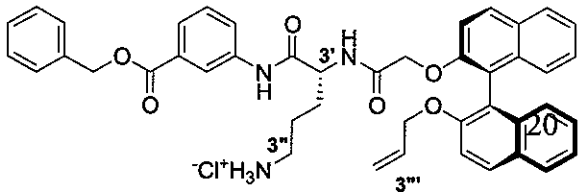
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **146** (56 mg, 0.077 mmol) to yield **155** (38 mg, 0.057 mmol, 74%) as a highly hydroscopic cream solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.02 (m, 2H, ArH); 7.92 (m, 2H, ArH); 7.75 (m, 2H, ArH); 7.34 (m, 8H, ArH); 7.06 (m, 2H, ArH); 5.71 (m, 1H, H2"'); 4.90 (m, 2H, H3"'); 4.59 (m, 5H, H6', H1"' and H3'); 3.93 (s, 3H, OCH_3); 2.76 (m, 2H, H3"); 1.67 (m, 2H, H1"); 1.30 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 75 MHz): δ 170.9, 1-CO; 170.6, C5'; 168.1, C2'; 155.4, ArC; 154.1, ArC; 139.8, C2"'; 138.0, ArC; 135.1, ArC; 134.9, ArC; 132.1, ArCH; 131.5, ArC; 131.3, ArC; 131.0, ArCH; 130.8, ArCH; 130.2, ArCH; 129.3, ArC; 129.2, ArCH; 127.6, ArCH; 127.3, ArCH; 127.1, ArCH; 126.4, ArCH; 126.3, ArCH; 126.0, ArCH; 125.5, ArCH; 125.3, ArCH; 124.8, ArCH; 122.1, ArC; 121.8, ArC; 117.0, C3"'; 117.0, ArCH; 116.2, ArCH; 70.9, C1"'; 67.4, C6'; 53.1, H3'; 52.6, OCH_3; 40.1, C3"; 30.3, C2"; 24.5, C1". Mass Spectrum (ES, +ve) *m/z* 632 (100%) [M^+]. HRMS calcd for $C_{38}H_{38}N_3O_6$ 632.2761, found 632.2777.

Methyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-(3-guanidylpropyl)-2,5-dioxohexyl)benzoate hydrochloride (156)



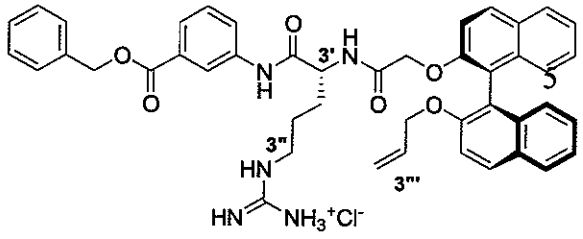
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **151** (49 mg, 0.056 mmol) to yield 156 (32 mg, 0.045 mmol, 80%) as a cream solid. Mp 124-126°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.28 (s, 1H, ArH); 7.90 (m, 4H, ArH); 7.32 (m, 9H, ArH); 7.07 (m, 2H, ArH); 5.73 (m, 1H, H2"'); 4.97 (m, 2H, H3"'); 4.52 (m, 5H, H6', H1"' and H3'); 3.92 (s, 3H, OCH_3); 3.01 (m, 2H, H3"); 1.63 (m, 2H, H1"); 1.17 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 75 MHz): δ. 171.0, 1-CO; 170.4, C5'; 168.0, C2'; 158.4, CN_3; 155.4, ArC; 154.2, ArC; 140.0, C2"'; 138.8, ArC; 135.1, ArC; 135.0, ArC; 132.0, ArCH; 131.3, ArC; 131.1, ArC; 131.0, ArCH; 130.7, ArCH; 130.2, ArCH; 129.4, ArC; 129.3, ArCH; 127.7, ArCH; 127.6, ArCH; 126.4, ArCH; 126.3, ArCH; 126.1, ArCH; 126.0, ArCH; 125.9, ArCH; 125.4, ArCH; 125.4, ArCH; 122.0, ArC; 121.9, ArC; 117.2, C3"'; 117.0, ArCH; 116.4, ArCH; 70.8, C1"'; 69.4, C6'; 53.5, H3'; 52.9, OCH_3; 41.8, C3"; 30.6, C2"; 25.8, C1". Mass Spectrum (ES, +ve) *m/z* 698 (25%) [MNa^+], 413 (100%). HRMS calcd for $C_{39}H_{40}N_5O_6$ 674.2979, found 674.2979.

Benzyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3-(3-aminopropyl)-1,4-diaza-2,5-dioxohexyl)benzoate hydrochloride (157)



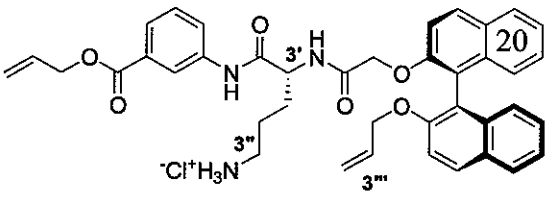
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **148** (35 mg, 0.043 mmol) to yield **157** (30 mg, 0.040 mmol, 93%) as a highly hydroscopic cream solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.25 (s, 1H, ArH); 7.80 (m, 7H, ArH); 7.28 (m, 11H, ArH); 5.58 (m, 1H, H2"'); 5.27 (s, 2H, $ArCH_2$); 4.79 (m, 2H, H3"'); 4.46 (m, 5H, H6', H1"' and H3'); 2.68 (m, 2H, H3"); 1.59 (m, 2H, H1"); 1.22 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 125 MHz): δ. 171.2, 1-CO; 169.8, C5'; 167.2, C2'; 153.9, ArC; 152.8, ArC; 137.2, C2"'; 136.4, ArC; 133.7, ArC; 133.6, ArC; 133.1, ArCH; 131.0, ArCH; 129.2, ArC; 129.0, ArC; 128.4, ArCH; 128.2, ArCH; 128.0, ArCH; 127.0, ArCH; 126.8, ArCH; 126.6, ArCJH; 126.4, ArCH; 125.2, ArCH; 126.0, ArCH; 125.6, ArCH; 125.2, ArCH; 124.4, ArCH; 123.9, ArCH; 123.0, ArC; 122.8, ArC; 121.0, ArCH; 120.8, ArCH; 119.5, ArC; 117.2, ArC; 116.2, C3"'; 115.0, ArCH; 112.3, ArCH; 70.2, C1"'; 67.7, C6'; 51.2, C3'; 40.4, C3"; 32.8, C2"; 23.0, C1". Mass Spectrum (ES, +ve) *m/z* 750 (35%) [MK^+], 360 (100%). HRMS calcd for $C_{44}H_{42}N_3O_6$ 708.3074, found 708.3062.

Benzyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-(3-guanidylpropyl)-2,5-dioxohexyl)benzoate hydrochloride (158)



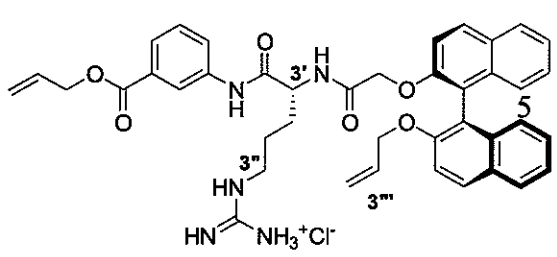
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **152** (15 mg, 0.016 mmol) to yield **158** (6 mg, 0.0076 mmol, 48%) as a highly hydroscopic cream solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.22 (s, 1H, ArH); 7.79 (m, 7H, ArH); 7.25 (m, 13H, ArH); 5.59 (m, 1H, H2"'); 5.27 (s, 2H, $ArCH_2$); 4.80 (m, 2H, H3"'); 4.47 (m, 4H, H1"' and H6'); 4.28 (dd, J = 5.0, 7.0 Hz, 1H, H3'); 2.92 (m, 2H, H3"); 1.54 (m, 2H, H1"); 1.08 (m, 2H, H2"). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 1-CO; 168.9, C5'; 166.4, C2'; 153.4, ArC; 152.7, ArC; 137.5, C2"'; 136.2, ArC; 133.4, ArC; 133.3, ArC; 133.2, ArCH; 131.4, ArC; 131.2, ArC; 130.5, ArCH; 130.4, ArCH; 129.7, ArCH; 129.4, ArC; 128.8, ArCH; 128.5, ArCH; 128.7, ArCH; 128.4, ArCH; 126.9, ArCH; 126.8, ArCH; 126.2, ArCH; 125.9, ArCH; 125.6, ArCH; 124.8, ArCH; 124.6, ArCH; 124.5, ArCH; 121.7, ArCH; 121.2, ArC; 120.9, ArC; 119.6, ArC; 116.9, C3"'; 116.5, ArCH; 114.7, ArCH; 70.2, C1"'; 68.5, C6'; 66.9, $ArCH_2$; 52.8, C3'; 40.3, C3"; 29.8, C2"; 25.3, C1". Mass Spectrum (ES, +ve) *m/z* 750 (100%) [M^+]. HRMS calcd for $C_{45}H_{44}N_5O_6$ 750.3292, found 750.3273.

Allyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3-(3-aminopropyl)-1,4-diaza-2,5-dioxohexyl)benzoate hydrochloride (159)



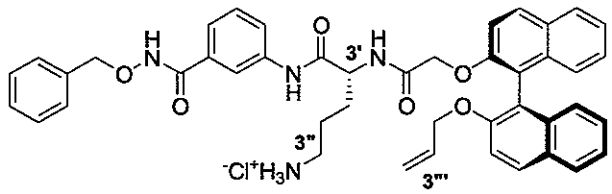
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **149** (8 mg, 0.011 mmol) to yield **159** (7 mg, 0.010 mmol, 92%) as a highly hydroscopic cream solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.20 (s, 1H, ArH); 7.89 (m, 7H, ArH); 7.26 (m, 8H, ArH); 6.02 (m, 1H, CH-ester); 5.62 (m, 1H, H2"'); 5.34 (dd, J = 1.5, 15.5 Hz, 1H, $H3_a$-ester); 5.20 (dd, J = 1.5, 10.5 Hz, 1H, $H3_b$-ester); 4.83 (m, 2H, H3"'); 4.81 (m, 2H, H1-ester); 4.50 (m, 5H, H6', H3' and H1"'); 2.68 (m, 2H, H3"); 1.59 (m, 2H, H1"); 1.12 (m, 2H, H2"). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 1-CO; 169.2, C5'; 166.0, C2'; 154.2, ArC; 152.6, ArC; 138.4, ArC; 133.9, C2-ester; 133.8, C2"'; 133.7, ArC; 132.5, ArC; 131.2, ArC; 130.9, ArCH; 130.4, ArCH; 129.9, ArC; 129.7, ArC; 129.6, ArCH; 128.9, ArCH; 128.4, ArCH; 128.2, ArCH; 126.9, ArCH; 126.0, ArCH; 125.8, ArCH; 125.4, ArCH; 125.3, ArCH; 124.6, ArCH; 124.5, ArCH; 124.0, ArCH; 120.8, ArC; 119.8, ArC; 118.5, C3-ester; 116.8, C3"'; 116.1, ArCH; 114.9, ArCH; 70.7, C1-ester; 68.7, C1"'; 66.4, C6'; 52.2, C3'; 39.3, C3"; 28.6, C2"; 26.2, C1". Mass Spectrum (ES, +ve) *m/z* 698 (30%) [MK^+], 123 (100%). HRMS calcd for $C_{40}H_{40}N_3O_6$ 658.2917, found 658.2918.

Allyl (3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-(3-guanidinopropyl)-2,5-dioxohexyl)benzoate hydrochloride (160)



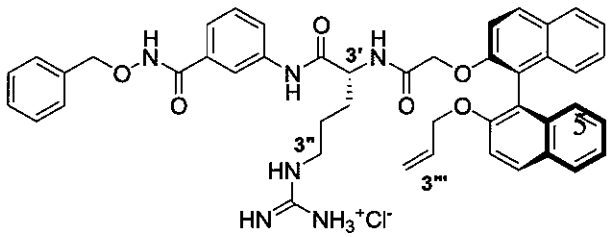
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **153** (40 mg, 0.044 mmol) to yield **160** (11 mg, 0.015 mmol, 34%) as a highly hydroscopic cream solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.38 (s, 1H, ArH); 7.99 (t, *J* = 7.5 Hz, 2H, ArH); 7.88 (t, *J* = 7.5, 2H, ArH); 7.76 (t, *J* = 8.0 Hz, 2H, ArH); 7.52 (d, *J* = 9.0 Hz, 1H, ArH); 7.45 (d, *J* = 9.0, 1H, ArH); 7.40 (t, *J* = 8.0 Hz, 1H, ArH); 7.31 (dd, *J* = 7.0, 14.5 Hz, 2H, ArH); 7.19 (t, *J* = 7.0 Hz, 2H, ArH); 7.07 (m, 2H, ArH); 6.82 (d, *J* = 8.0 Hz, 1H, NH); 6.04 (m, 1H, CH-ester); 5.70 (m, 1H, H2'''); 5.30 (m, 2H, H3-ester); 4.92 (m, 2H, H3'''); 4.53 (m, 6H, H6', H1-ester and H1'''); 4.43 (m, 1H, H3'); 3.04 (m, 2H, H3"); 1.68 (m, 2H, H1"); 1.20 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 125 MHz): δ. 171.0, 1-CO; 167.3, C2'; 158.4, CN_3; 155.3, ArC; 154.0, ArC; 139.9, ArC; 135.1, C2-ester; 135.0, C2'''; 134.8, ArC; 131.9, ArC; 130.9, ArCH; 130.9, ArC; 130.8, ArC; 130.1, ArCH; 129.2, ArCH; 129.1, ArCH; 127.6, ArCH; 127.5, ArCH; 126.3, ArCH; 126.2, ArC; 125.8, ArCH; 125.7, ArCH; 125.7, ArCH; 125.3, ArCH; 124.9, ArCH; 122.2, ArC; 122.1, ArCH; 121.8, ArCH; 120.4, ArC; 118.6, C3-ester; 117.1, C3'''; 117.0, ArCH; 116.1, ArCH; 72.4, C1-ester; 70.9, C1'''; 69.4, C6'; 66.7, $ArCH_2$; 53.5, C3'; 41.8, C3"; 30.4, C2"; 25.6, C1". Mass Spectrum (ES, +ve) *m/z* 700 (100%) [M^+]. HRMS calcd for $C_{41}H_{42}N_5O_6$ 700.3135, found 700.3129.

(3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-3-[(3-aminopropyl]-1,4-diaza-2,5-dioxohexyl)-*N*-benzyloxybenzamide hydrochloride(161)



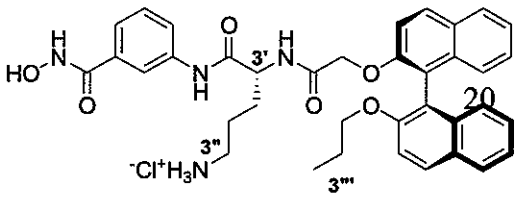
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **150** (73 mg, 0.089 mmol) to yield **161** (67 mg, 0.088 mmol, 99%) as a hydroscopic white solid. ^{1}H NMR (CD_3OD, 500 MHz): δ δ 7.50 (m, 20H, ArH); 5.63 (m, 1H, H2'''); 4.90 (m, 2H, H3'''); 4.46 (m, 6H, H6', H1''' and $ArCH_2$); 3.90 (m, 1H, H3'); 3.23 (m, 2H, H3"); 1.62 (m, 2H, H1"); 1.15 (m, 2H, H2"). ^{13}C NMR (CD_3OD, 75 MHz): δ 170.7, 1-CO; 170.5, C5'; 167.7, C2'; 155.4, ArC; 154.0, ArC; 139.9, C2'''; 137.3, ArC; 135.1, ArC; 134.9, ArC; 134.8, ArCH; 134.1, ArC; 131.6, ArC; 131.0, ArCH; 130.9, ArCH; 130.8, ArCH; 130.6, ArCH; 130.4, ArCH; 130.2, ArCH; 129.6, ArCH; 129.5, ArCH; 129.3, ArCH; 129.2, ArCH; 127.8, ArCH; 127.6, ArCH; 126.8, ArCH; 125.6, ArCH; 125.2, ArCH; 123.8, ArC; 121.9, ArC; 120.6, ArCH; 120.2, ArCH; 118.8, ArCH; 118.4, ArCH; 117.4, C3'''; 116.6, ArC; 79.2, C1'''; 71.0, $ArCH_2$; 69.5, C6'; 53.2, C3'; 40.0, C3"; 30.3, C2"; 24.5, C1". Mass Spectrum (ES, +ve) *m/z* 723 (20%) [M^+], 360 (100%). HRMS calcd for $C_{44}H_{43}N_4O_6$ 723.3183, found 723.3137.

(3*R*)-3-(6-(2-[2'-allyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-1,4-diaza-3-[(3-guanidinopropyl]-2,5-(dioxohexyl)-*N*-benzyloxybenzamide hydrochloride(162)



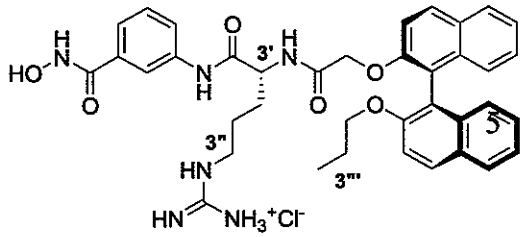
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **154** (16 mg, 0.017 mmol) to yield **162** (7 mg, 0.0087 mmol, 51%) as a cream solid. Mp 142°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.95 (m, 4H, ArH); 7.33 (m, 16H, ArH);); 5.60 (m, 1H, H2'''); 4.96 (m, 2H, H3'''); 4.49 (m, 6H, H6', H1''' and $ArCH_2$); 3.97 (m, 1H, H3'); 3.04 (m, 2H, H3''); 1.66 (m, 2H, H1''); 1.20 (m, 2H, H2''). ^{13}C NMR (CD_3OD, 75 MHz): δ 172.6, 1-CO; 171.1, C5'; 167.7, C2'; 158.4, CN_3; 155.4, ArC; 154.0, ArC; 139.8, C2'''; 136.8, ArC; 135.1, ArC; 135.0, ArC; 134.9, ArCH; 134.0, ArC; 131.4, ArC; 130.9, ArCH; 130.9, ArCH; 130.8, ArCH; 130.4, ArCH; 130.2, ArCH; 130.0, ArCH; 129.7, ArCH; 129.5, ArCH; 129.3, ArCH; 129.2, ArCH; 127.6, ArCH; 127.5, ArCH; 126.4, ArCH; 125.9, ArCH; 124.6, ArC; 123.8, ArC; 121.9, ArC; 120.4, ArCH; 120.3, ArCH; 118.8, ArCH; 118.0, ArCH; 117.0, C3'''; 116.2, ArC; 79.2, C1'''; 71.0, $ArCH_2$; 69.4, C6'; 53.6, C3'; 41.8, C3''; 30.5, C2''; 25.7, C1''. Mass Spectrum (ES, +ve) *m/z* 765 (20%) [M^+], 102 (100%). HRMS calcd for $C_{45}H_{45}N_6O_6$ 765.3401, found 765.3375.

(3*R*)-(3-(3-aminopropyl)-1,4-diaza-7-oxa-2,5-dioxohexyl-3-(6-(2-[2'-propyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-*N*-hydroxybenzamide hydrochloride (163)



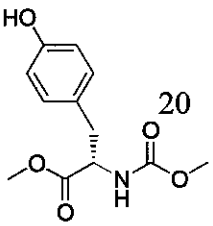
To a solution of **150** (28 mg, 0.034 mmol) in THF (3 mL) was added palladium on activated carbon (15 mg). The resulting mixture was flushed with hydrogen gas and allowed to stir for 16 h. The mixture was filtered through celite and evaporated to dryness. This intermediate product was then subjected to the general acid deprotection procedure (Procedure A) to yield the title compound (16 mg, 0.024 mmole, 70%) as a white solid. Mp 116°C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.89 (m, 5H, ArH); 7.30 (m, 9H, ArH); 4.56 (m, 2H, H6'); 4.08 (m, 1H, H3'); 3.88 (m, 2H, H1'''); 3.66 (m, 2H, H3''); 1.67 (m, 2H, H1''); 1.35 (m, 4H, H2'' and H2'''); 0.76 (m, 3H, H3'''). ^{13}C NMR (CD_3OD, 125 MHz): δ 170.9, 1-CO; 170.7, C5'; 166.3, C2'; 155.9, ArC; 154.1, ArC; 139.7, ArC; 135.3, ArCH; 135.1, ArCH; 131.0, ArC; 130.9, ArCH; 130.7, ArCH; 130.5, ArCH; 130.4, ArC; 130.2, ArC; 130.1, ArCH; 129.5, ArCH; 129.3, ArCH; 129.1, ArCH; 127.5, ArCH; 126.9, ArCH; 126.4, ArCH; 125.9, ArCH; 125.6, ArCH; 125.3, ArC; 124.7; ArC; 124.5, ArC; 117.0, ArCH; 116.9, ArCH; 116.2, ArC; 72.1, C6'; 69.5, C1'''; 53.1, C3'; 40.0, C3''; 30.4, C2''; 24.8, C2'''; 23.7, C1''; 10.5, C3'''. Mass Spectrum (ES, +ve) *m/z* 636 (50%) [M^+], 623 (100%). HRMS calcd for $C_{37}H_{39}N_4O_6$ 635.2870, found 635.2863.

(3*R*)-(1,4-diaza-3-(3-guanidinopropyl)-7-oxa-2,5-dioxohexyl-3-(6-(2-[2'-propyloxy-{1,1'}-(*S*)-binaphthalen-2-yloxy])-*N*-hydroxybenzamide hydrochloride (164)



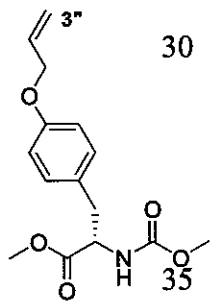
To a solution of **154** (39 mg, 0.040 mmol) in THF (3 mL) was added palladium on activated carbon. The resulting mixture was flushed with hydrogen gas and allowed to stir for 16 h. The mixture was filtered through celite and evaporated to dryness. This intermediate product was then subjected to the general acid deprotection procedure (Procedure A) to yield the title compound (24 mg, 0.034 mmole, 84%) as a white solid. Mp 158-160°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 9.96 (bs, 1H, OH); 7.95 (m, 5H, ArH); 7.24 (m, 9H, ArH); 4.45 (AB_q, J = 14.1 Hz, 2H, H6'); 4.09 (m, 1H, H3'); 3.92 (m, 2H, H1'''); 3.03 (m, 2H, H3"); 1.62 (m, 2H, H1"); 1.40 (m, 2H, H2'''); 1.17 (m, 2H, H2"); 0.51 (t, J = 7.2 Hz, 3H, H3'''). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 1-CO; 170.8, C5'; 170.8, C2'; 158.5, CN_3; 155.9, ArC; 154.0, ArC; 139.9, ArC; 135.2, ArCH; 135.1, ArCH; 131.5, ArC; 131.0, ArC; 130.9, ArCH; 130.7, ArCH; 130.2, ArC; 130.1, ArC; 129.3, ArCH; 129.1, ArCH; 127.6, ArCH; 127.5, ArCH; 126.4, ArCH; 125.9, ArCH; 125.3, ArCH; 124.7, ArCH; 124.4, ArCH; 124.2, ArCH; 123.6, ArC; 122.0, ArC; 120.3, ArC; 116.9, ArCH; 116.2, ArCH; 72.1, C6'; 69.4, C1'''; 52.5, C3'; 41.9, C3"; 30.5, C2"; 25.7, C2'''; 23.7, C1"; 10.5, C3'''. Mass Spectrum (ES, +ve) *m/z* 677 (100%) [M^+]. HRMS calcd for $C_{38}H_{41}N_6O_6$ 677.3088, found 677.3130.

Methyl (2*S*)-3-(4-hydroxyphenyl)-2-methoxycarboxamidopropanoate (170)



To a solution of methyl (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoate hydrochloride (189 mg, 0.82 mmol) and sodium bicarbonate (210 mg, 2.5 mmol) in THF (3 mL) and water (3 mL) at 0°C was added methyl chloroformate (86 mg, 0.9 mmol) and the resulting mixture was allowed to stir for 3 h. The reaction was quenched with water (30 mL) and extracted with EtOAc (30 mL) and DCM (2 x 30 mL). The combined organic fractions were dried and evaporated to dryness to yield the title compound (195 mg, 0.77 mmol, 94%) as a clear oil, which had spectral data in agreement with that reported.[127] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.95 (d, J = 8.7 Hz, 2H, ArH2' and ArH6'); 6.73 (d, J = 8.4 Hz, 2H, ArH3' and ArH5'); 5.31 (d, J = 8.4 Hz, 1H, NH); 4.59 (m, 1H, H2); 3.71 (s, 3H, CH_3, $NCOOCH_3$); 3.65 (s, 3H, OCH_3); 3.01 (m, 2H, C3). Mass Spectrum (ES, +ve) *m/z* 254 (100%) [MH^+]. HRMS calcd for $C_{12}H_{16}NO_5$ 254.1029, found 254.1036.

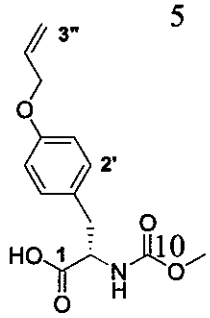
Methyl (2*S*)-3-(4-allyloxyphenyl)-2-methoxycarboxamidopropanoate (171)



To a solution of **170** (195 mg, 0.77 mmol) in DMF (6 mL) was added K_2CO_3 (213 mg, 1.54 mmol) and the resulting mixture was allowed to stir at RT under N_2 for 20 min before the addition of allyl bromide (0.14 mL, 1.54 mmol). After 16 h the reaction was quenched with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with water (5 x 30 mL) and brine (30 mL). The remaining organic fractions were dried and evaporated to dryness to yield the title compound (220 mg, 0.75 mmol, 98%) as a white solid. Mp 145-146°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.02 (d, J = 8.7 Hz, ArH2' and ArH6'); 6.83 (d, J = 8.4 Hz, ArH3' and ArH5'); 6.04 (m, 1H, H2"); 5.40 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$"); 5.27 (dd, J = 1.2,

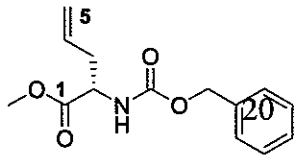
10.5 Hz, 1H, $H3_b$"); 5.18 (d, J = 7.5 Hz, NH); 4.60 (m, 1H, H2); 4.50 (d, J = 5.1 Hz, 2H, H1"); 3.71 (s, 3H, $NCOOCH_3$); 3.66 (s, 3H, OCH_3); 3.03 (m, 2H, C3). Mass Spectrum (ES, +ve) *m/z* [MH^+]. HRMS calcd for $C_{15}H_{20}NO_5$ 294.1342, found 294.1346.

(2*S*)-3-(4-Allyloxyphenyl)-2-methoxycarboxamidopropanoic acid (172)



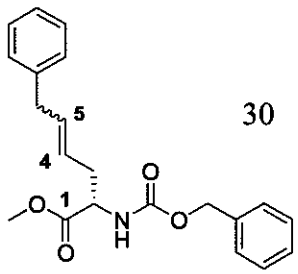
To a solution of **171** (220 mg, 0.75 mmol) in THF/water (3:1, 10 mL) was added lithium hydroxide (63 mg, 1.50 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation *in vacuo*. The aqueous layer was washed with DCM (30 mL) to remove unreacted starting material. The pH of the aqueous phase was adjusted to pH 3 with 10% HCl and the resulting precipitate was extracted with DCM (3 x 40 mL). The combined organic fractions were dried, and evaporated to dryness to yield the title compound (186 mg, 0.67 mmol, 89%) as a white solid. Mp 170-172°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.39 (bs, 1H, COOH); 7.07 (d, J = 8.7 Hz, ArH2' and ArH6'); 6.84 (d, J = 8.4 Hz, ArH3' and ArH5'); 6.03 (m, 1H, H2"); 5.39 (dd, J = 1.2, 17.1 Hz, 1H, $H3_a$"); 5.27 (dd, J = 1.2, 10.5 Hz, 1H, $H3_b$"); 4.62 (dd, J = 6.0, 13.2 Hz 1H, H2); 4.50 (d, J = 5.4 Hz, C1"); 3.65 (s, 3H, $NCOOCH_3$); 3.08 (m, 2H, H3). Mass Spectrum (CI, +ve) *m/z* 280 (50%) [MH^+], 220 (100%) [MH^+ less methoxycarbonate] HRMS calcd for $C_{14}H_{17}NO_5$ 279.1107, found 279.1114.

Methyl (2*S*)-2-benzyloxycarboxamido-4-pentenoate (173)



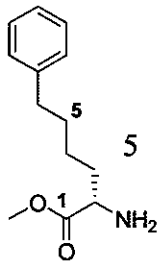
To a solution of methyl (2*S*)-2-amino-4-propenoate hydrochloride (422 mg, 2.56 mmol) and $NaHCO_3$ (645 mg, 7.68 mmol) in THF/water (3 mL/3 mL, 1:1) was added benzyl chloroformate (482 mg, 2.82 mmol) and the mixture was allowed to stir for 16 h. The reaction was quenched with 3% HCl (20 mL) and extracted with DCM (3 x 20 mL), dried and concentrated to give the title compound (676 mg, 2.56 mmol, 100%) as a clear oil, which had spectral data in agreement with that reported.[128] $[\alpha]_D^{20}$ + 9.1 (*c*. 0.15 in $CHCl_3$) (lit. $[\alpha]_D^{20}$ + 6.4 (*c*. 1.05 in MeOH))[128] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (m, 5H, ArH); 5.69 (m, 1H, H4); 5.56 (d, J = 7.8 Hz, 1H, NH); 5.12 (m, 4H, $ArCH_2$, C5); 4.47 (m, 1H, H2); 3.72 (s, 3H, OCH_3); 2.54 (m, 2H, H3). Mass Spectrum (CI, +ve) *m/z* 264 (20%) [MH^+], 113 (100%). HRMS calcd for $C_{14}H_{18}NO_4$ 264.12358, found 264.12421.

Methyl (2*S*,4*E/Z*)-2-benyloxycarboxamido-6-phenyl-4-hexenoate (174)



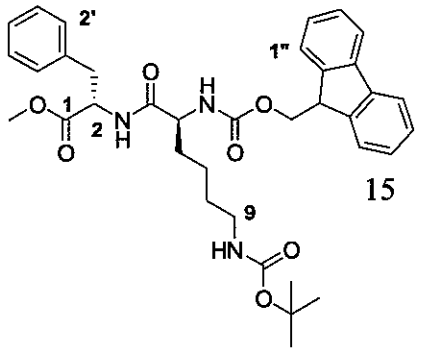
To a solution of **173** (181 mg, 0.69 mmol) in DCM (13.8 mL) was added allylbenzene (163 mg, 1.38 mmol) and Grubbs' first generation catalyst (28 mg, 0.0345 mmol). The mixture was heated at reflux for 16 h. The solvent was removed and the crude product purified by flash column chromatography (4:1, hexane/EtOAc) to yield the title compound as a 1:1 ratio mixture of *E* and *Z* isomers (103 mg, 0.29 mmol, 42%) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (m, 10H, ArH); 5.72 (m, 1H, H4); 5.42 (m, 2H, NH and H5); 5.13 (s, 2H, $ArCH_2O$); 5.50 (m, 1H, H2); 3.74/3.71 (s, 3H, OCH_3 [*E* & *Z*]); 3.39/3.34 (d, J = 7.5, 6.6 Hz, 2H, H6); 2.54 (m, 2H, H3). Mass Spectrum (CI, +ve) *m/z* 354 (20%) [MH^+], 263 (100%). HRMS calcd for $C_{21}H_{24}NO_4$ 354.17053, found 354.17077.

Methyl (2*S*)-2-amino-6-phenylhexanoate (175)



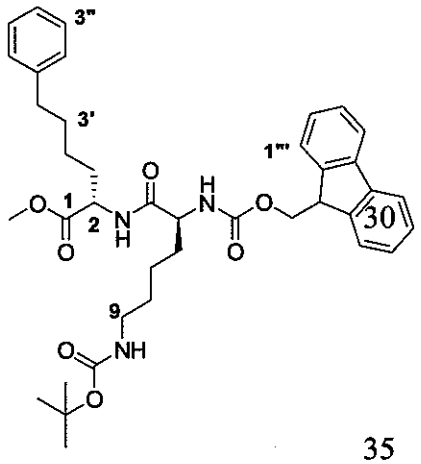
To a solution of **174** (118 mg, 0.33 mmol) in THF (30 mL) was added palladium on activated carbon (62 mg, 0.029 mmol). The flask was evacuated and twice filled with H_2 gas before stirring at RT for 16 h. The reaction mixture was filtered through celite and evaporated to dryness to yield the title compound (73 mg, 0.33 mmol, 100%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (m, 5H, ArH); 3.71 (m, 6H, OCH_3, NH_2 and H2); 2.60 (m, 2H, H6); 1.62 (m, 6H, H3, H4 and H5). Mass Spectrum (CI, +ve) *m/z* 222 (30%) [MH^+], 113 (100%). HRMS calcd for $C_{13}H_{20}NO_2$ 222.14940, found 222.14934.

Methyl (2*S*,5*S*)-3-aza-2-benzyl-9-(*tert*-butoxycarboxamido)-5-(9*H*-9-fluorenylmethyloxycarboxamido)-4-oxononanoate (176)



The title compound was synthesized using the general coupling procedure (Procedure B) from (1*S*)-2-phenyl-1-methoxycarbonylethylammonium chloride (300 mg, 1.39 mmol) and (2*S*)-6-*tert*-butoxycarboxamido-2-(9*H*-9-fluorenylmethyloxy)carboxamido hexanoic acid (769 mg, 1.64 mmol) to afford **176** (848 mg, 1.35 mmol, 97%) as a white solid. Mp 87-90°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75 (d, *J* = 7.2 Hz, 2H, ArH1" and ArH8); 7.58 (d, *J* = 7.2 Hz, 2H, ArH4" and ArH5"); 7.39 (t, *J* = 7.2 Hz, 2H, ArH3" and ArH6); 7.30 (t, *J* = 6.9 Hz, 2H, ArH2" and ArH7"); 7.21 (m, 2H, ArH3' and ArH5'); 7.07 (m, 1H, ArH4'); 6.61 (d, *J* = 7.2 Hz, 1H, NH); 5.56 (d, *J* = 8.4 Hz, 1H, NH); 4.85 (dd, *J* = 6.3, 14.1 Hz, 1H, H2); 5.69 (bs, 1H, NH); 4.36 (m, 2H, OC<u>H</u>$_2$-H9"); 4.19 (m, 2H, H5 and H9"); 3.69 (s, 3H, OCH_3); 3.09 (m, 2H, H2-C<u>H</u>$_2$); 3.04 (m, 2H, H9); 1.77 (m, 2H, H7); 1.63 (m, 2H, H6); 1.42 (s, 9H, C(C<u>H</u>$_3$)$_3$); 1.33 (m, 2H, H8). Mass Spectrum (ES, +ve) *m/z* 630 (10%) [MH^+], 104 (100%). HRMS calcd for $C_{36}H_{44}N_3O_7$ 630.3179, found 630.3189.

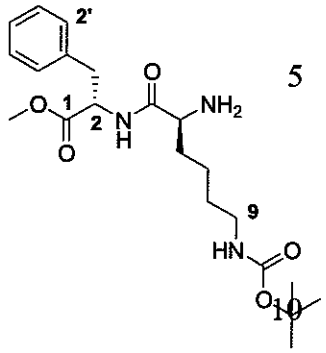
Methyl (2*S*,5*S*)-3-aza-9-(*tert*-butoxycarboxamido)-5-(9*H*-9-fluorenylmethyloxycarboxamido)-4-oxo-3-(4'-phenylbutyl)nonanoate (177)



The title compound was synthesized using the general coupling procedure (Procedure B) from **175** (63 mg, 0.29 mmol) and (2*S*)-6-*tert*-butoxycarboxamido-2-(9*H*-9-fluorenylmethyloxy)carboxamido hexanoic acid (113 mg, 0.24 mmol) to afford **177** (138 mg, 0.21 mmol, 86%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (d, *J* = 7.2 Hz, 2H, ArH1"' and ArH8"'); 7.57 (d, *J* = 5.4 Hz, 2H, ArH4"' and ArH5"'); 7.37 (t, *J* = 7.8 Hz, 2H, ArH3"' and ArH6""); 7.19 (m, 7H, ArH2"', ArH7"', ArH1", ArH2", ArH3", ArH4", ArH5" and ArH6); 6.80 (d, *J* = 7.2 Hz, 1H, NH); 5.71 (d, *J* = 7.8 Hz, 1H, NH); 4.78 (bs, 1H, NH); 4.55 (m, 1H, H2); 4.37 (d, *J* = 6.9 Hz, 2H, OC<u>H</u>$_2$-H9"'); 4.20 (m, 2H, H5 and H9"'); 3.69 (s, 3H, OCH_3); 3.07 (m, 2H, H9); 2.53 (t, *J* = 7.8 Hz, 2H, H4'); 1.84 (m, 2H, H7); 1.62 (m, 2H, H6); 1.42 (s, 9H, C(C<u>H</u>$_3$)$_3$);

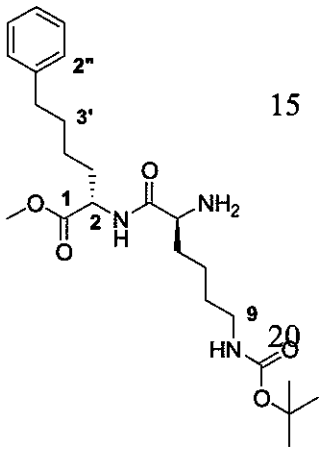
1.36 (m, 2H, H8); 1.26 (m, 4H, H2' and H3'). Mass Spectrum (ES, +ve) *m/z* 673 (100%) [MH^+]. HRMS calcd for $C_{39}H_{50}N_3O_7$ 672.3649, found 672.3624.

Methyl (2*S*,5*S*)-5-amino-3-aza-2-benzyl-9-(*tert*-butoxycarboxamido)-4-oxononanoate (178)



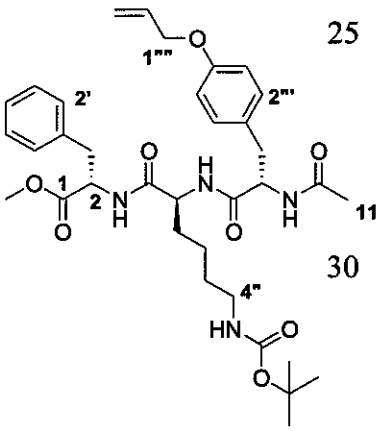
The title compound was synthesized using the general *N*-Fmoc deprotecting procedure (Procedure C) from **176** (836 mg, 1.33 mmol) to afford **178** (142 mg, 0.35 mmol, 26%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66 (d, J = 7.8 Hz, 1H, NH); 7.22 (m, 3H, ArH3', ArH4' and ArH5'); 7.10 (m, 2H, ArH2' and ArH6'); 4.83 (m, 1H, H2); 4.60 (bs, 1H, NH); 3.69 (s, 3H, OCH_3); 3.29 (dd, J = 4.5, 7.5 Hz, 1H, H5); 3.08 (m, 2H, H2-C$\underline{H}_2$); 3.06 (m, 2H, H9); 1.67 (m, 2H, H7); 1.46 (m, 2H, H6); 1.41 (s, 9H, $C(CH_3)_3$); 1.24 (m, 2H, H8). Mass Spectrum (ES, +ve) *m/z* 409 (100%) [MH^+].

Methyl (2*S*,5*S*)-2-amino-3-aza-9-(*tert*-butoxycarboxamido)-4-oxo-2-(4-phenylbutyl)nonanoate (179)



The title compound was synthesized using the general *N*-Fmoc deprotecting procedure (Procedure C) from **177** (138 mg, 0.21 mmol) to afford **179** (78 mg, 0.17 mmol, 81%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (d, J = 8.1 Hz, 1H, NH); 7.22 (m, 5H, ArH); 4.56 (m, 2H, H2 and H5); 3.72 (s, 3H, OCH_3); 3.11 (m, 2H, H9); 2.60 (t, J = 7.5 Hz, 2H, H4'); 1.83 (m, 2H, H7); 1.66 (m, 6H, H1', H2' and H3'); 1.44 (s, 9H, $C(C\underline{H}_3)_3$); 1.29 (m, 2H, H8); 0.86 (m, 2H, H6). Mass Spectrum (ES, +ve) *m/z* 450 (100%) [MH^+]. HRMS calcd for $C_{24}H_{40}N_3O_5$ 450.2968, found 450.2950.

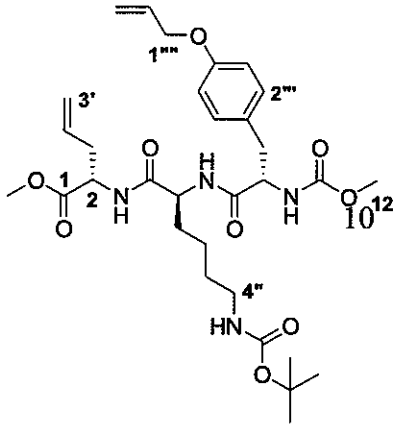
Methyl (2*S*,5*S*,8*S*)-8-(4-allyloxybenzyl)-3,6,9-triaza-2-benzyl-5-(4-[*tert*-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate (180)



The title compound was synthesized using the general peptide coupling procedure (Procedure B) from **16** (76 mg, 0.29 mmol) and **178** (142 mg, 0.35 mmol) to afford **180** (135 mg, 0.21 mmol, 72%) as an off-white solid. Mp 122-126°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 3H, ArH3', ArH4' and ArH5'); 7.12 (m, 2H, ArH2' and ArH6'); 7.05 (d, J = 8.7 Hz, 2H, ArH2''' and ArH6'''; 6.79 (d, J = 8.4 Hz, 1H, ArH3''' and ArH5'''; 6.50 (d, J = 6.9 Hz, 1H, NH); 6.01 (m, 1H, H2''''); 5.37 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$''''); 5.25, J = 1.2, 10.5 Hz, 1H, $H3_b$''''); 4.87 (bs, 1H, NH); 4.79 (m, 1H, H2); 4.68 (m, 1H, H5); 4.45 (d, J = 5.1 Hz, 2H, H1''''); 4.43 (m, 1H, H8); 3.69 (s, 3H, OCH_3); 3.06 (m,

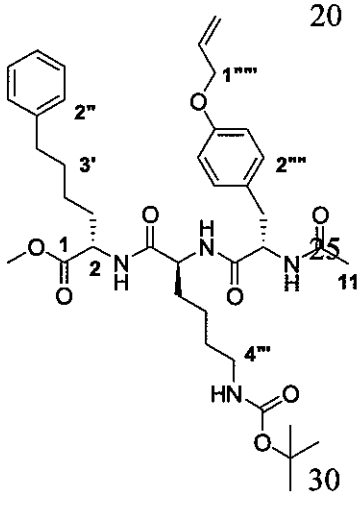
4H, 2-CH_2 and 8-CH_2); 2.93 (m, 2H, H4"); 1.95 (s, 3H, H11); 1.75 (m, 2H, H2"); 1.55 (m, 2H, H1"); 1.32 (s, 9H, $C(C\underline{H}_3)_3$); 1.26 (m, 2H, H3"). Mass Spectrum (ES, +ve) *m/z* 653 (10%) [MH^+]; 104 (100%). HRMS calcd for $C_{35}H_{48}N_4O_8Na$ 675.3370, found 675.3358.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]butyl)-11-oxa-4,7,10-trioxododecanoate (181)



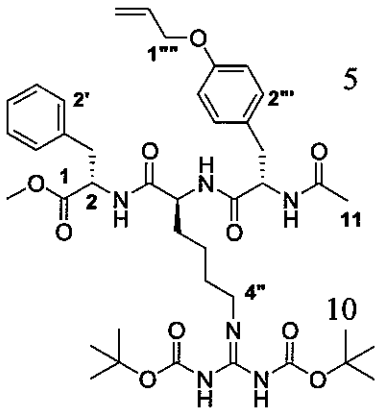
The title compound was synthesized using the general peptide coupling procedure (Procedure B) from **24** (340 mg, 0.95 mmol) and **172** (148 mg, 0.53 mmol) to afford **181** (264 mg, 0.43 mmol, 81%) as an off-white solid. Mp 90-91°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08 (d, *J* = 9.0 Hz, 2H, ArH2"' and ArH6"'); 7.00 (d, *J* = 7.5 Hz, 1H, NH); 6.81 (d, *J* = 8.7 Hz, 2H, ArH3"' and ArH5"'); 6.03 (m, 1H, H2""); 5.63 (m, 1H, H2'); 5.39 (dd, *J* = 1.5, 17.1 Hz, 1H, $H3_a$""); 5.27 (dd, *J* = 1.5, 10.8 Hz, 1H, $H3_b$""); 5.12 (m, 2H, H3'); 4.93 (bs, 1H, NH); 4.61 (m, 1H, H2); 4.51 (m, 2H, H5 and H8); 4.49 (d, *J* = 5.1 Hz, 2H, H1""); 3.74 (s, 3H, $NCOOC\underline{H}_3$); 3.62 (s, 3H, OCH_3); 3.00 (m, 4H, H4" and $ArCH_2$); 2.51 (m, 2H, H1'); 1.80 (m, 2H, H2"); 1.60 (m, 2H, H1"); 1.43 (s, 9H, $C(C\underline{H}_3)_3$); 1.28 (m, 2H, H3"). Mass Spectrum (ES, +ve) *m/z* 619 (60%) [MH^+]; 641 (100%) [M^++Na]. HRMS calcd for $C_{31}H_{46}N_4O_9Na$ 641.3162, found 641.3184.

Methyl (2*S*,5*S*,8*S*)-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]butyl)-4,7,10-trioxo-2-(4-phenylbutyl)undecanoate (182)



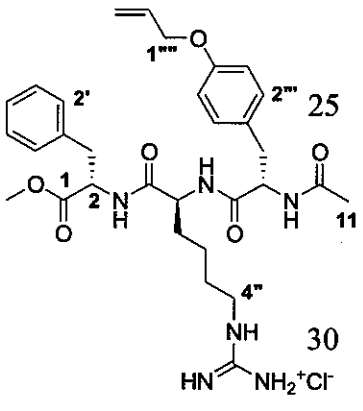
The title compound was synthesized using the general peptide coupling procedure (Procedure B) from **16** (37 mg, 0.14 mmol) and **179** (78 mg, 0.17 mmol) to afford **182** (72 mg, 0.10 mmol, 74%) as an off-white solid. Mp 112-117°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (m, 5H, ArH); 7.09 (d, *J* = 8.4 Hz, 2H, ArH2"" and ArH6""); 6.82 (d, *J* = 8.7 Hz, 2H, ArH3"" and ArH5""); 6.45 (m, 2H, NH); 6.09 (m, 1H, NH); 6.02 (m, 1H, H2""'); 5.39 (dd, *J* = 1.5, 17.1 Hz, 1H, $H3_a$""'); 5.27 (dd, *J* 1.5, 10.5 Hz, 1H, $H3_b$""'); 4.79 (bs, 1H, NH); 4.60 (m, 1H, H2); 4.48 (m, 3H, H5 and H1""'); 4.35 (m, 1H, H8); 3.72 (s, 3H, OCH_3); 3.02 (m, 4H, H4"', 8-CH_2); 2.60 (t, *J* = 8.1 Hz, 2H, H4'); 1.97 (s, 3H, H11); 1.84 (m, 2H, H2"'); 1.66 (m, 6H, H1', H2' and H3'); 1.43 (s, 9H, $C(C\underline{H}_3)_3$); 1.32 (m, 4H, H1"' and H3)'. Mass Spectrum (ES, +ve) *m/z* 695 (100%) [MH^+]. HRMS calcd for $C_{38}H_{55}N_4O_8$ 695.4020, found 695.4008.

Methyl (2*S*,5*S*,8*S*)-8-(4-allyloxybenzyl)-3,6,9-triaza-2-benzyl-5-(4[{di-*tert*-butoxycarbonyl}guanidino]butyl)-4,7,10-trioxoundecanoate (183)



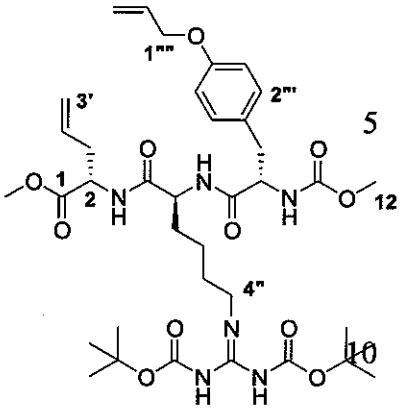
To a solution of **180** (125 mg, 1.19 mmol) in DCM (2 mL) was added TFA (2 mL) and the resulting mixture was allowed to stir for 3 h. The solvent was removed by evaporation and the oily intermediate was precipitated by the addition of diethyl ether (5 mL) which was decanted and the solid product was dried *in vacuo*. To the salt was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (82 mg, 0.21 mmol), triethylamine (0.1 mL) and DCM (3 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was removed by evaporation *in vacuo*, and the crude product was purified by flash chromatography (20:1, DCM/ MeOH) to yield the title compound (177 mg, 0.21 mmol, 100%) as an off white solid. Mp 228°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (m, 3H, ArH3', ArH4' and ArH5'); 7.08 (m, 4H, ArH2', ArH6', ArH2''' and ArH6'''); 6.81 (d, J = 8.7 Hz, 2H, ArH3''' and ArH5'''); 6.46 (t, J = 8.4 Hz, 2H, NH); 6.21 (d, J = 7.8 Hz, 1H, NH); 6.00 (m, 1H, H2''''); 5.37 (dd, J = 1.2, 16.8 Hz, 1H, $H3_a$''''); 5.26 (dd, J = 1.5, 10.8 Hz, 1H, $H3_b$''''); 4.78 (m, 1H, H2); 4.61 (m, 1H, H5); 4.47 (d, J = 5.4 Hz, 2H, H1''''); 4.32 (m, 1H, H8); 3.71 (s, 3H, OCH_3); 3.31 (m, 2H, 2-CH_2); 3.08 (m, 2H, 8-CH_2); 2.97 (d, J = 6.9 Hz, 2H, H4''); 1.98 (s, 3H, H11); 1.76 (m, 2H, H2''); 1.52 (m, 2H, H1''); 1.48 (s, 18H, $C(CH_3)_3$); 1.25 (m, 2H, H3''). Mass Spectrum (ES, +ve) *m/z* 795 (20%) [MH^+]; 104 (100%). HRMS calcd for $C_{41}H_{59}N_6O_{10}$ 795.4293, found 795.4310.

Methyl (2*S*,5*S*,8*S*)-8-(4-allyloxybenzyl)-3,6,9-triaza-2-benzyl-5-(4-guanidinobutyl)-4,7,10-trioxoundecanoate hydrochloride (165)



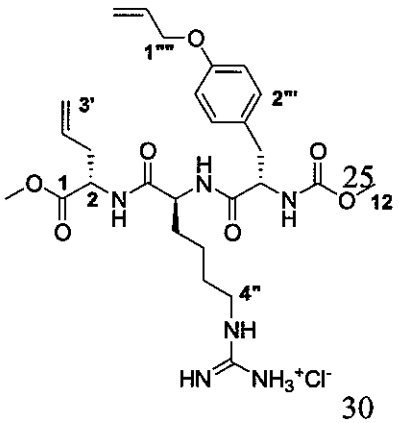
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) from **183** (157 mg, 0.20 mmol) to yield **165** (93 mg, 0.15 mmol, 74%) as a white solid. Mp 175-179°C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.20 (m, 5H, ArH'); 7.11 (d, J = 8.1 Hz, 2H, ArH2''' and ArH6'''); 6.78 (d, J = 8.4 Hz, 2H, ArH3''' and ArH5'''; 6.01 (m, 1H, H2''''); 5.35 (dd, J = 1.2, 16.8 Hz, 1H, $H3_a$''''); 5.20, J = 1.5, 10.8 Hz, 1H, $H3_b$''''); 4.60 (dd, J = 5.7, 8.1 Hz, 1H, H2); 4.45 (m, 1H, H5); 4.47 (d, J = 5.4 Hz, 2H, H1''''); 4.34 (dd, J = 4.8, 8.4 Hz, 1H, H8); 3.65 (s, 3H, OCH_3); 3.05 (m, 4H, 2-CH_2 and 8-CH_2); 2.77 (m, 2H, H4''); 1.90 (s, 3H, H11); 1.73 (m, 2H, H2''); 1.56 (m, 2H, H1''); 1.37 (m, 2H, H3''). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.6, C7; 173.4, C4; 173.3, C2; 173.0, C10; 158.7, CN_3; 158.4, ArC4'''; 137.8, ArCH2' and ArCH6'; 134.8, C2''''; 131.0, ArCH2''' and ArC6'''; 130.3, ArC1'''; 130.1, ArCH4'; 129.4, ArC1'; 127.8, ArCH3' and ArCH5'; 117.2, C3''''; 115.6, ArCH3''' and ArCH5'''; 69.7 C1''''; 56.6, C2; 55.2, C5; 54.0, OCH_3; 52.7, C8; 42.2, C4''; 38.3, 2-CH_2; 37.8, 8-CH_2; 32.6, C1''; 28.2, C3''; 23.6, C11; 22.5, C2''. Mass Spectrum (ES, +ve) *m/z* 596 (100%) [MH^+]. HRMS calcd for $C_{31}H_{43}N_6O_6$ 595.3244, found 595.3225.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-{[di-*tert*-butoxycarbonyl]guanidino}butyl)-11-oxa-4,7,10-trioxododecanoate (184)



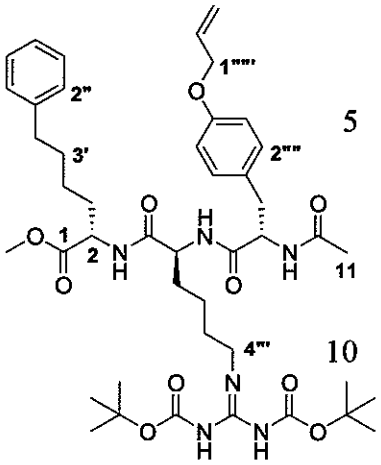
To a solution of **181** (250 mg, 0.40 mmol) in DCM (3 mL) was added TFA (3 mL) and the resulting mixture was allowed to stir for 3 h. The solvent was removed by evaporation *in vacuo,* and the oily intermediate was precipitated by the addition of diethyl ether (5 mL) which was decanted and the solid product was dried *in vacuo*. To the remaining salt was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (172 mg, 0.44 mmol), triethylamine (0.5 mL) and DCM (3 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was removed and the crude product was purified by flash chromatography (20:1, DCM/MeOH) to yield the title compound (309 mg, 0.40 mmol, 100%) as an off white oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.33 (bs, 1H, NH); 7.08 (d, *J* = 8.7 Hz, 2H, ArH2"' and ArH6"'); 6.83 (d, *J* = 8.7 Hz, 2H, ArH3"' and ArH5"'); 6.69 (t, *J* = 6 Hz, 2H, NH); 6.03 (m, 1H, H2""); 5.67 (m, 1H, H2'); 5.40 (dd, *J* = 1.2, 17.1 Hz, 1H, $H3_a$""); 5.33 (d, *J* = 7.8 Hz, 1H, NH); 5.27 (m, *J* = 1.5, 10.5 Hz, 1H, $H3_b$""); 5.12 (m, 2H, H3'); 4.57 (m, 1H, H2); 4.50 (d, *J* = 5.1 Hz, 2H, H1""); 4.40 (m, 2H, H5 and H8); 3.74 (s, 3H, H12); 3.62 (s, 3H, OCH_3); 3.35 (t, *J* = 6.0 Hz, 2H, H4"); 2.99 (m, 2H, $ArCH_2$); 2.52 (m, 2H, H1'); 1.83 (m, 2H, H2"); 1.57 (m, 2H, H1"); 1.48 (s, 18H, $C(C\underline{H}_3)_3$); 1.32 (m, 2H, H3"). Mass Spectrum (ES, +ve) *m/z* 761 (100%) [MH^+]. HRMS calcd for $C_{37}H_{57}N_6O_{11}$ 761.4085, found 761.4067.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-{guanidino}butyl)-11-oxo-4,7,10-trioxododecanoate hydrochloride (166)



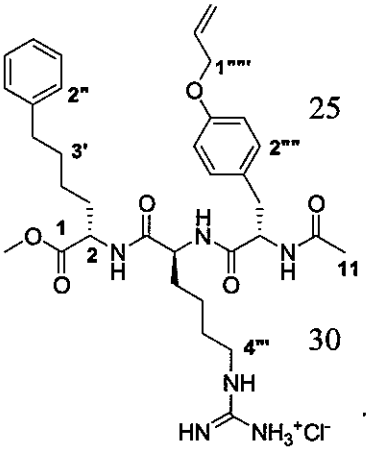
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) from **184** (290 mg, 0.38 mmol) to yield **166** (171 mg, 0.29 mmol, 76%) as a highly hydroscopic white solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.24 (d, *J* = 7.2 Hz, 1H, NH); 8.09 (d, *J* = 7.8 Hz, 1H, NH); 7.13 (d, *J* = 8.7 Hz, 2H, ArH2"' and ArH6"); 6.82 (d, *J* = 8.7 Hz, 2H, ArH3"' and ArH5"'); 6.03 (m, 1H, H2""); 5.77 (m, 1H, H2'); 5.37 (dd, *J* = 1.8, 17.4 Hz, 1H, $H3_a$""); 5.22 (dd, *J* = 1.5, 10.5 Hz, 1H, $H3_b$""); 5.11 (m, 2H, H3'); 4.50 (d, *J* = 5.1 Hz, 2H, H1""); 4.42 (m, 2H, H5 and H8); 4.31 (dd, *J* = 5.4, 9.0 Hz, 1H, H2); 3.70 (s, 3H, H12); 3.58 (s, 3H, OCH_3); 3.17 (t, *J* = 6.9 Hz, 2H, H4"); 2.91 (m, 2H, $ArCH_2$); 2.52 (m, 2H, H1'); 1.82 (m, 2H, H2"); 1.62 (m, 2H, H1"); 1.43 (m, 2H, H3"). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.0, C7; 173.6, C1; 172.9, C4; 158.5, CN_3; 158.2, ArC4"'; 158.2, C12; 134.7, C2'; 133.9, C2""; 131.1, ArCH2"' and ArCH6"'; 130.3, ArC1"'; 118.9, C3'; 117.3, C3""; 114.5, ArCH3"' and ArCH5"'; 69.6, C1""; 57.9, C8; 54.2, C5; 53.6, C2; 52.8, OCH_3; 42.3, C12; 38.2, C4"; 36.6, $ArCH_2$; 32.7, C1'; 29.2, C1"; 23.6, C3"; 15.5, C2". Mass Spectrum (ES, +ve) *m/z* 658 (100%) [MH^+ less Cl^-]. HRMS calcd for $C_{27}H_{41}N_6O_7$ 561.3037, found 561.3016.

Methyl (2*S*,5*S*,8*S*)-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4[{di-*tert*-butoxycarbonyl}guanidino]butyl)-4,7,10-trioxo-2-(4-phenylbutyl)undecanoate (185)



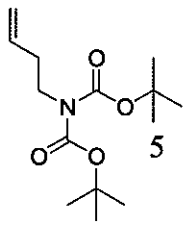
To a solution of **182** (40 mg, 0.058 mmol) in DCM (2 mL) was added TFA (2 mL) and the resulting mixture was allowed to stir for 3 h. The solvent was removed and the oily intermediate was solidified upon the addition of diethyl ether (5 mL) which was decanted and the solid product was dried *in vacuo*. To the remaining salt was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (34 mg, 0.086 mmol), triethylamine (0.1 mL) and DCM (2 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was removed and the crude product was purified by flash chromatography (20:1, DCM/MeOH) to yield the title compound (46 mg, 0.054 mmol, 95%) as an off white solid. Mp 198°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (m, 5H, ArH); 7.08 (d, J = 8.4 Hz, 2H, ArH2"" and ArH6""); 6.81 (d, J = 8.4 Hz, 2H, ArH3"" and ArH5""); 6.71 (d, J = 7.8 Hz, 1H, NH); 6.45 (d, J = 7.8 Hz, 1H, NH); 6.02 (m, 1H, H2""'); 5.38 (dd, J = 1.5, 17.4 Hz, 1H, $H3_a$""'); 5.26 (dd, J 1.2, 10.5 Hz, 1H, $H3_b$""'); 4.65 (m, 1H, H2); 4.47 (d, J = 5.1 Hz, 2H, H1""'); 4.40 (m, 2H, H5 and H8); 3.97 (s, 1H, NH); 3.71 (s, 3H, OCH_3); 3.37 (bs, 2H, H4"'); 2.98 (m, 2H, 8-CH_2); 2.59 (t, J = 7.8 Hz, 2H, H4'); 1.96 (s, 3H, C11); 1.84 (m, 2H, H2"'); 1.63 (m, 6H, H1', H2'and H3'); 1.49 (s, 18H, $C(C\underline{H}_3)_3$); 1.36 (m, 4H, H1"'and H3). Mass Spectrum (ES, +ve) *m/z* 837 (100%) [MH^+]. HRMS calcd for $C_{44}H_{65}N_6O_{10}$ 837.4762, found 837.4744.

Methyl (2*S*,5*S*,8*S*)-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-guanidinobutyl)-4,7,10-trioxo-2-(4-phenylbutyl)undecanoate hydrochloride (167)



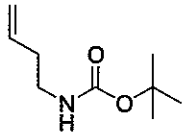
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) from 185 (40 mg, 0.048 mmol) to yield 167 (18 mg, 0.026 mmol, 56%) as a white solid. Mp 180-188°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.23 (d, J = 7.2 Hz, 1H, NH); 8.08 (d, J = 7.2 Hz, 1H, NH); 7.15 (m, 7H, ArH); 6.81 (d, J = 8.7 Hz, 2H, ArH3"" and ArH5""); 6.02 (m, 1H, H2""'); 5.36 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$""'); 5.21 (dd, J = 1.5, 10.5 Hz, 1H, $H3_b$""'); 4.49 (m, 3H, H2 and H1""'); 4.36 (m, 2H, H5 and H8); 3.68 (s, 3H, OCH_3); 3.16 (m, 2H, H4"'); 2.92 (m, 2H, 8-CH_2); 2.60 (t, J = 7.2 Hz, 2H, H4'); 1.91 (s, 3H, H11); 1.82 (m, 2H, H2"'); 1.61 (m, 8H, H1', H2', H3' and H1"'); 1.42 (m, 2H, H3). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.1, C7; 173.9, C4; 174.4, C1; 159.0, C10; 158.6, CN_3; 143.5, ArC4""; 135.0, ArC1"; 131.2, C2""'; 130.4, ArC1""; 129.4, ArCH2"" and ArCH6""; 129.3, ArCH3" and ArCH5";126.8, ArCH4"; 117.4, C3""'; 115.7, ArCH3"" and ArCH5""; 69.7, C1""'; 56.6, C5; 53.9, C2; 53.7, OCH_3; 52.7, C8; 42.3, C4"'; 37.9, 8-CH_2; 36.6, C4'; 32.7, C1'; 32.2, C3'; 32.1, C1"'; 29.2, C3"'; 26.4, C11; 23.6, C2'; 22.4, C2"'. Mass Spectrum (ES, +ve) *m/z* 638 (100%) [M^+]. HRMS calcd for $C_{34}H_{49}N_6O6_5$ 637.3714, found 637.3745.

Di-*tert*-butyl *N*-3-butenyliminodicarboxylate (186)



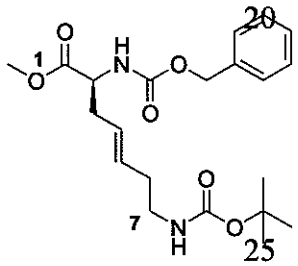
To a solution of di-*tert*-butyliminodicarboxylate (868 mg, 4 mmol), cesium carbonate (2.61 g, 8 mmol), and lithium iodide (28 mg, 0.2 mmol) in 2-butanone (20 mL) was added 4-bromobutene (812 mg, 6mmol) and the mixture was heated at reflux for 48 h. The reaction was allowed to cool and was quenched with brine (40 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic fractions were washed with brine (30 mL), dried, and evaporated to yield the title compound (1.01 g, 3.7 mmol, 93%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.77 (m, 1H, H3); 5.04 (m, 2H, H4); 3.62 (dd, J = 6.0, 8.7 Hz, 2H, H1); 2.30 (m, 2H, H2); 1.51 (s, 18H, 2 x $(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 310 (55%) [MK^+], 294 (30%) [MNa^+], 272 (40%) [MH^+]. HRMS calcd for $C_{14}H_{26}NO_4$ 272.1862, found 272.1848.

***tert*-Butyl *N*-3-butenylcarbamate (187)**



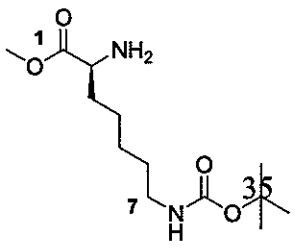
To a solution of **186** (708 mg, 2.60 mmol) in DCM (20 mL) was added trifluoroacetic acid (593 mg, 5.20 mmol) and the mixture was allowed to stir for 5 min before being quenched with 2M NaOH (25 mL) and extracted with DCM (3 x 20 mL). The combined organic fractions were dried, and concentrated to yield the title compound (429 mg, 2.50 mmol, 96%) as a light brown oil, which had spectral data in agreement with that reported.[104] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (m, 1H, H3); 5.08 (m, 2H, H4); 4.59 (bs, 1H, NH); 3.20 (dd, J = 6.3, 12.6 Hz, 2H, H1); 2.24 (dd, J = 6.9, 12.6 Hz, 2H, H2); 1.44 (s, 9H, $(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 116 (100%) [MH^+ less 56 (Boc rearrangement].

Methyl (2*S*,4*E*/*Z*)-2-(benzyloxycarboxamido)-7-(*tert*-butoxycarboxamido)-4-heptenoate (188)



To a solution of **187** (220 mg, 1.29 mmol) in DCM (13 mL) was added **173** (169 mg, 0.64 mmol) and Grubbs' first generation catalyst (53 mg, 0.064 mmol). The mixture was heated at reflux under N_2 for 16 h. The solvent was removed and the crude product purified by flash column chromatography (6:1, hexane/EtOAc) to yield the title compound (180 mg, 0.44 mmol, 69%) as a brown oil as a 1:1 mixture of *E* and *Z* isomers. $[\alpha]_D^{24}$ - 34.6 (*c*. 0.3 in EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (m, 5H, ArH); 5.43 (m, 3H, H4, H5, NH); 5.11/5.10 (s, 2H, OCH_2Ph[*E* and *Z*]); 4.61 (bs, 1H, NH); 4.43 (m, 1H, H2); 3.75/3,72 (s, 3H, OCH_3[*E* and *Z*]); 3.11 (m, 2H, H7); 2.47 (m, 2H, H3); 2.17 (m, 2H, H6); 1.43 (s, 9H, $(CH_3)_3$). Mass Spectrum (ES, +ve) *m/z* 429 (100%) [MNa^+], 407 (20%) [MH^+]. HRMS calcd for $C_{21}H_{31}N_2O_6$ 407.2182, found 407.2171.

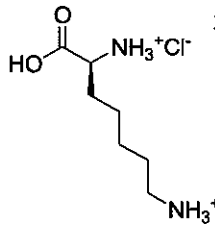
Methyl (2*S*)-2-amino-7-(*tert*-butoxycarboxamido)-4-heptanoate (189)



To a solution of **188** (25 mg, 0.061 mmol) in THF (4 mL) was added palladium on activated carbon (13 mg, 0.0061 mmol) The reaction vessel was evacuated, flushed with H_2 and allowed to stir for 16 h. The resulting crude product was filtered through celite and evaporated to yield the title compound (15 mg, 0.055 mmol, 90 %) as a clear oil. $[\alpha]_D^{24}$ + 9.6 (*c*. 0.1 in EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.55

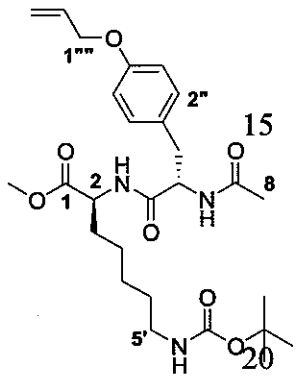
(bs, 1H, NH); 3.72 (s, 3H, OCH_3); 3.44 (t, J = 6.0 Hz, 1H, H2); 3.10 (m, 2H, H7); 1.86 (m, 4H, H3, H4); 1.44 (s, 9H, $(CH_3)_3$); 1.37 (m, 4H, H5, H6). Mass Spectrum (ES, +ve) *m/z* 275 (90%) [MH^+]; 219 (100%). HRMS calcd for $C_{13}H_{27}N_2O_4$ 275.1971, found 275.1967.

(2*S*)-2,7-Diaminoheptanoic acid dihydrochloride (193)



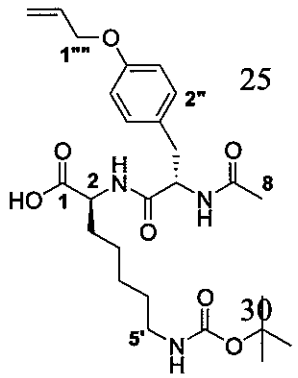
A solution of **189** (16 mg, 0.058 mmol) in 10M HCl (3 mL) was allowed to stir for 48 h. The product was isolated by evaporation and dried over P_2O_5 to yield the title compound (14 mg, 0.058 mmol, 100%) as a hydroscopic white solid, which had spectral data in agreement with that reported.[106] $[\alpha]_D^{22}$ + 10.9 (*c*. 0.1 in HCl) (Lit. $[\alpha]_D^{23}$ +14.4)[106] ^{1}H NMR (D_2O, 300 MHz): δ 3.90 (t, J = 6.3 Hz, 1H, H2); 2.83 (t, J = 7.5 Hz, 2H, H7); 1.81 (m, 2H, H3); 1.64 (m, 2H, H5); 1.52 (m, 2H, H6); 1.30 (m, 2H, H4). Mass Spectrum (ES, +ve) *m/z* 161 (100%) [M^{2+}]. HRMS calcd for $C_7H_{17}N_2O_2$ 161.1290, found 161.1294.

Methyl (2*S*,5*S*)-5-(4-allyloxybenzyl)-3,6-diaza-2-(5-[*tert*-butoxycarboxamido]pentyl)-4,7-dioxooctanoate (190)



The title compound was synthesized using the general peptide coupling procedure (Procedure B) from **16** (53 mg, 0.20 mmol) and **189** (65 mg, 0.24 mmol) to afford **190** (103 mg, 0.20 mmol, 100%) as an off-white solid. Mp 96-103°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11 (d, J = 8.7 Hz, 2H, ArH2" and ArH6"); 6.82 (d, J = 8.7 Hz, 2H, ArH3" and ArH5"); 6.50 (d, J = 7.8 Hz, 1H, NH); 6.03 (m, 1H, H2"'); 5.39 (dd, J = 1.8, 17.4 Hz, 1H, $H3_a$"'); 5.26 (dd, J = 1.8, 9.3 Hz, 1H, $H3_b$"'); 4.66 (m, 2H, H2 and H5); 4.48 (m, 2H, H1"'); 3.69 (s, 3H, OCH_3); 2.98 (m, 4H, H5' and $ArCH_2$); 1.96 (s, 3H, H8); 1.75 (m, 2H, H1'); 1.64 (m, 2H, H3'); 1.43 (s, 9H, $C(CH_3)_3$); 1.26 (m, 4H, H2' and H4'). Mass Spectrum (ES, +ve) *m/z* 520 (100%) [MH^+]. HRMS calcd for $C_{27}H_{41}N_3O_7$ 542.2842, found 542.2855.

(2*S*,5*S*)-5-(4-Allyloxybenzyl)-3,6-diaza-2-(5-[*tert*-butoxycarboxamido]pentyl)-4,7-dioxooctanoic acid (191)



To a solution of **190** (70 mg, 0.13 mmol) in THF/water, 3:1 (8 mL) was added lithium hydroxide monohydrate (11 mg, 0.26 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation. The aqueous layer was extracted with DCM (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with DCM (3 x 40 mL). The combined organic fractions were dried and evaporated to yield the title compound (39 mg, 0.08 mmol, 62%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.09 (d, J = 8.7 Hz, 2H, ArH2" and ArH6"); 6.82 (d, J = 8.7 Hz, 2H, ArH3" and ArH5"); 6.05 (m, 1H, H2"'); 5.39 (dd, J = 1.8, 17.4 Hz, 1H, $H3_a$"'); 5.25 (dd, J = 1.8, 9.3 Hz, 1H, $H3_b$"'); 4.63 (t, J = 6.9 Hz, 1H, H2); 4.47 (m, 3H, H1"' and H5); 3.05 (m, 4H, H5' and $ArCH_2$); 1.95 (s, 3H, H8); 1.84 (m, 2H, H1'); 1.69 (m, 2H, H3'); 1.44 (s, 9H, $C(CH_3)_3$); 1.28 (m, 4H, H2' and H4').

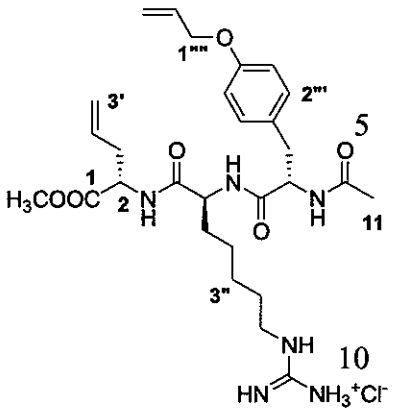
Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[*tert*-butoxycarboxamido]pentyl)-4,7,10-trioxoundecanoate (192)

The title compound was synthesized using the general peptide coupling procedure (Procedure B) from **18** (14 mg, 0.084 mmol) and **191** (35 mg, 0.07 mmol) to afford **192** (31 mg, 0.048 mmol, 69%) as an off-white solid. Mp 130-136°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07 (d, J = 8.7 Hz, 2H, ArH2"' and ArH6"'); 6.80 (d, J = 8.7 Hz, 2H, ArH3"' and ArH5"'); 6.59 (d, J = 8.1 Hz, 1H, NH); 6.49 (d, J = 7.2 Hz, 1H, NH); 6.43 (d, J = 7.5 Hgz, 1H, NH); 6.02 (m, 1H, H2""); 5.67 (m, 1H, H2'); 5.39 (dd, J = 1.5, 17.4 Hz, 1H, $H3_a$""); 5.26 (dd, 1.5, 10.5 Hz, 1H, $H3_b$""); 5.10 (m, 2H, H3'); 4.70 (m, 1H, H2); 4.58 (m, 1H, H5); 4.48 (m, 2H, H1""); 4.41 (m, 1H, H8); 3.73 (s, 3H, OCH_3); 3.04 (m, 2H, H5"); 2.98 (t, J = 6.0 Hz, 2H, $ArCH_2$); 2.53 (m, 2H, H1'); 1.96 (s, 3H, H11); 1.76 (m, 2H, H1"); 1.58 (m, 2H, H3"); 1.43 (s, 9H, $C(CH_3)_3$); 1.28 (m, 4H, H2" and H4"). Mass Spectrum (ES, +ve) *m/z* 639 (100%) [MNa^+], 617 (10%) [MH^+], 517 (95%) [MH^+ less Boc]. HRMS calcd for $C_{32}H_{48}N_4O_8Na$ 639.3370, found 639.3371.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[{di-*tert*-butoxycarbonyl}guanidino]pentyl)-4,7,10-trioxoundecanoate (195)

To a solution of **192** (20 mg, 0.032 mmol) in DCM (2 mL) was added TFA (2 mL) and the resulting mixture was allowed to stir for 3 h. The solvent was removed and the oily intermediate was solidified upon the addition of diethyl ether (5 mL) which was decanted and the solid product was dried *in vacuo*. To the remaining salt was added *N*1-*tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (34 mg, 0.086 mmol), triethylamine (0.1 mL) and DCM (2 mL). The resulting solution was allowed to stir for 16 h under N_2. The solvent was removed and the crude product was purified by flash chromatography (20:1, DCM/MeOH) to yield the title compound (23 mg, 0.030 mmol, 95%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.31 (bs, 1H, NH); 7.08 (d, J = 8.7 Hz, 2H, ArH2"' and ArH6"'); 6.82 (d, J = 8.7 Hz, 2H, ArH3"' and ArH5"'); 6.72 (d, J = 8.1 Hz, 1H, NH); 6.60 (d, J = 7.5 Hz, 1H, NH); 6.41 (d, J = 7.8 Hz, 1H, NH); 6.03 (m, 1H, H2""); 5.65 (m, 1H, H2'); 5.40 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$""); 5.27 (dd, 1.5, 10.5 Hz, 1H, $H3_b$""); 5.11 (m, 2H, H3'); 4.66 (m, 1H, H2); 4.57 (m, 1H, H5); 4.49 (m, 2H, H1""); 4.38 (m, 1H, H8); 3.74 (s, 3H, OCH_3); 3.34 (m, 2H, H5"); 2.98 (m, 2H, $ArCH_2$); 2.52 (m, 2H, H1'); 1.97 (s, 3H, H11); 1.80 (m, 2H, H1"); 1.70 (m, 2H, H3"); 1.49 (s, 18H, $C(CH_3)_3$); 1.32 (m, 4H, H2" and H4"). Mass Spectrum (ES, +ve) *m/z* 759 (100%) [MH^+]. HRMS calcd for $C_{38}H_{59}N_6O_{10}$ 759.4293, found 759.4272.

Methyl (2*S*,5*S*,8*S*)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-guanidinopentyl)-4,7,10-trioxoundecanoate hydrochloride (168)



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) from **195** (20 mg, 0.026 mmol) to yield **168** (10 mg, 0.017 mmol, 65%) as a white hydroscopic solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.13 (d, J = 8.4 Hz, 2H, ArH2"' and ArH6"'); 6.82 (d, J = 8.4 Hz, 2H, ArH3"' and ArH5"'); 6.03 (m, 1H, H2""); 5.76 (m, 1H, H2'); 5.37 (dd, J = 1.5, 17.1 Hz, 1H, $H3_a$""); 5.22 (dd, 1.5, 10.5 Hz, 1H, $H3_b$""); 5.10 (m, 2H, H3'); 4.50 (m, 2H, H1""); 4.38 (m, 3H, H2, H5 and H8); 3.69 (s, 3H, OCH_3); 3.15 (m, 2H, H5"); 2.92 (m, 2H, $ArCH_2$); 2.51 (m, 2H, H1'); 1.90 (s, 3H, H11); 1.78 (m, 2H, H1"); 1.58 (m, 2H, H3"); 1.38 (m, 4H, H2" and H4"). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.1, C7; 173.8, C1; 173.3, C4; 168.9, C10; 159.0, CN_3; 158.6, ArC4"'; 134.4, C2'; 131.4, C2""; 131.2, ArCH2"' and ArCH6"'; 130.4, ArC1"'; 118.9, C3'; 117.4, C3""; 115.7, ArCH3"' and ArCH5"'; 69.8, C1""; 56.5, C5; 54.1, OCH_3; 53.6, C8; 52.7, C2; 42.2, C5"; 37.9, $ArCH_2$; 36.7, C1'; 33.1, C1"; 29.6, C4"; 27.1, C3"; 26.0, C11; 22.3, C2". Mass Spectrum (ES, +ve) *m/z* 559 (100%) [M^+]. HRMS calcd for $C_{28}H_{43}N_6O_6$ 559.3244, found 559.3226.

Antibacterial Screening Methodology for Compounds of Example 2

Bacterial Strain

- All assays used the *Staphylococcus aureus* strain ATCC 6538P.
- Assays described in Chapter 5 additionally used the vancomycin-resistant enterococci and vancomycin-sensitive enterococci strains E*f*243, E*f*449, E*f*820 and E*f*487.

Culture Media

- **Mueller-Hinton Broth Medium (MHB):** MHB (Oxoid CM405) was prepared with final concentrations of 1 μg/mL $MgCl_2$ and 2 μg/mL $CaCl_2$. Culture medium was pre-warmed for approximately 2-3 h at 37°C before use.
- **Mueller-Hinton Agar Medium (MHA):** MHB containing 1.5% Agar (Merck Agar 1.01614).

Maintenance of Bacteria

- From a thawed cryovial, the bacteria was streaked onto MHA and the plate incubated overnight at 37°C.
- From this plate, 10 cryovials were prepared by looping several colonies into 0.5 mL of 20% glycerol solution. The cryovials were immediately stored at -140°C.

Preparation of Seed Cultures

- A cryovial was removed from -140°C storage and thawed at room temperature.

- An MHA plate was streaked with a loopful of bacterial suspension and incubated overnight at 37°C to create a parent plate (P1).
- A daughter plate (D1) was streaked from the parent plate and incubated overnight at 37°C. The parent plate was stored at 4°C.
- A loop of colony from the daughter plate was used to innoculate a 125 mL flask containing 20 mL of MHB containing 25 µg/mL $CaCl_2.2H_2O$ and 12.5 µg/mL $MgCl_2.6H_2O$.
- The flask was shaken at 260 rpm for 18 h at 37°C on an orbital incubator shaker.
- The parent plate (P1) was reused within 9 days to generate another daughter plate (D2), which was used to inoculate a broth culture.
- Parent plates were used twice (to generate D1 and D2 plates) before a new one was prepared from the previously thawed cryovial. The second parent plate (P2) was used to generate two additional daughter plates using the procedure outlined above before being discarded.
- Cryovials were used twice to prepare parent plates (P1 and P2) before being discarded.

Preparation of Standardized Inocula for Assays

- A 1/10 dilution of seed cultures was prepared by adding 250 µL of the cultures to 2,250 µL of MHB in a disposable cuvette.
- The OD_{650} was read and multiplied by a factor of 10 to calculate the optical density of the undiluted culture.
- The required dilution factor for the preparation of standardized inocula was calculated by dividing the observed OD_{650} by the standard OD_{650} (previously determined as an OD_{650} of 4.75 from optimization studies).
- A 10 mL sample of standardized inocula was prepared as illustrated by the following example:

Sample calculation:

OD_{650} = 0.492 (1/10 dilution)

10 x 0.492 = 4.92

as; 4.75/4.92 = 0.97

- Add 0.97 mL of *S. aureus* seed culture to 9.03 mL of MHB as the first dilution.
- Sufficient volumes of the final inoculum cultures were prepared in pre-warmed MHB (37°C) by diluting the standardized cultures to the required final concentration (*S. aureus* required a 10^8 dilution).

Assay Procedure (for 96-well Microtitre Plates)

- To each well of the 96-well microtitre plate was added 50 µL of liquid medium.

- The peptoid compounds to be tested were dissolved in a 50% MeOH/H_2O solution to give a concentration of 1 mg/mL
- 50 µL of test solution was added in triplicate to the top row of the microtitre plate (2 peptoid samples were tested per plate). A vancomycin control set (triplicate) and a compound negative control set (triplicate) were also included on each plate (Figure 1).
- The inoculated culture medium was incubated at 37°C for 30 min, with shaking at 130 rpm.
- Using a multichannel pipette, the contents of the first row were mixed before 50 µL was transferred to the second row. The pipette tips were changed and the process repeated by 50 µL of the mixed broth solutions in the second row being transferred to the third row. This process was repeated until the last row contained either the diluted test compound or a control (vancomycin or compound-negative). 50 µL was discarded from this final row so that each well contained 50 µL of liquid medium.
- Using a multistepper pipette, 50 µL of the inoculum was added to each well of the plate except for the last row in the compound-negative control set, which received 50 µL of liquid broth.
- The plates were incubated at 37°C for 18 h, with shaking at 100 rpm in an environment of approximately 90% humidity.
- The results were recorded as the highest dilution of test compound that prevented bacterial growth (MIC).

Antibacterial Testing of compounds of Example 2

Introduction

The specific testing procedures and protocols are outlined in the section "Antibacterial Screening Methodology for the Compounds of Example 2". The antibacterial testing was performed on a vancomycin-susceptible strain of *S. aureus*, and compounds that showed promising activity were subsequently tested against a variety of vancomycin resistant and vancomycin sensitive enterococcal strains (*Enterococcus faecium*) (see Chapter 5).

Antibacterial Testing Results

The antibacterial activity results are measured by minimum inhibitory concentration (MIC), which is the lowest concentration of compound necessary to prevent bacterial growth. The activities ranged from MIC 7.8 µg/mL for compound **75** to MIC >125 µg/mL (inactive) for a number of compounds. Some testing was done in the earlier stages of the project at higher concentration ranges up to 500 µg/mL, while later testing was performed with an upper limit of 125 µg/mL. For consistency, activity values greater than 125 µg/mL have been designated inactive, whilst an activity of 125 µg/mL is considered weakly active. Vancomycin was used as the standard/control and typically had an MIC range of 1.25-2.5 µg/mL. The antibacterial testing results for *S. aureus* are tabulated in Table 1.

Table 1: Tabulated antibacterial testing results on *S. aureus*

Compound	Antibacterial activity (MIC μg/mL)
69	125
70	125
71	125
72	125
73	31.3
74	15.6
75	7.8
76	15.6
77	125
83	125
12	62.5
43	125
48	125
32	62.5
37	125
65	15.6
56	125

Antibacterial Testing of Linear Cationic Peptides of Example 2

Introduction

The antibacterial testing was performed using the same protocols as those used previously described in the section "Antibacterial Testing of compounds of Example 2", using a vancomycin-susceptible strain of *S. aureus*, and an additional three strains of vancomycin-sensitive or partially sensitive enterococci (*E.f*243 , *E.f*449 and *E.f*987: vancomycin MIC 1.95, 62.5 and <0.98 μg/mL respectively) and one fully vancomycin-resistant *Enterrococci faecium* strain (*E.f*820: vancomycin MIC >125 μg/mL).

Antibacterial Testing Results

The testing results again are measured by minimum inhibitory concentration (MIC), on a scale from 0.98 μg/mL to 125 μg/mL. Vancomycin was used as the standard/control. The antibacterial testing results for the linear cationic peptides are described in Tables 2 and 3

Table 2

Compound	Antibacterial activity μg/mL				
	S.a	*E.f*243	*E.f*449	*E.f*820	*E.f*987
Vancomycin	1.95	1.95	62.5	>125	<0.98
118	31.3	>125	>125	>125	>125
119	15.6	>125	>125	>125	>125
120	3.9	62.5	62.5	62.5	62.5
121	7.8	125	125	125	>125
132	3.9	31.3	31.3	31.3	62.5
90	1.95	31.3	31.3	31.3	31.3
134	3.9	62.5	62.5	62.5	125
135	7.8	125	62.5	62.5	125
136	7.8	125	62.5	62.5	125
137	3.9	62.5	31.3	31.3	62.5
138	3.9	31.3	15.6	15.6	31.3
139	15.6	>125	>125	>125	>125
140	7.8	>125	>125	>125	>125
141	3.9	31.3	31.3	31.25	62.5

Table 3

Compound	Antibacterial activity µg/mL				
	S.a	*E.f*243	*E.f*449	*E.f*820	*E.f*987
155	7.8	>125	125	125	>125
156	3.9	125	125	62.5	62.5
157	15.6	>125	125	125	>125
158	7.8	62.5	62.5	31.3	62.5
159	62.5	125	125	62.5	>125
160	7.8	62.5	62.5	62.5	125
161	15.6	-	-	62.5	-
162	3.9	>125	>125	>125	>125
163	15.6	>125	>125	>125	>125
164	7.8	>125	>125	>125	>125

Testing of Compounds of Example 2 Against the HIV Integrase Enzyme

HIV Integrase Initial Screening Results

Compounds synthesized in Example 2 were additionally included in a random database screening strategy against the HIV integrase enzyme.

The compounds that were chosen to be tested against HIV integrase were **78, 81, 88** and **89** and the results are represented in Table 4.

Table 4

Compound	Conc. (µg/mL)	% Inhibition
78	50	15%
81	50	70%
88	50	95%
89	50	4%

These results represent promising hits as the compounds are significantly different in structure from previously known HIV integrase inhibitors. These results formed a preliminary set of structure activity relationships (SAR's) with regard to the stereochemistry of the amino acid residues and the length and functionality of the basic side-chain.

Testing Against the HIV Integrase Enzyme

The results for the screening of the four target molecules **165-168** against the HIV integrase enzyme yielded some encouraging results which supported the proposed mechanism of binding in the active binding trench of the HIV integrase enzyme. The testing procedure for the four target compounds differed from the original screening protocols employed. The original screening measured inhibition against the 3' processing function of the enzyme at the fixed concentration of 50 μg/mL, whereas the four target molecules were tested in an assay adapted from a literature procedure,[107] which measures inhibition against the 3' strand transfer function of the enzyme. This allows a result to be obtained as an inhibition constant (IC_{50}) concentration, which is the standard measurement of inhibition within the literature. Along with the four target molecules, **88** was also re-tested in the 3' strand transfer assay to determine the IC_{50} for direct comparison with the literature. The results for the testing of the four target molecules and the re-testing of **88** against HIV integrase are summarized in Table 5.

Table 5

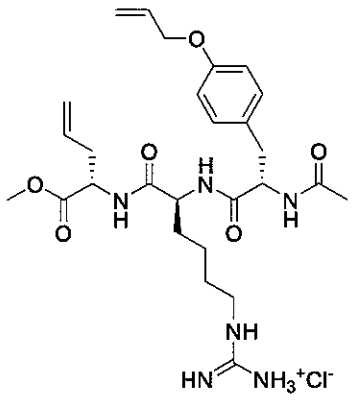
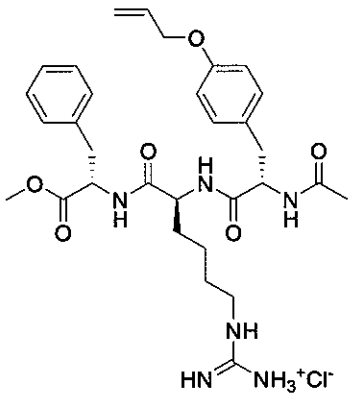
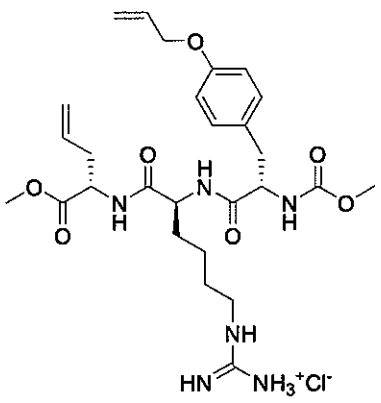
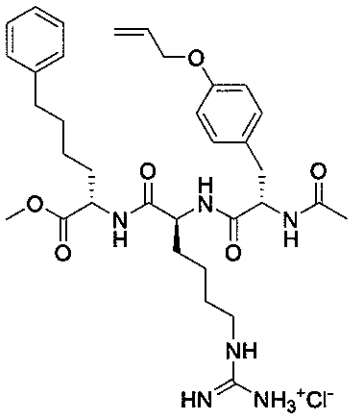
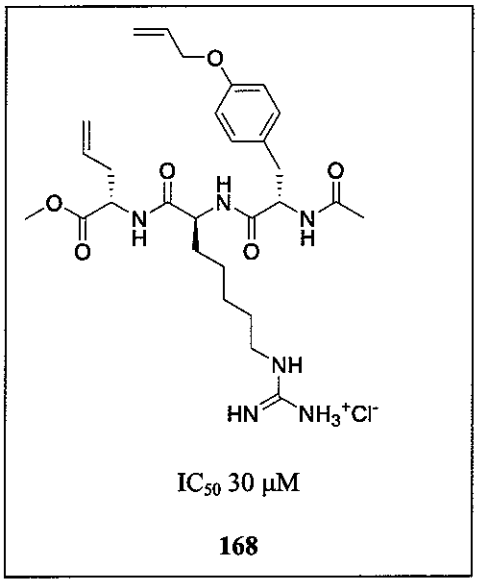
Compound	
 IC_{50} 12 μM **88**	 IC_{50} 60 μM **165**
 IC_{50} 50 μM **166**	 30% inhibition at 100 μM **167**

Table 5 Cont.

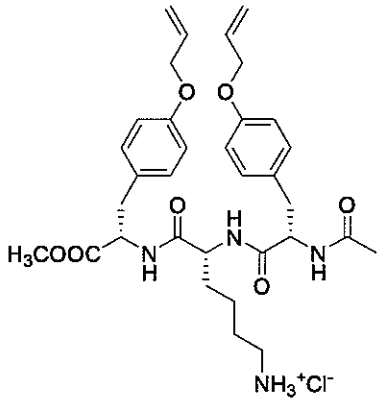
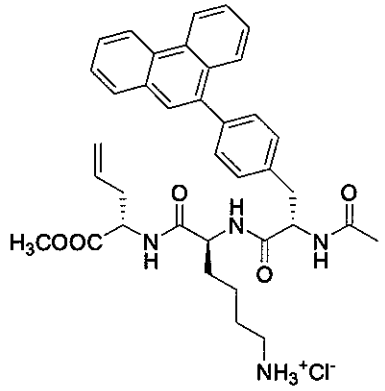
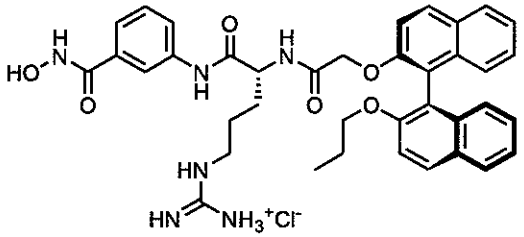
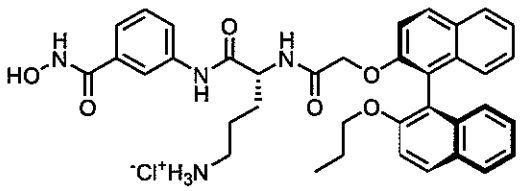


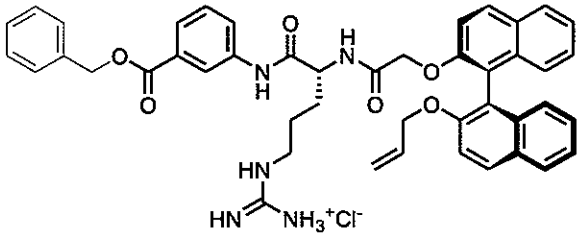
IC_{50} 30 μM

168

After these compounds and the computer modelling studies had become established, all compounds that were sent for screening in the antibacterial assay were then also cross tested for their ability to inhibit the HIV integrase enzyme. Several compounds are active with moderate levels of inhibition and compound **163**, one of the hydroxamic acid binaphthyl derivatives, appears to be almost as active as the original lead **88**, and is again structurally unique with the large hydrophobic binaphthyl moiety. The results of these compounds are summarized in Table 6.

Table 6

Compound	
	
IC_{50} 55 μM	IC_{50} 41 μM
83	**119**
	
IC_{50} 25 μM	IC_{50} 15 μM
164	**163**



IC_{50} 95 μM

158

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

All publications mentioned in this specification are herein incorporated by reference. Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed anywhere before the priority date of each claim of this application.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

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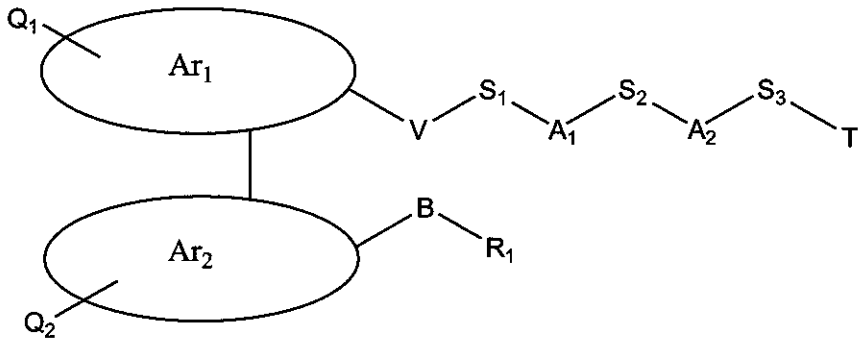
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CLAIMS

1. A compound of formula I,



I

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

B is selected from –O-, -S-, -S(O)-, -$S(O)_2$-, -NH-, and –N(C_1-C_6alkyl)-;

R_1 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkylC_6-C_{10}aryl, C_2-C_6alkenyl, C_2-C_6alkynyl, a polyoxyalkylene having from 2 to 6 carbon atoms, and when B is -S-, -S(O)-, -$S(O)_2$-, -NH- or –N(C_1-C_6alkyl)- then R_1 may be hydroxyl;

V is a linker group selected from –O-,–O-L-C(O), -O-L-NR_6-, -C(O)-, -NR_6-, -S(O)-, -$S(O)_2$-, -O-L-S(O)-, -$S(O)_2$-L-C(O)-, -$S(O)_2$-L-NR_6-, $P(O)_2O$-;

wherein L is selected from C_1-C_{12}alkyl, C_2-C_8 alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10}aryl and C_1-C_6alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12}alkyl;

A_1 and A_2 are the same or different and are basic amino acid residues;

each of S_1, S_2 and S_3 is either present or absent and is an independently selected amino acid residue;

T is present or absent and is selected from –C(O)OR_8, -OR_8, -NHR_8, $NHOR_8$, -NH-C_6aryl-CO-R_8, -NH-C_6aryl-CO-NHR_8, -NH-C_6aryl-$CONHOR_8$, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

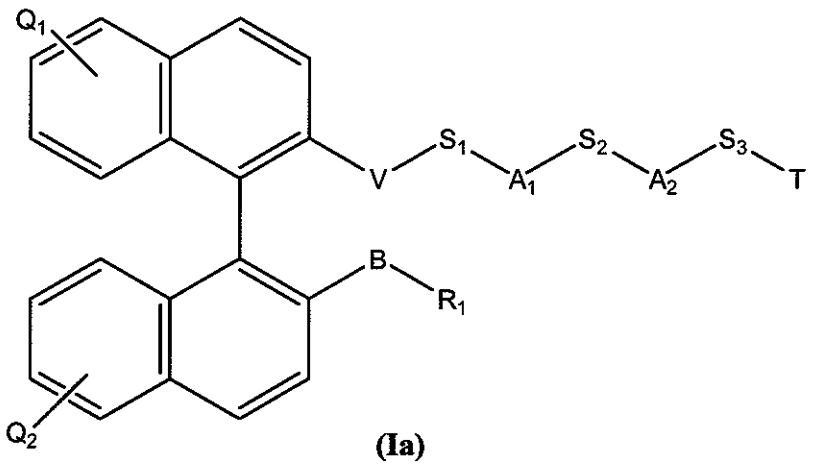
wherein when T is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

2. A compound according to claim 1 wherein A_1 and A_2 are each independently selected from the group consisting of lysine, arginine and ornithine.

3. A compound according to claim 2 wherein A_1 is selected from lysine and ornithine and A_2 is selected from arginine.

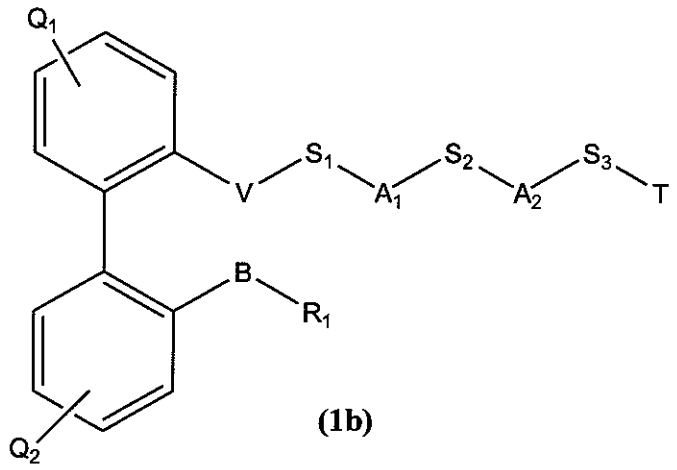
4. A compound according to any one of claims 1 to 3 wherein S_1 and S_2 are absent.

5. A compound according to any one of claims 1 to 4 wherein the compound of formula I is of formula Ia.



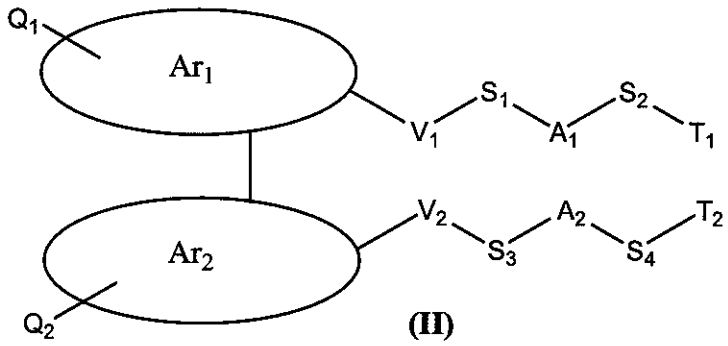
(Ia)

6. A compound according to any one of claims 1 to 4 wherein the compound of formula I is of formula Ib.



(1b)

7. A compound of formula II,



(II)

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

each of V_1 and V_2 is a linker group independently selected from –O-,–O-L-C(O), -O-L-NR_6-, -C(O)-, -NR_6-, -S(O)-, -$S(O)_2$-, -O-L-S(O)-, -$S(O)_2$-L-C(O)-, -$S(O)_2$-L-NR_6-, -$P(O)_2$O-;

wherein L is selected from C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10}aryl and C_1-C_{16}alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12}alkyl;

A_1 and A_2 are the same or different and are basic amino acid residues;

each of S_1, S_2, S_3 and S_4 is either present or absent and is an independently selected amino acid residue;

T_1 is either present or absent and is independently selected from -C(O)OR_8, -OR_8, -NHR_8, -$NHOR_8$, -NH-C_6aryl-COR_8, -NH-C_6aryl-$CONHR_8$, -NH-C_6aryl-$CONHOR_8$, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T1 forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T1 is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T1 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene;

T_2 is either present or absent and is independently selected from -C(O)OR_9, -OR_9, -NHR_9, $NHOR_9$, -NH-C_6aryl-CO-R_9, -NH-C_6aryl-CO-NHR_9, -NH-C_6aryl-$CONHOR_9$, -NH-C_6aryl-CONHOH, -C(O)NHR_8, -(NH)-SO_2C_6aryl, -(NH)COR_8;

or T_2 forms a carboxylate isostere, optionally substituted with R_9, which replaces the carboxylic acid group of the amino acid to which T_2 is connected;

wherein R_9 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

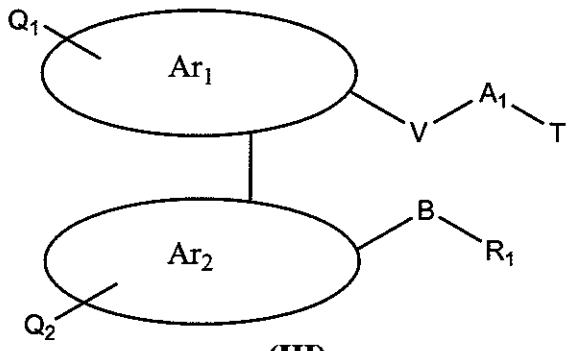
wherein when T_2 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

8. A compound according to claim 7 wherein A_1 and A_2 are each independently selected from the group consisting of lysine, arginine and ornithine.

9. A compound according to claim 7 or claim 8 wherein A_1 and A_2 are the same.

10. A compound according to any one of claims 7 to 9 wherein S_1, S_2, S_3 and S_4 are absent.

11. A compound of formula III,



(III)

or pharmaceutically acceptable derivatives thereof, wherein:

Ar_1 and Ar_2 are each independently selected from an aromatic or heterocyclic ring system or partially or fully reduced derivatives thereof;

Q_1 and Q_2 are each independently selected from hydrogen, C_1-C_{12}alkyl, C_3-C_6cycloalkyl, C_1-C_{12}alkyloxy, nitro, halogen, hydroxyl, amino, mono or dialkylamino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide wherein each C_1-C_{12}alkyl, C_1-C_{12}alkyloxy or C_3-C_6cycloalkyl is optionally substituted with hydroxyl, amino, carboxylic acid or a salt or ester thereof, sulphonic acid or a salt or ester thereof, phosphoric acid or a salt or ester thereof, or a nitrogen containing group such as carboxamide, sulphonamide or phosphoramide;

B is selected from –O-, -S-, -S(O)-, $-S(O)_2$-, -NH-, and $-N(C_1$-C_6alkyl)-;

R_1 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkylC_6-C_{10}aryl, C_2-C_6alkenyl, C_2-C_6alkynyl, a polyoxyalkylene having from 2 to 6 carbon atoms, and when B is -S-, -S(O)-, $-S(O)_2$-, -NH- or $-N(C_1$-C_6alkyl)- then R_1 may be hydroxyl;

V_1 is a linker group selected from selected from –O-, –O-L-C(O), -O-L-NR_6-, -C(O)-NR_6-, -S(O)-, $-S(O)_2$-, -O-L-S(O)-;,$-S(O)_2$-L-C(O)-, $-S(O)_2$-L-NR_6-, $P(O)_2O$-

wherein L is selected from C_1-C_{12}alkyl, C_2-C_8alkenyl, C_3-C_6cycloalkyl, polyoxyalkylene having from 2 to 6 carbon atoms, C_6-C_{10} aryl and C_1-C_6alkylC_6-C_{10}aryl and wherein R_6 is selected from H, C_1-C_{12} alkyl;

A_1 is a is a basic amino acid residue;

each of S_1 and S_2 is either present or absent and is an independently selected amino acid residue;

T is present or absent and is selected from –
$C(O)OR_8$, $-OR_8$, $-NHR_8$, $-NHOR_8$, -NH-C_6aryl-COR_8, -NH-C_6aryl-$CONHR_8$, -NH-C_6aryl-$CONHOR_8$, -NH-C_6aryl-CONHOH, $-C(O)NHR_8$, -(NH)-SO_2C_6aryl, -(NH)COR_8;

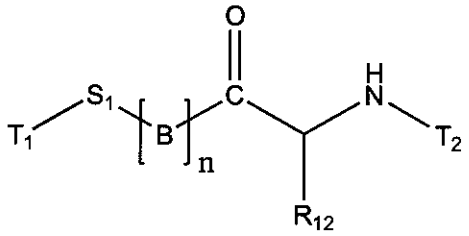
or T forms a carboxylate isostere, optionally substituted with R_8, which replaces the carboxylic acid group of the amino acid to which T is connected;

wherein R_8 is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene.

12. A compound according to claim 11 wherein A_1 is selected from lysine, arginine and ornithine.

13. A compound of formula IV,



IV

or pharmaceutically acceptable derivatives thereof, wherein

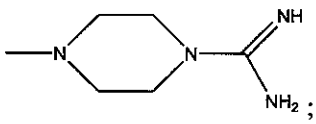
R_{12} is an alkylaromatic or alkylpolyaromatic group optionally substituted with -OC_{1-6}alkyl or -OC_{2-6}alkenyl;

each B is a basic amino acid residue;

n = 1 or 2;

S_1 is present or absent and is an independently selected amino acid residue;

T_1 is selected
from $-NHR_{13}$, $-NHOR_{13}$, -NH-C_6aryl-COR_{13}, -NH-C_6aryl-$CONHR_{13}$, -NH-C_6aryl-$CONHOR_{13}$,



-NH-C_6aryl-CONHOH, -(NH)-SO_2C_6aryl, -(NH)COR_{13} or ;

or T1 forms a carboxylate isostere, optionally substituted with R_{13}, which replaces the carboxylic acid group of the amino acid to which T1 is connected;

wherein R_{13} is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

wherein when T_1 is connected to the C-terminus of an amino acid residue then the carbonyl group of the amino acid residue may be reduced to methylene;

T_2 is selected from $-C(O)R_{14}$, $-C(O)OR_{14}$, $-OR_{14}$, $-C(O)NHR_{14}$;

wherein R_{14} is selected from hydrogen, C_1-C_{12}alkyl, C_1-C_6alkylC_6-C_{10}aryl, C_1-C_6alkylC_3-C_6cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, and CH_2-fluorene;

wherein the optional substituent of R_{12} and the side-chain of S1 may together form a -OC_{1-6}alkylene linking group.

14. A compound according to claim 13 wherein R_{12} is selected from–CH_2-phenyl-$OCH_2CH{=}CH_2$ and -CH_2-phenylanthracene.

15. A compound according to claim 13 or 14 wherein S_1 is selected from allylglycine.

16. A compound according to any one of claims 13 to 15 wherein T_2 is $-C(O)CH_3$.

17. A compound according to any one of claims 13 to 16 wherein T_1 is CH_3O-.

18. A compound according to any one of claims 13 to 17 wherein B is lysine or arginine.

19. A compound of Example 2.

20. A compound according to claim 19 wherein the compound of Example 2 is selected from **69**, **70**, **71**, **72**, **73**, **74**, **75**, **76**, **83**, **32**, **37**, **65**, **56**, **118**, **119**, **120**, **121**, **132**, **90**, **134**, **135**, **136**, **137**, **139**, **140**, **141**, **159**, **160**, **163**, **164**, **78**, **81**, **88**, **87**, **89**, **165**, **166**, **167**, and **168**.

21. A composition comprising a compound according to any one of claims 1 to 20, a salt or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers or adjuvants.

22. A method of treating a bacterial infection in a mammal comprising administering an effective amount of compound according to any one of claims 1 to 20, a salt or a pharmaceutically acceptable derivative thereof.

23. Use of a compound according to any one of claims 1 to 20 in the preparation of a medicament for treating or preventing bacterial infection.

24. A method for treatment or prophylaxis of HIV in a subject comprising administering to said subject an effective amount of a compound according to any one of claims 1 to 20, a salt or a pharmaceutically acceptable derivative thereof.

25. A method according to claim 24 wherein the compound is selected from one or more of the following compounds of Example 2: **78**, **81**, **88**, **89**, **165**, **166**, **167**, **168**, **83**, **119**, **164**, **163**, **158**.