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Abstract

As part of a program investigating cyclic peptides with an internal aromatic hydrophobic scaffold as potential novel anti-bacterial agents, we explored the synthesis of simple tyrosine-based systems. These were prepared via key intermediates containing internal allylglycine and allyltyrosine residues for subsequent ring closing metathesis reactions. Although the resulting anti-bacterial activity against Staphylococcus aureus was modest, this represents a novel and simple route to this class of compounds. One intermediate acyclic dipeptide precursor showed good activity against S. aureus with an MIC of 7.8 μg/mL.

Keywords

cyclic peptide, anti-bacterial, cyclic peptoid, RCM, metathesis, peptide macrocycles

Disciplines

Life Sciences | Medicinal-Pharmaceutical Chemistry | Organic Chemistry | Physical Sciences and Mathematics | Social and Behavioral Sciences

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New Cyclic Peptides via Ring-Closing Metathesis Reactions and Their Anti-Bacterial Activities

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Abstract

As part of a program investigating cyclic peptides with an internal aromatic hydrophobic scaffold as potential novel anti-bacterial agents, we explored the synthesis of simple tyrosine-based systems. These were prepared *via* key intermediates containing internal allylglycine and allyltyrosine residues for subsequent ring closing metathesis reactions. Although the resulting anti-bacterial activity against *Staphylococcus aureus* was modest, this represents a novel and simple route to this class of compounds. One intermediate acyclic dipeptide precursor showed good activity against *S. aureus* with an MIC of 7.8 µg/mL.

1. Introduction

The need for new, novel anti-bacterial agents is becoming increasingly important with the escalating number of cases of multi-drug resistant bacterial infections being reported.[1,2] A number of compounds targeting these resistant strains have recently been reported, *e.g.* linezolid,[3] however, resistance to these new molecules has already started to emerge.[4-6] Vancomycin has long been cast as the drug-of-last-resort and has been in use for a number of years, despite the increasing prevalence of VRE (vancomycin resistant *Enterococci*)[7] and now vancomycin resistant *Staphylococcus aureus*.[8] The complicated ring systems of vancomycin limits investigations into extensive structure-activity relationships based on the parent structure. Therefore, we instigated a programme investigating the synthesis of potential anti-bacterial agents using some structural elements of vancomycin, but dramatically simplifying the hydrophobic scaffold to simple moieties that hold a tripeptide in a defined conformation. Thus far, we have reported cyclic peptides containing hydrophobic scaffolds based on 1,1′-binaphthyls,[9] carbazoles,[10,11] indoles[12] and benzo[*b*]thiophenes[13] with numerous derivatives showing significant anti-bacterial activity (Figure 1). We report here the synthesis and anti-bacterial activity against *S. aureus* of an additional, simpler hydrophobic scaffold based on a phenyl unit, exemplified by the cyclic tripeptide **4**, together with acyclic peptide precursors of this system.

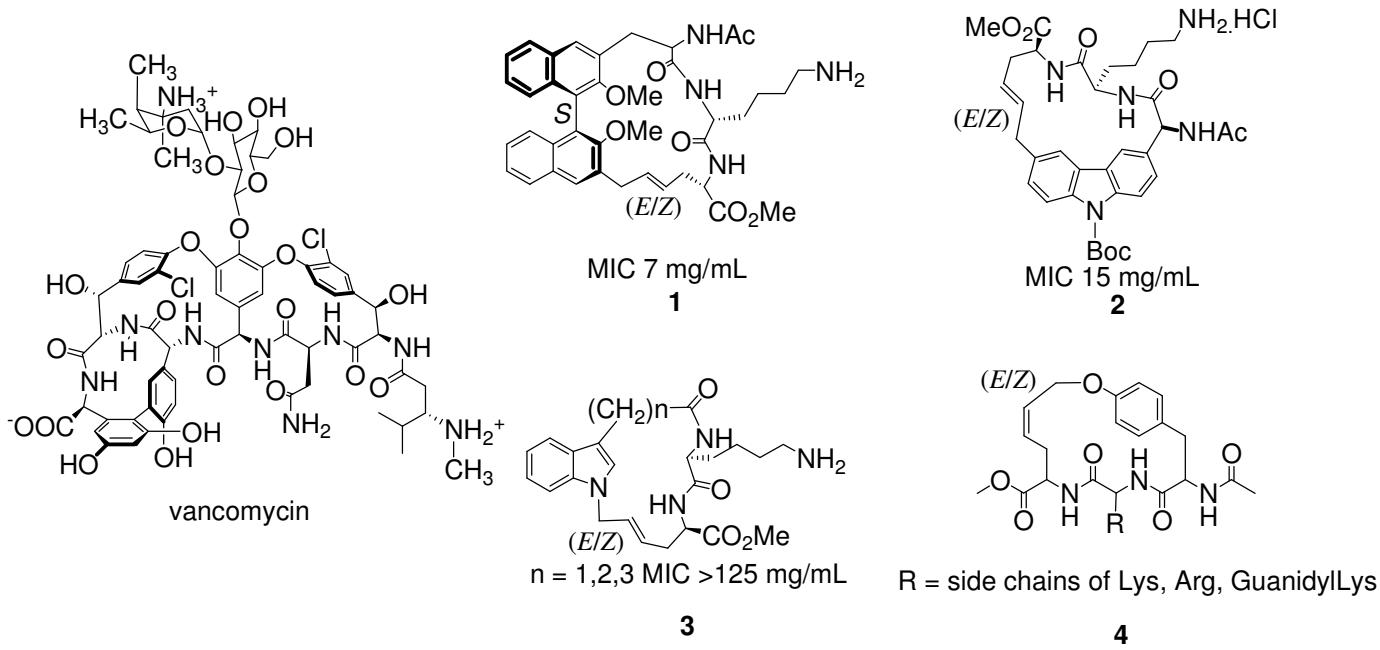
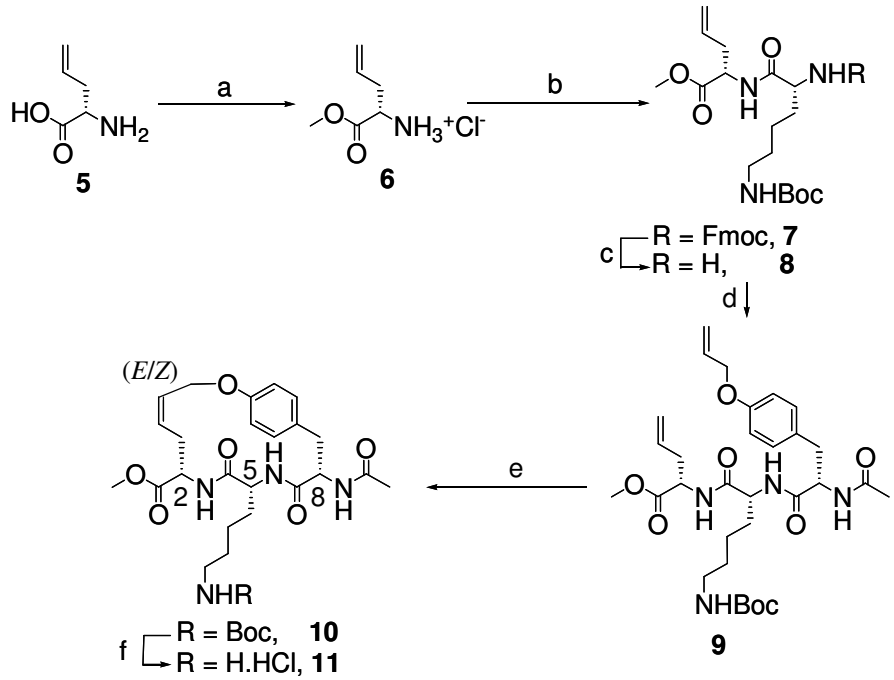


Figure 1

2. Results and Discussion

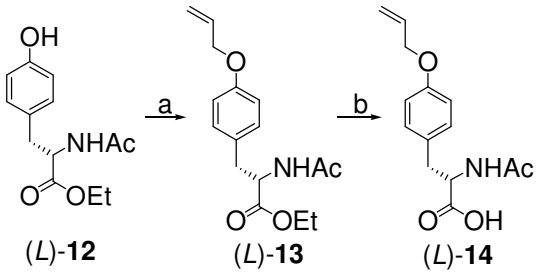
Our target structure is typified by the cyclic peptide **11** (Scheme 1), the hydrochloride salt of **4** (R = Lys or Arg side chains). The tripeptide precursor of **11** features a key protected terminal amino group-containing amino acid (Lys; in later work this was replaced by an Arg residue with a protected guanidino moiety) and an allyltyrosine which provides two roles: the aromatic moiety serves as the hydrophobic unit and the olefin enables the cyclisation to be undertaken via a reliable ring-closing metathesis (RCM) reaction[14] with the third unit of the tripeptide, an allylglycine unit. The modular synthetic strategy also allows for the rapid generation of analogues including variations in the amino acid configuration (*R* or *S*) as well as variations in the amino acid side-chains themselves, *e.g.* the RCM of two incorporated allyltyrosine units.

The synthesis of **11** was realized (Scheme 1) in a six-step sequence starting with commercially available L-allylglycine **5**. The acid **5** was esterified[15] using thionyl chloride in a solution of anhydrous methanol at 0 ^{o}C, to give **6** in quantitative yield. The synthesis of the dipeptide **7** used typical EDCI/HOBt peptide coupling conditions[16] reacting **6** with commercially available Fmoc-D-Lys(Boc)-OH and resulted in a 94% yield of **7** after column chromatography. Removal of the base labile Fmoc group from the dipeptide **7** was achieved using standard conditions[17] of a 1% piperidine/acetonitrile solution to yield the free amine **8** in 99% yield.

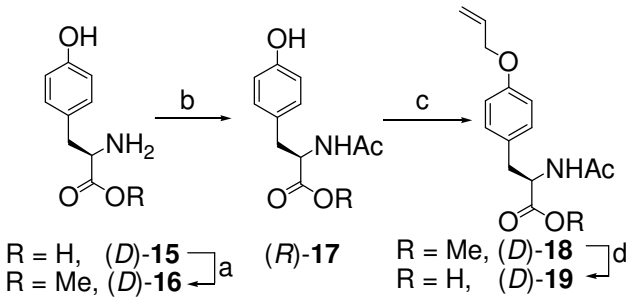


Scheme 1: Synthesis of Cyclic Peptides: a) MeOH, $SOCl_2$, 0 °C-RT, 16 h, 100%. b) Fmoc-D-Lys(Boc)-OH, EDCI, HOBt, DIPEA, DMF, 0 °C-RT, 16 h, 94%. c) 1% piperidine/CH_3CN, RT, 3 h, 99%. d) **14**, EDCI, HOBt, DMF, 0 °C-RT, 16 h, 69%. e) Grubbs [Ru] catalyst, benzylidene bis(tricyclohexylphosphine)dichlororuthenium, CH_2Cl_2, Δ, 48 h, 75%. f) i) TFA/ CH_2Cl_2 (1:1); ii) 1M HCl/ether, RT, 3 h, 49%.

We next required the N-protected allyltyrosine **14** which was generated by treating commercially available ethyl (2*S*)-2-acetamido-3-(4-hydroxyphenyl)propanoate **12** with K_2CO_3 and then allylbromide to produce the L-*O*-allyl-tyrosine derivative **13** in quantitative yield with no further purification required (Scheme 2). The ethyl ester of **13** was hydrolysed by reaction with 2 equivalents of LiOH in 3:1 THF-H_2O and afforded, after acidification, the free carboxylic acid **16** in quantitative yield (Scheme 2). The corresponding D-analogue of **14** was also required for the generation of analogues, but this required a slightly modified synthetic strategy based upon the commercial availability of compounds (Scheme 3). Therefore, the acid catalysed esterification of D-tyrosine **15** with thionyl chloride in methanol yielded the methyl ester **16** in quantitative yield as the ammonium salt which was then treated with 5 M sodium acetate at 0 ^{o}C to produce the free amine. Acetic anhydride was added to the aqueous solution and the *N*-acetyl derivative **17** precipitated in 76% yield. The last two steps of the synthesis were performed in the same manner as described for the synthesis of **13** and **14** to yield the corresponding D-analogues **18** and **19** in 85 and 88% yield, respectively.



Scheme 2: Synthesis of L-*N*-acetyl-*O*-allyltyrosine: a) allyl bromide, DMF, K_2CO_3, RT, 16 h, 100%. b) i. 2 eq. LiOH, THF/H_2O, RT, 16 h; ii. 10% HCl, 100%.



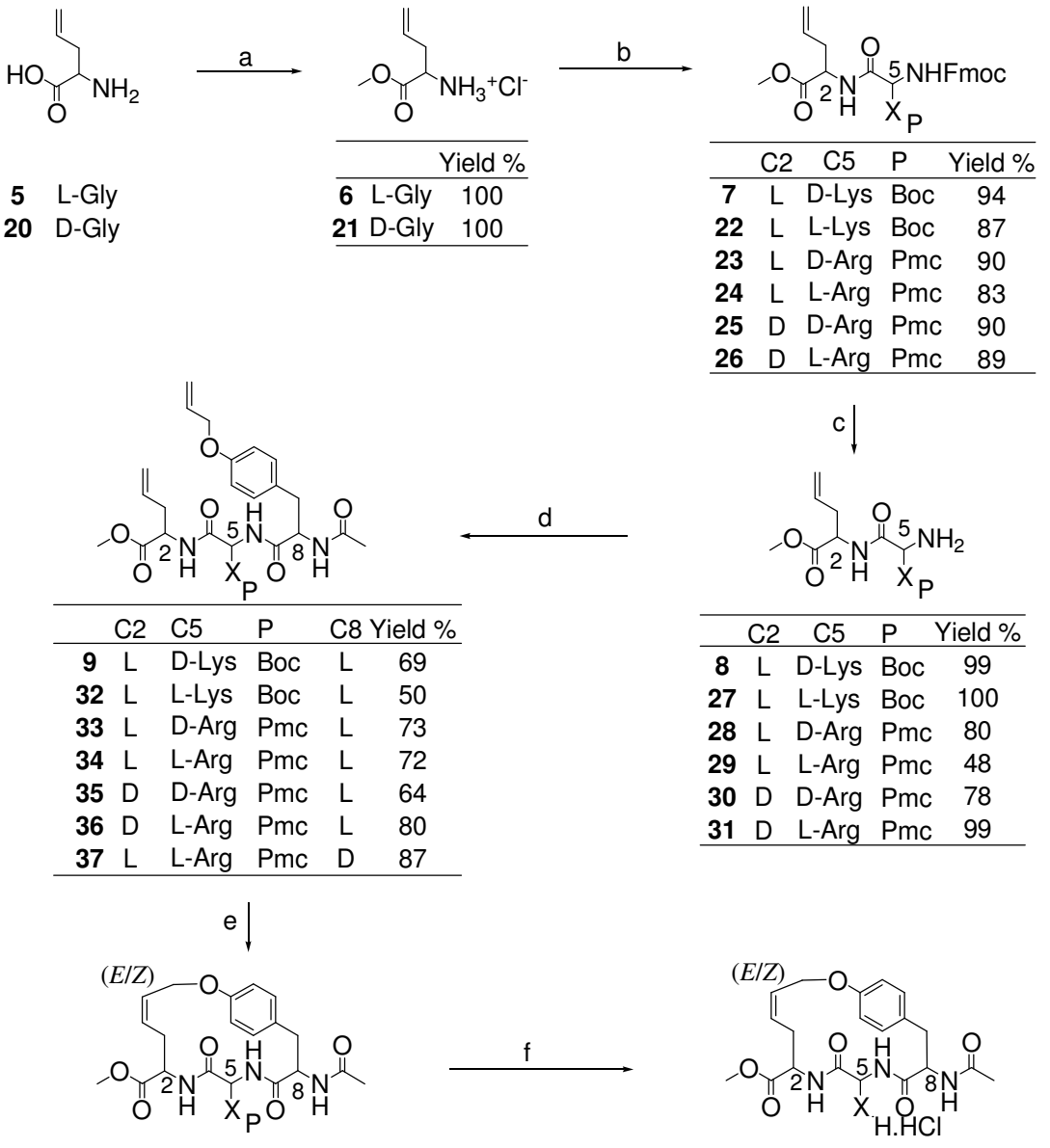
Scheme 3: Synthesis of D-*N*-acetyl-*O*-allyltyrosine: a) MeOH, $SOCl_2$, 0 °C-RT, 16 h, 100%. b) Ac_2O, NaOAc, 0 °C, 76%. c) allyl bromide, DMF, K_2CO_3, RT 16 h, 85%. d) LiOH, THF/H_2O, RT, 16 h, 88%.

The coupling of the α-amino dipeptide **8** to the allyltyrosine **14** (Scheme 8) used standard EDCI/HOBt peptide coupling conditions to yield **9** in 69% yield after purification by column chromatography. A ring closing metathesis (RCM) reaction of the peptide **9** with Grubbs′ first generation catalyst (benzylidene bis(tricyclohexylphosphene)dichlororuthenium) gave **10** as a mixture of *E* and *Z* isomers in 75% yield, which could not be separated. The *E*:*Z* ratio and alkene coupling constants could not be determined by analysis of the ^{1}H NMR spectra due to overlapping peaks, but all the spectroscopic data was consistent with the cyclic structure **10**. Subsequent Boc deprotection of **10** with TFA and anion exchange by treatment with HCl/ether followed by precipitation gave the amine hydrochloride salt **11** in 49% yield.

This modular approach to novel cyclic peptide synthesis allowed for the rapid generation of analogues to probe structure-activity relationships (SARs) upon testing for anti-bacterial activity. Therefore, we synthesised and tested a series of analogues that included:

a) Variations in the stereochemistry at C2 (D- and L-allylGly), C5 (D- and L-amino acids) and C8 (D- and L-allyltyrosine).
b) Variations in the C5 amino acid including the N-terminal side chains of Lys, Arg and *N*-guanidylLys.
c) Some of the N-deprotected acyclic di- and tripeptide intermediates synthesised.

d) The replacement of allylGly with a second allyltyrosine.



		Yield %
6	L-Gly	100
21	D-Gly	100

	C2	C5	P	Yield %
7	L	D-Lys	Boc	94
22	L	L-Lys	Boc	87
23	L	D-Arg	Pmc	90
24	L	L-Arg	Pmc	83
25	D	D-Arg	Pmc	90
26	D	L-Arg	Pmc	89

	C2	C5	P	Yield %
8	L	D-Lys	Boc	99
27	L	L-Lys	Boc	100
28	L	D-Arg	Pmc	80
29	L	L-Arg	Pmc	48
30	D	D-Arg	Pmc	78
31	D	L-Arg	Pmc	99

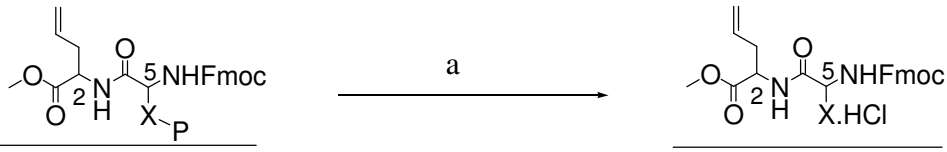
	C2	C5	P	C8	Yield %
9	L	D-Lys	Boc	L	69
32	L	L-Lys	Boc	L	50
33	L	D-Arg	Pmc	L	73
34	L	L-Arg	Pmc	L	72
35	D	D-Arg	Pmc	L	64
36	D	L-Arg	Pmc	L	80
37	L	L-Arg	Pmc	D	87

	C2	C5	P	C8	Yield %
10	L	D-Lys	Boc	L	75
38	L	L-Lys	Boc	L	76
39	L	D-Arg	Pmc	L	100
40	L	L-Arg	Pmc	L	95
41	D	D-Arg	Pmc	L	99
42	D	L-Arg	Pmc	L	86
43	L	L-Arg	Pmc	D	87

	C2	C5	C8	Yield %
11	L	D-Lys	L	49
44	L	L-Lys	L	79
45	L	D-Arg	L	91
46	L	L-Arg	L	59
47	D	D-Arg	L	35
48	D	L-Arg	L	86
49	L	L-Arg	D	34

Scheme 4: 'X' in structures represents the amino acid side chain as defined under 'C5' in the associated tables. a) MeOH, $SOCl_2$, 0 °C-RT, 16 h. b) Fmoc-D or L-Lys(Boc)-OH, EDCI, HOBt, DIPEA, DMF, 0 °C-RT, 16 h. c) 1% pip/CH_3CN, RT, 3 h. d) **14** or **19**, EDCI, HOBt, DMF, 0 °C-RT, 16 h. e) Grubb [Ru] catalyst - benzylidene bis(tricyclohexylphosphine)dichlororuthenium, CH_2Cl_2, Δ, 48 h. f) i. TFA/ CH_2Cl_2 (1:1) ii. 1M HCl/ether, RT, 3 h, 49%.

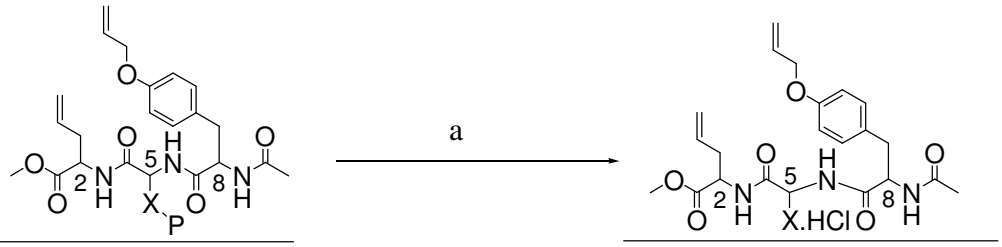
While not exhaustively producing all possible variations defined above, a selection of target compounds were synthesised using the same synthetic strategy as outlined in Scheme 1. Scheme 4 shows the generation of deprotected cyclic tyrosine-based molecules **11** and **44** – **49**. Schemes 5 and 6 summarise the deprotection of the intermediate di- and tripeptides respectively that were also tested for anti-bacterial activity. The acyclic *N*-guanidineLys derivatives **62** and **63** were also N-deprotected (Scheme 7) to allow for biological testing as their hydrochloride salts and the corresponding cyclic tyrosine versions of these derivatives were more conveniently synthesised from **10** and this is exemplified by the synthesis of **65** (Scheme 8).



	C2	C5	P
23	L	D-Arg	Pmc
24	L	L-Arg	Pmc
25	D	D-Arg	Pmc
26	D	L-Arg	Pmc

	C2	C5	Yield %
50	L	D-Arg	75
51	L	L-Arg	47
52	D	D-Arg	80
53	D	L-Arg	51

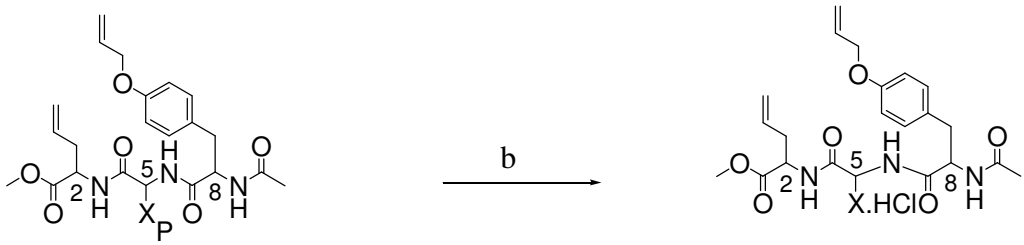
Scheme 5: Synthesis of the deprotected acyclic dipeptide derivatives. a) i) TFA/CH_2Cl_2, (1:1), ii. 1M HCl/ether, RT, 3 h. 'X' in structures represents the amino acid side chain as defined under 'C5' in the associated tables.



	C2	C5	P	C8
9	L	D-Lys	Boc	L
32	L	L-Lys	Boc	L
33	L	D-Arg	Pmc	L
34	L	L-Arg	Pmc	L
35	D	D-Arg	Pmc	L
36	D	L-Arg	Pmc	L

	C2	C5	C8	Yield %
54	L	D-Lys	L	37
55	L	L-Lys	L	60
56	L	D-Arg	L	74
57	L	L-Arg	L	85
58	D	D-Arg	L	100
59	D	L-Arg	L	56

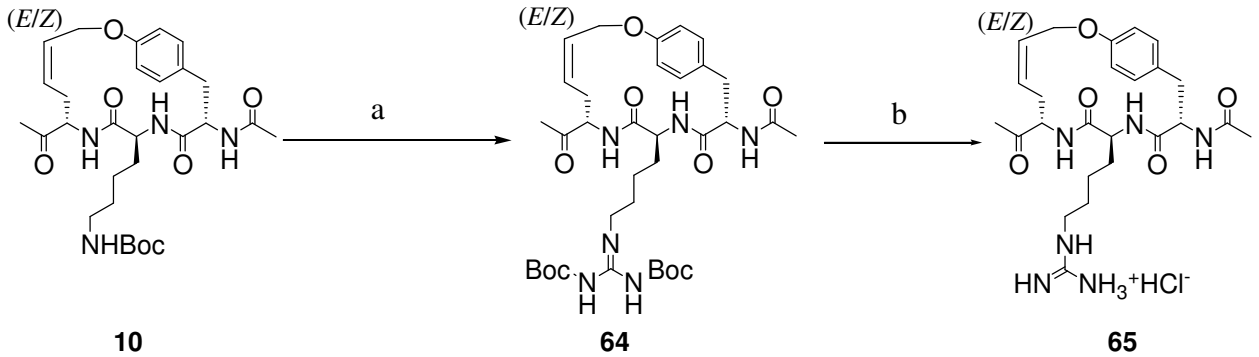
Scheme 6: Synthesis of the deprotected acyclic tripepetide derivatives. a) i) TFA/CH_2Cl_2, (1:1), ii. 1M HCl/ether, RT, 3 h. 'X' in structures represents the amino acid side chain as defined under 'C5' in the associated tables.



	C2	C5	P	C8	Yield %
9	L	D-Lys	Boc	L	-
32	L	L-Lys	Boc	L	-
60	L	D-*N*-guanidineLys	diBoc	L	100
61	L	L-*N*-guanidineLys	diBoc	L	74

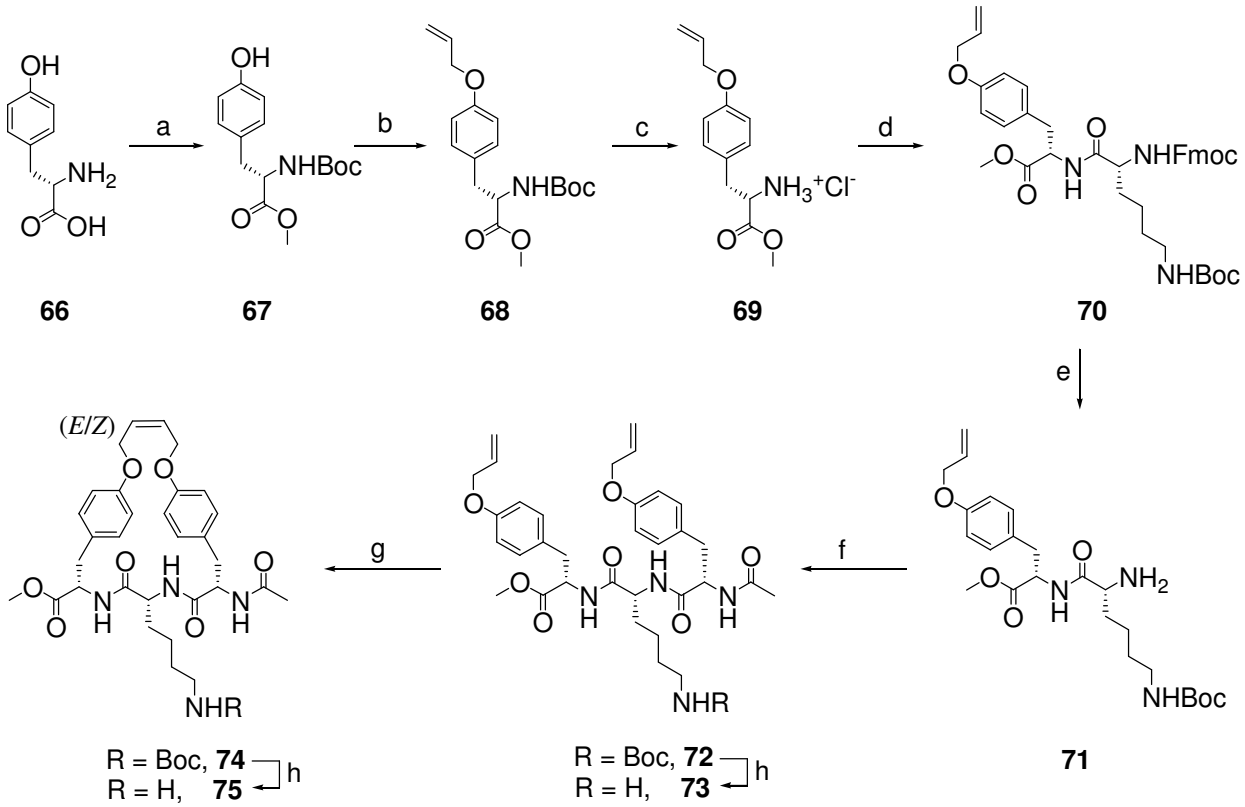
	C2	C5	C8	Yield %
62	L	D-*N*-guanidineLys	L	78
63	L	L-*N*-guanidineLys	L	35

Scheme 7: Synthesis of the deprotected acyclic tripeptide derivatives containing the guanidated lysine amino acid side chain. a) i. TFA, CH_2Cl_2 (1:1); ii. Tf-N=C(NHBoc)$_2$, Et_3N, RT, 16 h. b) i) TFA/CH_2Cl_2, (1:1), ii. 1M HCl/ether, RT, 3 h. 'X' in structures represents the amino acid side chain as defined under 'C5' in the associated tables.

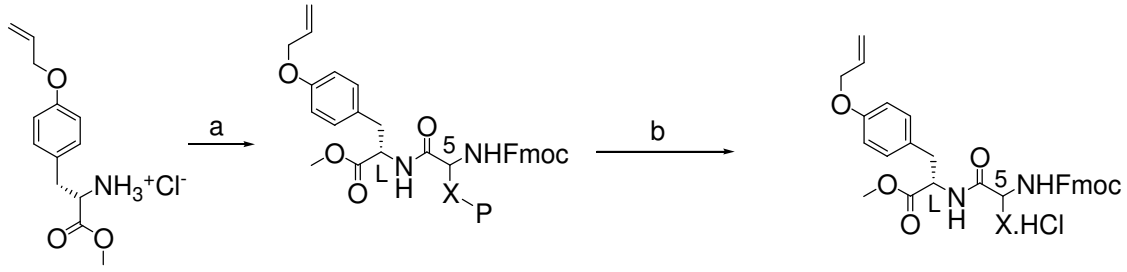


Scheme 8: Synthesis of the cyclic tripeptide containing the guanidated lysine amino acid side chain. a) i. TFA/CH_2Cl_2 (1:1), ii) Tf-N=C(NHBoc)$_2$, Et_3N, RT,16 h. b) i. TFA/CH_2Cl_2, (1:1), ii. 1M HCl/ether, RT, 3 h, 87% (2 steps).

The synthesis of the cyclic tripeptides containing two tyrosine residues is outlined in Scheme 9. This necessitated access to the ester protected allyltyrosine **69** which was generated analogously to those established in the synthesis of the tyrosines **14** and **19** (Schemes 2 and 3). The completion of the synthesis of the cyclic dityrosine derivatives also used standard conditions as indicated in Scheme 9. Some acyclic tyrosine dipeptides **70** - **82** were also generated to supplement SAR studies and these are summarised in Scheme 10.



Scheme 9: a) i) MeOH, $SOCl_2$, 0 °C-RT, 16 h; ii) $(Boc)_2O$, DMF, RT; 16% (2 steps) b) allyl bromide, DMF, K_2CO_3, RT 16 h, 76%. c) TFA/CH_2Cl_2 (1:1) ii. 1 M HCl/ether, RT, 3 h, 100% d) Fmoc-D-Lys(Boc)-OH, EDCI, HOBt, DIPEA, DMF, 0 °C-RT, 16 h, 75%. e) 1% pip/CH_3CN, RT, 3 h, 97%. f) **14**, EDCI, HOBt, DMF, 0 °C-RT, 16 h, 37%. g) Grubbs [Ru] catalyst - benzylidene bis(tricyclohexylphosphine)dichlororuthenium, CH_2Cl_2, Δ, 48 h, 41%. h) i. TFA/CH_2Cl_2 (1:1) ii. 1M HCl/ether, RT, 3 h, 49%.



	C5	P	Yield %
70	D-Lys	Boc	75
76	L-Lys	Boc	77
77	D-Arg	Pmc	71
78	L-Arg	Pmc	84

	C5	Yield %
79	D-Lys	79
80	L-Lys	68
81	D-Arg	79
82	L-Arg	83

Scheme 10: Synthesis of the L-allyltyrosine dipeptide derivatives: a) Fmoc-D- or L-Lys(Boc)-OH *or* Fmoc-D- or L-Arg(PMC)-OH, EDCI, HOBt, DIPEA, DMF, 0 °C-RT, 16 h. b) i. TFA/CH_2Cl_2 (1:1) ii. 1M HCl/ether, RT, 3 h. 'X' in structures represents the amino acid side chain as defined under 'C5' in tables.

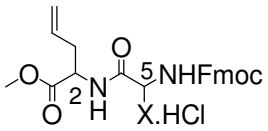
3. Anti-bacterial Testing Results

The anti-bacterial activity results against *S. aureus* ATCC6538P (Figure 2) were measured as minimum inhibitory concentration (MIC), the lowest concentration of compound necessary to prevent bacterial growth. The activities ranged from an MIC of 7.8 μg/mL for compound **81** to an MIC >125 μg/mL (inactive) for a number of compounds. Vancomycin was used as the standard/control and typically had an MIC range of 1.25-2.5 μg/mL.

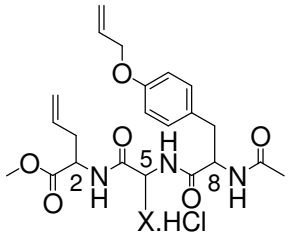
The most active cyclic compound tested was the dityrosine peptide **75**, which had a moderate activity of 15.6 μg/mL. As expected, the D-lysine cyclic peptide **11**, which is conformationally similar to the binaphthyl lead compound **1** (Figure 1), had moderate activity (MIC 62.5 μg/mL) and was the most active of the mono-tyrosine compounds. The D-arginine and D-lysine cyclic peptides (**45** and **11** respectively) had the same activity indicating no advantage in arginine over lysine as the basic residue, although the lack of activity with the presence of the homoarginine sidechains suggests an optimum chain length for antibacterial activity. Generally the presence of a *C*-terminal residue L-amino acid residue and an adjacent D-amino acid with a basic residue gives rise to better activity, *e.g* **49** versus **45** versus **48**.

The greatest activity was found, unexpectedly, with the dipeptide intermediate **81** which was as active as the binaphthyl lead compound **1** with an MIC of 7.8 μg/mL. This can be attributed to the Fmoc group acting as a hydrophobic scaffold, in a similar manner to the binaphthyl moiety of **1**. As the molecule also contains a protonated sidechain it meets our previously established criteria for antibacterial activity. This compound also has the minimal structural features consistent with the anti-staphylococcal pharmacophore proposed for short cationic peptides[18] The other dipeptide analogues featuring *O*-allyltyrosine (**79**, **80** and **82**) as the *C*-terminal residue instead of C2-allylglycine (**50**-**53**) also resulted in promising antibacterial activity (MIC 15.6-31.5 μg/mL). The allylglycine analogues, with either the D- or L-configuration, all showed poor anti-bacterial activity (MIC of 125 μg/mL) significantly less active than the corresponding *O*-allyltyrosine compounds Indicating that some form of hydrophobic moiety is required at the *C*-terminal end. The tripeptide acyclic intermediates failed to produce any significant anti-bacterial activity.

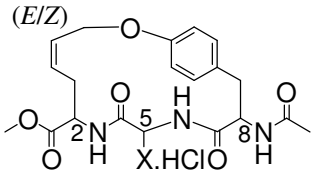
The location of the *O*-allyltyrosine residue at the *C*-terminus is more favourable than a C2-allylglycine residue (*e.g.* **81** *vs* **51**) suggesting that a hydrophobic entity is required for optimum activity at this end of the molecule. The acyclic dipeptides also show a preference for arginine over lysine basic side chains. These smaller dipeptides have a degree of conformational freedom and it is most likely beneficial, and synthetically easier, to develop smaller acyclic compounds.



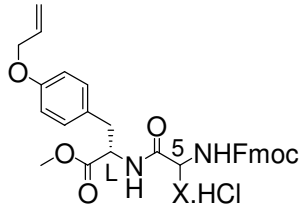
	C2	C5	MIC μg/mL
50	L	D-Arg	125
51	L	L-Arg	125
52	D	D-Arg	125
53	D	L-Arg	125



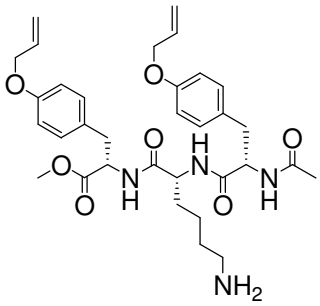
	C2	C5	C8	MIC μg/mL
9	L	D-Lys	L	125
32	L	L-Lys	L	>125
33	L	D-Arg	L	>125
34	L	L-Arg	L	>125
35	D	D-Arg	L	>125
36	D	L-Arg	L	>125
37	L	L-Arg	D	-
62	L	D-*N*-guanidineLys	L	>125
63	L	L-*N*-guanidineLys	L	>500



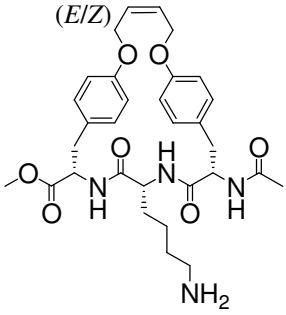
	C2	C5	C8	MIC μg/mL
11	L	D-Lys	L	62.5
44	L	L-Lys	L	>125
45	L	D-Arg	L	62.5
46	L	L-Arg	L	125
47	D	D-Arg	L	125
48	D	L-Arg	L	125
49	L	L-Arg	D	125
65	L	L-*N*-guanidineLys	L	>125



	C5	MIC μg/mL
79	D-Lys	31.3
80	L-Lys	15.6
81	D-Arg	7.8
82	L-Arg	15.6



73
MIC μg/mL = 125



75
MIC μg/mL = 15.6

Figure 2: Minimum inhibitory concentration (MIC) data for the anti-bacterial testing of the acyclic di- and tripeptides and the cyclic tripeptide derivatives synthesisied.

The third major observation was the hydrophobicity of the molecules. The tyrosine derivative **81**, which mimics the binaphthyl in the lead compound **1**, is significantly smaller and less hydrophobic than the scaffold/template of the lead **1**. The Fmoc fluorenyl ring system (*e.g.* in **81**) is more

hydrophobic than a tyrosine residue and more isosteric with the binaphthyl ring system of the lead compound. It is clear that the presence of the more hydrophobic Fmoc group increases the activity of the compounds in relation to the tyrosine derivative.

4. Conclusions

We have synthesised a series cyclic peptides based upon allyltyrosine and allylglycine moieties. The key cyclisation was achieved *via* a ring closing metathesis reaction. The anti-bacterial activity of the cyclic peptides and their acyclic precursors revealed that for optimum activity:

- The compounds do not have to be macrocyclic, but can be straight chain peptides.
- The D-Configuration is preferred for the basic residue, and arginine is preferable over lysine. Also, the side chain in homoarginine is too long and renders the compounds inactive.
- The L-configuration is preferred for the *C*-terminal amino acid residue.
- A small hydrophobic group is required near the *C*-terminus whereas a larger hydrophobic group is required at the *N*-terminus.

5. Experimental

5.1 General

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 (ESI) 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. 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. All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and TLC analysis. The Grubbs ruthenium catalyst used was specifically

benzylidene bis(tricyclohexylphosphine) dichlororuthenium. Other general experimental procedures have been reported previously.[11]

Proton and carbon NMR spectra for all compounds were assigned using the numbering systems as illustrated in Figure 3. 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.[19]

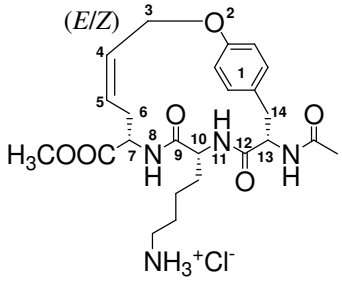


Figure 3: 'Superatom' convention for the numbering of macrocycles.[19]

5.2. General Synthetic Procedures

5.2.1. N-Boc and Pmc Deprotection (Procedure A)

The *N*-Boc or Pmc protected amine (1 equiv.) was stirred for 3 h in 1:1 CH_2Cl_2/ TFA solution at rt. The solvent was removed under reduced pressure, and the residue was re-suspended in a minimal volume of methanol. The solution was then treated with an excess of 1M HCl/ diethyl ether solution and the solvent again evaporated. The crude product was purified by recrystallization/ precipitation from $CH_2Cl_2$and/ or MeOH by addition of diethyl ether.

5.2.2. Peptide Coupling (Procedure B)

To a solution of the acid (1 equiv.) in DMF at rt 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 the reaction was quenched with water until precipitation occurred. The solid was collected by vacuum filtration, and washed thoroughly with water. The amorphous product was dried under vacuum over P_2O_5 to yield the desired peptide.

5.2.3. N-Fmoc Deprotection (Procedure C)

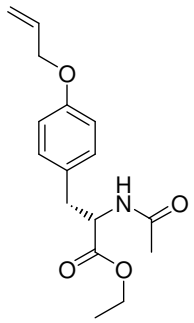
The Fmoc protected amine was stirred in 1% piperidine/acetonitrile for 3 h at rt. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (15:1, CH_2Cl_2/MeOH) to yield the free amine.

5.2.4. Macrocyclization by Olefin Metathesis (Procedure D)

To a solution of the precursor tripeptide in CH_2Cl_2 (to 0.004 M) was added Grubbs ruthenium 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, CH_2Cl_2/MeOH) to yield the corresponding macrocycle.

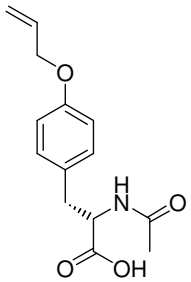
5.3. Synthesis of Allylated Tyrosine Amino Acids

*5.3.1. Ethyl (2S)-2-acetamido-3-(4-allyloxyphenyl)propanoate (**13**)*



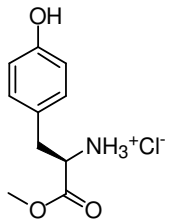
To a solution of ethyl (2*S*)-2-acetamido-3-(4-hydroxyphenyl) propanoate monohydrate **12** (2.69 g, 9.98 mmol) and anhydrous K_2CO_3 (2.75 g, 20.0 mmol) in DMF (15 mL) was added allyl bromide (2.42 g, 19.96 mmol). The resulting mixture was allowed to stir for 16 h under nitrogen before the reaction was quenched with water (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts 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.[20] $[\alpha]_D^{25}$ +23.1 (*c*. 0.1, EtOH).[20] Mp 69-70 °C (lit. 69.5 °C).[20]

*5.3.2. (2S)-2-Acetamido-3-(4-allyloxyphenyl)propanoic acid (**14**)*



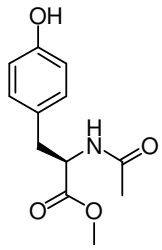
To a solution of **13** (2.90 g, 9.98 mmol) in THF/water, (3:1, 80 mL) was added lithium hydroxide monohydrate (838 mg, 20.0 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation. The aqueous layer was extracted with CH_2Cl_2 (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with CH_2Cl_2 (3 x 40 mL). The combined extracts 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.[20] Mp 170-172 °C (lit. 200 °C).[20]

*5.3.3. Methyl (2R)-2-amino-(4-hydroxyphenyl)-2-propanoate hydrochloride (**16**)*



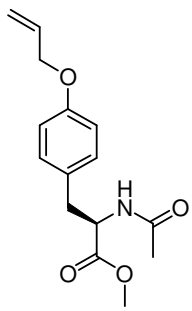
To a solution of (2*R*)-2-amino-3-(4-hydroxyphenyl)propanoic acid **15** (1.07 g, 5.9 mmol) in anhydrous MeOH (10 mL) at 0 °C was added dropwise thionyl chloride (2 mL). The resulting mixture was allowed to stir for 16 h before the solvent was removed by evaporation to yield the title compound (1.36 g, 5.9 mmol, 100%) as a white solid, which was spectroscopically identical to that reported.[21] $[\alpha]_D^{23}$ -27.7 (*c*. 0.1, EtOH). (lit. $[\alpha]_D^{24}$ -27.1 (*c*. 2.0, MeOH))[21] Mp 176 °C (lit. 134-136 °C).[21]

*5.3.4. Methyl (2R)-2-acetamido-3-(4-hydroxyphenyl)propanoate (**17**)*



A solution of the HCl salt **16** (1.09 g, 6.02 mmol) in water (3 mL) was cooled to 0 °C before the addition of 5 M 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 was spectroscopically identical to that reported.[21] $[\alpha]_D^{25}$ -27.2 (*c*. 0.1, EtOH) (lit. $[\alpha]_D^{25}$ -26.6 (*c*. 0.1, MeOH)[21] Mp 132-133 °C (lit. 134-135.5 °C).[21]

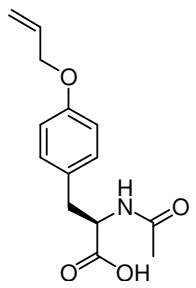
*5.3.5. Methyl (2R)-2-acetamido-3-(4-allyloxyphenyl)propanoate (**18**)*



To a solution of **17** (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); 6.07 – 5.95 (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, $H3_b''$); 4.83 – 4.77 (m, 1H, H2); 4.47 (d, J = 5.5 Hz, 2H, H1″); 3.68 (s, 3H, OCH_3); 3.08 – 2.94 (m, 2H, H3); 1.99 (s, 3H, NCOC<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, C1; 169.6, NCO; 157.6, ArC4′; 133.1, C2″; 130.1, ArCH2′ and ArCH6′; 127.9, ArC1′; 117.5, C3″; 114.7, ArCH3′ and ArCH5′; 68.6, C1″; 53.2, C2; 52.2, OCH_3; 36.9, C3; 22.9, NCO<u>C</u>H$_3$. MS (CI, +ve) *m/z* 278 (100%) [MH^+]. HRMS (ESI) calcd for $C_{15}H_{19}NO_4$ 277.131408, found 277.130309.

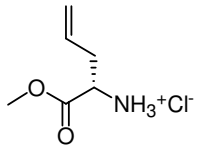
*5.3.6. (2R)-2-Acetamido-3-(4-Allyloxyphenyl)propanoic acid (**19**)*



To a solution of **18** (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 CH_2Cl_2 (3 x 40 mL). The combined CH_2Cl_2 fractions were dried and concentrated 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′); 6.12 – 6.00 (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 = 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, NCOC<u>H</u>$_3$). ^{13}C NMR (D_6 acetone, 75 MHz): δ 173.1, C1; 170.4, NCO; 158.4, ArC4′; 134.8, C2″; 131.1, ArCH2′ and ArCH6′; 130.2, ArC1′; 117.2, C3″; 115.3, ArCH3′ and ArCH5′; 69.2, C1″; 54.5, C2; 37.3, C3; 22.6, NCO<u>C</u>H$_3$. MS (CI, +ve) *m/z* 264 (100%) [MH^+]. HRMS calcd for $C_{14}H_{18}NO_4$ 264.123583, found 264.123770.

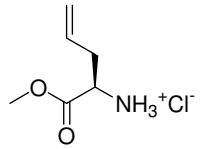
*5.4. Synthesis of methylester allyl glycines (**6** and **21**)*

5.4.1. *Methyl (2S)-2-amino-4-pentenoate hydrochloride (**6**)*



To a suspension of (2*S*)-2-amino-4-pentanoic acid **5** (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.[15] Mp 172-174 °C (lit. 174-176 °C).[15]

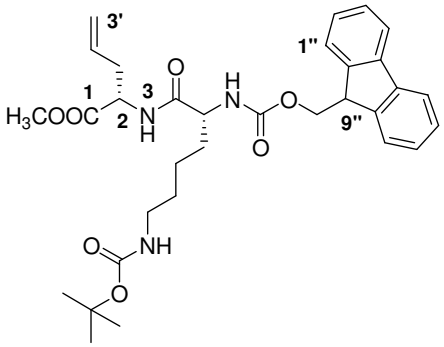
*5.4.2. Methyl (2R)-2-amino-4-pentenoate hydrochloride (**21**)*



This was prepared from (2*R*)-2-amino-4-pentenoic acid (200 mg, 1.74 mmol) in methanol (6 mL) using the same procedure as for the synthesis of **6** above, to yield the title compound (287 mg, 1.74 mmol, 100%) as a white solid which was spectroscopically identical to that reported.[22] Mp 135-140 °C.

*5.5. Synthesis of Protected Dipeptides (**7**, **22**-**26**)*

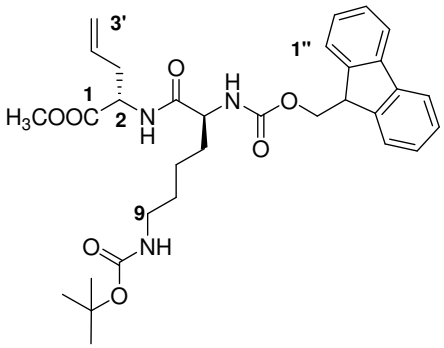
*5.5.1. Methyl (2S,5R)-2-allyl-3-aza-9-(tert-butoxycarboxamido)-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxononanoate (**7**)*



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **6** (186 mg, 1.62 mmol) and (2*R*)-6-*tert*-butoxycarboxamido-2-(9*H*-9-fluorenylmethyloxycarboxamido)hexanoic acid (633 mg, 1.35 mmol) to afford **7** (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 (ddd, *J* = 9.0, 7.2, 1.2 Hz, 2H, ArH2″ and ArH7″); 6.75 (d, *J* = 7.2 Hz,

1H, NH); 5.74 – 5.57 (m, 1H, H2′); 5.11 – 5.05 (m, 2H, H3′); 4.70 – 4.62 (m, 2H, H2 and NH); 4.38 (d, J = 6.7 Hz, 2H, OC$\underline{H}_2$-H9″); 4.26 – 4.18 (m, 2H, H5 and H9″); 3.71 (s, 3H, OCH_3); 3.10 (d, J = 6.3 Hz, 2H, H9); 2.62 – 2.44 (m, 2H, H1′); 1.88 – 1.83 (m, 2H, H8); 1.70 – 1.63 (m, 2H, H7); 1.49 – 1.37 (m 2H, H7); 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.6, C4; 171.2, C1; 156.0, NCO_2; 156.0, NCO_2; 143.5, ArC8a″ and ArC9a″; 141.1, ArC4a″ and ArC4b″; 131.9, C2′; 127.6, ArCH3″ and ArCH6″; 126.9, ArCH2″ and ArCH7″; 125.0, ArCH1″ and ArCH8″; 119.8, C3′; 119.2, ArCH4″ and ArCH5″; 79.1, $\underline{C}(CH_3)_3$; 67.1, $\underline{C}H_2$-C9″; 54.7, C5; 52.5, OCH_3; 51.5, C2; 47.1, C9″; 39.8, C9; 36.4, C6; 32.2, C6; 29.7, C8; 28.5, $C(\underline{C}H_3)_3$; 22.4, C7. MS (ESI, +ve) *m/z* 579.9 (80%) [MH^+], 479.9 (100%) [MH^+ - Boc)]. HRMS calcd for $C_{32}H_{42}N_3O_7$ 580.3023, found 580.3041.

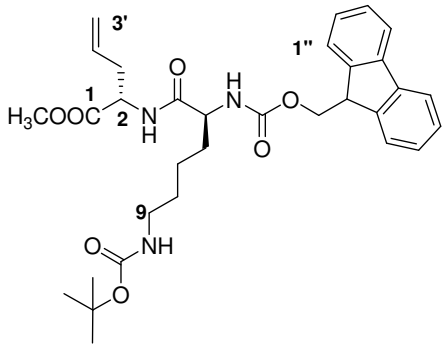
*5.5.2. Methyl (2S,5S)-2-allyl-3-aza-9-(tert-butoxycarboxamido)-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxononanoate (**22**)*



To a solution of **6** (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 CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2/ 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); 5.73 – 5.62 (m, 1H, H2′); 5.44 (s, 1H, NH); 5.12 – 5.07 (m, 2H, H3′); 4.80 (bs, 1H, NH); 4.65 – 4.61 (m, 1H, H2); 4.39 (d, J = 7.2 Hz, 2H, OC$\underline{H}_2$-

H9″); 4.23 – 4.19 (m, 1H, H5); 4.17 (bs, 1H, H9″); 3.74 (s, 3H, OCH_3); 3.16 – 3.05 (m, 2H, H9); 2.64 – 2.47 (m, 2H, H1′); 1.94 – 1.76 (m, 2H, H7); 1.75 – 1.64 (m, 2H, H6); 1.55 – 1.48 (m 2H, H8); 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, C4; 171.6, C1; 156.2, NCO_2; 143.7, ArC8a″ and ArC9a″; 142.7, ArC4a″ and ArC4b″; 131.9, C2′; 127.7, ArCH3″ and ArCH6″; 127.0, ArCH2″ and ArCH7″; 125.0, ArCH1″ and ArCH8″; 119.9, C3′; 119.3, ArCH4″ and ArCH5″; 79.1, $\underline{C}(CH_3)_3$; 67.0, $\underline{C}H_2$-C9″; 54.5, C5; 52.4, OCH_3; 50.6, C2; 47.0, C9″; 39.8, C9; 36.1, C1′; 32.0, C6; 29.9, C8; 28.3, $C(\underline{C}H_3)_3$; 22.2, C7. MS (ESI, +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.

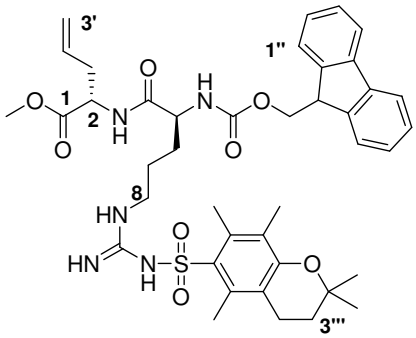
*5.5.3. Methyl (2S,5R)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (**23**)*



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **6** (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 **23** (1.01 g, 1.31 mmol, 90%) as a brown solid; $[\alpha]_D^{23}$ +11.5 (*c* 0.011, MeOH). IR (neat) ν_{max} 1538, 1445, 1238, 1166, 1109, 736. 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); 5.78 – 5.56 (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″); 4.17 – 4.02 (m, 2H, H5 and H9″); 3.63 (s, 3H, OCH_3); 3.30 – 3.12 (m, 2H, H8); 2.57 (s, 3H, 7‴-CH_3); 2.54 (s, 3H, 5‴-CH_3); 2.50 – 2.47 (m, 4H, H1′ and H4‴); 2.06 (s, 3H, 8‴-CH_3); 1.96 – 1.78 (m, 2H, H7); 1.71 (t, *J* = 6.6 Hz, 2H, H3‴); 1.66 – 1.52 (m, 2H, H6); 1.24 (s, 6H, 2 x 2‴-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, C4; 171.8, C1;

156.2, ArC6‴; 153.5, 5-NCO_2; 143.6, ArC8a‴; 143.5, CN_3; 141.0, ArC8a″ and ArC9a″; 135.3, ArC4a″ and ArC4b″; 134.7, ArC7‴; 132.9, ArC5‴; 132.3, C2′; 127.5, ArCH3″ and ArCH6″; 126.9, ArCH2″ and ArCH7″; 125.0, ArCH4″ and ArCH5″; 124.0, ArC8‴; 119.7, ArCH1″ and ArCH8″; 118.8, C3′; 117.8, ArC4a‴; 73.6, C2‴; 67.2, $\underline{C}H_2$-C9″; 52.3, C5; 52.0, C2; 52.0, OCH_3; 47.0, C9″; 40.2, C8; 35.9, C1′; 32.7, C3‴; 29.8, C6; 26.7, C2‴-CH_3; 25.5, C7; 21.4, C5‴-CH_3; 18.6, C7‴-CH_3; 17.6, C4‴; 12.2, C8‴-CH_3. MS (ESI, +ve) *m/z* 774 (100%) [MH^+]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3559.

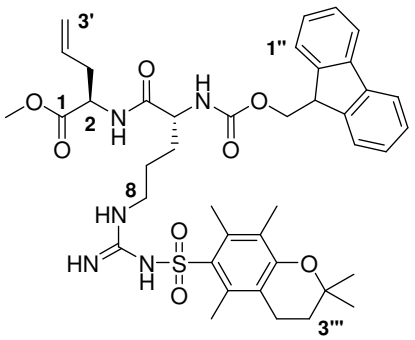
*5.5.4. Methyl (2S,5S)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (**24**)*



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **6** (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 **24** (936 mg, 1.21 mmol, 83%) as a brown solid; $[\alpha]_D^{23}$ +12.1 (*c* 0.013, MeOH). IR (neat) ν_{max} 1543, 1450, 1233, 1109, 741. Mp 90-94 °C. 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); 5.71 – 5.58 (m, 1H, H2′); 5.03 (d, *J* = 17.0 Hz, 1H, $H3_a$′); 4.98 (d, *J* = 10.0 Hz, 1H, $H3_b$′); 4.57 – 4.50 (m, 1H, H2); 4.40 – 4.32 (m, 1H, H5); 4.29 (d, *J* = 7.2 Hz, 2H, $OC\underline{H_2}$-H9″); 4.13 – 4.08 (m, 1H, H9″); 3.65 (s, 3H, OCH_3); 3.34 – 3.14 (m, 2H, H8); 2.58 (s, 3H, 7‴-CH_3); 2.55 (s, 3H, 5‴-CH_3); 2.54 – 2.42 (m, 4H, H1′ and H4‴); 2.07 (s, 3H, 8‴-CH_3); 1.95 – 1.82 (m, 2H, H6); 1.73 (t, *J* = 6.5 Hz, 2H, H3‴); 1.65 – 1.54 (m, 2H, H7); 1.26 (s, 6H, 2 x 2‴-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, C4; 171.0, C1; 156.3, ArC6‴; 153.5, 5-NCO_2; 143.6, CN_3; 143.5, ArC8a‴; 141.0, ArC8a″ and ArC9a″; 137.8, ArC4a″ and ArC4b″; 135.3, ArC7‴; 134.7,

ArC5‴; 132.9, C2′; 127.5, ArC3″ and ArC6″; 126.9, ArC2″ and ArC7″; 125.0, ArC4″ and ArC5″; 124.0, ArC8‴; 119.8, ArC1″ and ArC8″; 118.8, C3′; 117.8, ArC4a; 73.6, C2‴; 67.2, $\underline{C}H_2$-C9″; 54.1, C5; 52.4, C2; 52.3, OCH_3; 47.0, C9″; 40.5, C8; 35.7, C1′; 32.7, C3‴; 29.9, C6; 26.8, C2‴-CH_3; 25.2, C7; 21.4, 5‴-CH_3; 18.6, 7‴-CH_3; 17.6, C4‴; 12.2, 8‴-CH_3. MS (ESI, +ve) *m/z* 774 (20%) [MH^+], 130 (100%) [allylGly]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3517.

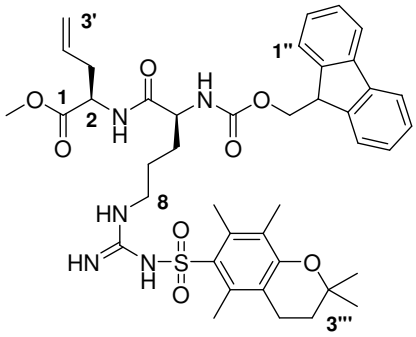
*5.5.5. Methyl (2R,5R)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (**25**)*



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **21** (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 **25** (1.01 g, 1.31 mmol, 90%) as a brown solid; $[\alpha]_D^{23}$ +5.3 (*c* 0.008, MeOH). IR (neat) ν_{max} 1724, 1545, 1449, 1236, 1167, 1108, 742. 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); 5.69 – 5.55 (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 (dd, *J* = 7.2, 12.9 Hz, 1H, H2); 4.36 (dd, *J* = 8.5, 12.5 Hz, 1H, H5); 4.29 (d, *J* = 7.0 Hz, 2H, 9″-CH_2); 4.08 – 4.04 (m, 1H, H9″); 3.65 (s, 3H, OCH_3); 3.28 – 3.17 (m, 2H, H8); 3.22 (bs, 1H, NH); 2.58 (s, 3H, 7‴-CH_3); 2.55 (s, 3H, 5‴-CH_3); 2.51 – 2.39 (m, 4H, H1′ and H4‴); 2.07 (s, 3H, 8‴-CH_3); 1.96 – 1.80 (m, 2H, H7); 1.73 (t, *J* = 6.5 Hz, 2H, H3‴); 1.66 – 1.54 (m, 2H, H6); 1.25 (s, 6H, 2 x 2‴-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, C4; 171.8, C1; 156.2, ArC6‴; 153.4, 5-NCO_2; 143.6, ArC8a‴; 143.5, CN_3; 141.0, ArC8a″ and ArC9a″; 135.2, ArC4a″ and ArC4b″; 134.6, ArC7‴; 133.0, ArC5‴; 132.2, C2′; 127.5, ArCH3″ and ArCH6″; 126.8, ArCH2″ and ArCH7″; 125.0, ArCH4″ and ArCH5″; 123.8, ArC8‴;

119.7, ArCH1″ and ArCH8″; 118.6, C3′; 117.8, ArC4a‴; 73.5, C2‴; 67.0, 9″-CH_3; 52.3, C5; 52.1, C2; 52.2, OCH_3; 47.0, C9″; 40.4, C8; 35.7, C1′; 32.7, C3‴; 29.8, C6; 26.7, C2‴-CH_3; 25.3, C7; 21.4, C5‴-CH_3; 18.6, C7‴-CH_3; 17.5, C4‴; 12.1, C8‴-CH_3. MS (ESI, +ve) *m/z* 774 (100%) [MH^+]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3524.

*5.5.6. Methyl (2R,5S)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (**26**)*

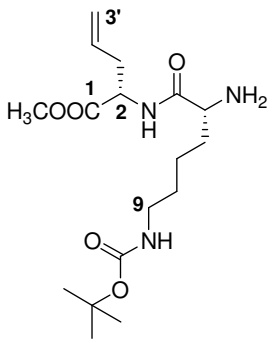


The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **21** (287 mg, 1.74 mmol) and (2*S*)-2-(9H-9-fluorenylmethyloxycarboxamido)-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-6-chromenylsulfonyl) guanidino]pentanoic acid (961 mg, 1.45 mmol) to afford **26** (1.00 g, 1.29 mmol, 89%) as a brown foam; $[\alpha]_D^{23}$ +60.2 (*c* 0.006, MeOH). IR (neat) ν_{max} 1667, 1541, 1449, 1237, 1166, 1107, 761, 741. 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); 5.60 – 5.69 (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); 2.41 – 2.51 (m, 4H, H1′ and H4‴); 2.07 (s, 3H, 8‴-CH_3); 1.86 – 1.94 (m, 2H, H6); 1.70 (t, *J* = 6.7 Hz, 2H, H3‴); 1.54 – 1.62 (m, 2H, H7); 1.23 (s, 6H, 2 x 2‴-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, C4; 171.8, C1; 156.2, ArC6‴; 153.2, 5-NCO_2; 143.6, CN_3; 143.5, ArC8a‴; 141.0, ArC8a″ and ArC9a″; 135.3, ArC4a″ and ArC4b″; 134.7, ArC7‴; 133.1, ArC5‴; 132.3, C2′; 127.5, ArC3″ and ArC6″; 126.9, ArC2″ and ArC7″; 125.0, ArC4″ and ArC5″; 123.9, ArC8‴; 119.7, ArC1″ and ArC8″; 118.8, C3′; 117.8, ArC4a; 73.5, C2‴; 67.2, 9″-CH_2; 52.3, C5; 52.2, C2; 51.9, OCH_3; 47.0, C9″; 40.5, C8; 35.9, C1′; 32.7, C3‴; 30.0, C6; 26.7, C2‴-CH_3; 25.5, C7; 21.4, 5‴-

CH_3; 18.6, 7‴-CH_3; 17.6, C4‴; 12.1, 8‴-CH_3. MS (ESI, +ve) *m/z* 774 (12%) [MH^+], 130 (100%) [allylGly]. HRMS calcd for $C_{41}H_{52}N_5O_8S$ 774.3537, found 774.3536.

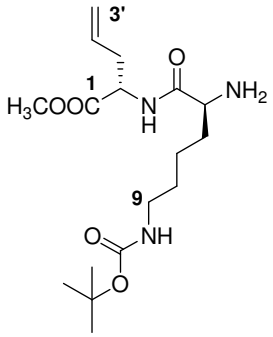
*5.6. Synthesis of Deprotected Dipeptides (**8, 27-31**)*

*5.6.1. Methyl (2S,5R)-2-allyl-5-amino-3-aza-9-(tert-butoxycarboxamido)-4-oxononanoate (**8**)*



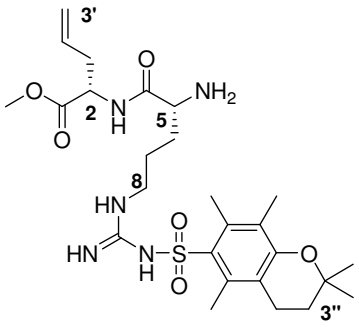
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **7** (715 mg, 1.23 mmol) to yield **8** (436 mg, 1.22 mmol, 99%) as a cream oil, and was spectroscopically identical to that reported in the literature.[9]

*5.6.2. Methyl (2S,5S)-2-allyl-5-amino-3-aza-9-(tert-butoxycarboxamido)-4-oxononanoate (**27**)*



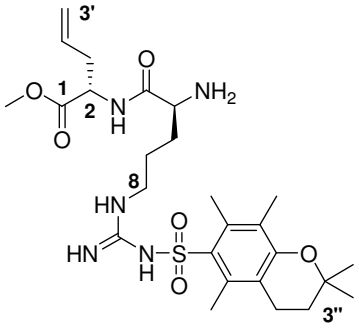
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **22** (1.27 g, 2.19 mmol) to yield **27** (778 mg, 2.18 mmol, 100%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, *J* = 8.0 Hz, 1H, NH); 5.85 – 5.45 (m, 1H, H2′); 5.15 – 5.02 (m, 2H, H3′); 4.76 (bs, 1H, NH); 4.60 – 4.50 (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); 2.65 – 2.42 (m, 2H, H1′); 1.85 – 1.45 (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. MS (ESI, +ve) *m/z* 358.5 (85%) [MH^+], 258.4 (100%) [MH^+ - Boc)]. HRMS calcd for $C_{17}H_{32}N_3O_5$ 358.2342, found 358.2339.

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



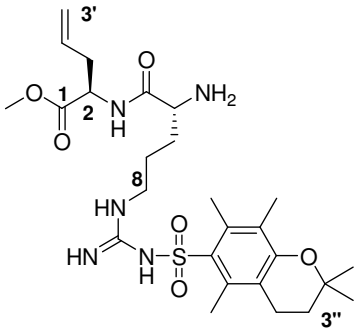
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **23** (717 mg, 0.93 mmol) to yield **28** (407 mg, 0.74 mmol, 80%) as a cream oil, and was spectroscopically identical to that reported in the literature.[11]

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



The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **24** (749 mg, 0.97 mmol) to yield **29** (259 mg, 0.47 mmol, 48%) as a cream oil, $[\alpha]_D^{23}$ -12.2 (*c* 0.013, MeOH), which was spectroscopically identical to that reported.[11]

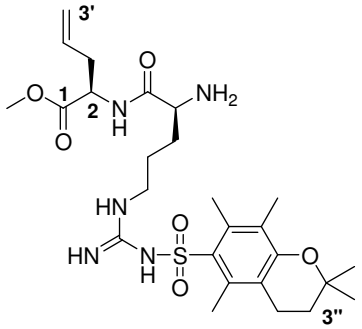
*5.6.5. Methyl (2R,5R)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (**30**)*



The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **25** (693 mg, 0.900 mmol) to yield **30** (387 mg, 0.0700 mmol, 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); 5.75 – 5.61 (m, 1H, H2′); 5.09 (d, *J* = 16.2 Hz, 1H, $H3_a'$); 5.09 (d, *J* = 12.0 Hz, 1H, $H3_b'$); 4.56 – 4.50 (m, 1H, H2); 3.72 (s, 3H, OCH_3); 3.43 – 3.40 (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); 2.66 – 2.50 (m, 2H, H1′); 2.10 (s, 3H, 8″-CH_3); 2.05 (bs, 2H, H7); 1.80 (t, *J* = 6.3 Hz, 2H, H2″); 1.58 – 1.56 (m, 2H, H6);

1.30 (s, 6H, 2 x 2″-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.2, C4; 172.0, C1; 156.1, ArC6″; 153.4, CN_3; 135.3, ArC7″; 134.6, ArC5″; 133.2, ArC8a″; 132.2, C2′; 123.9, ArC8″; 118.9, C3′; 117.8, ArC4a; 73.6, C2″; 54.2, C5; 52.4, OCH_3; 51.6, C2; 40.6, C8; 36.2, C1′; 32.8, C4″; 32.0, C6; 26.8, 2″-CH_3; 25.3, C7; 21.5, C3″; 18.6, 5″-CH_3; 17.5, 7″-CH_3; 12.2, 8″-CH_3. MS (ESI, +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.

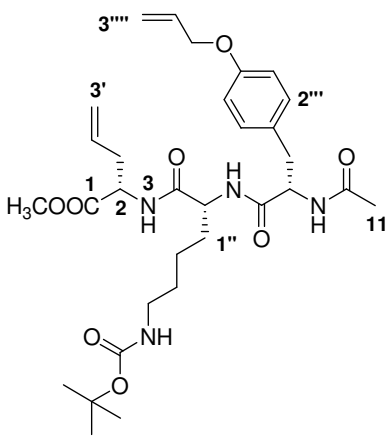
*5.6.6. Methyl (2R,5S)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]-4-oxooctanoate (**31**)*



The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **26** (788 mg, 1.01 mmol) to yield **31** (552 mg, 1.00 mmol, 99%) as a cream oil; $[\alpha]_D^{23}$ +11.6 (*c* 0.017, MeOH). IR (neat) ν_{max} 1672, 1543, 1445, 1238, 1166, 1109. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, *J* = 7.5 Hz, 1H, NH); 6.33 (bs, 3H, NH); 5.74 – 5.60 (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); 3.23 – 3.15 (m, 2H, H8); 2.64 – 2.43 (m, 2H, H1′); 2.57 (s, 3H, 7″-CH_3); 2.55 (s, 3H, 5″-CH_3); 2.10 (s, 3H, 8″-CH_3); 1.82 – 1.71 (m, 4H, H7 and H3″); 1.63 – 1.52 (m, 2H, H6); 1.30 (s, 6H, 2 x 2″-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.2, C4; 172.0, C1; 156.1, ArC6″; 153.3, CN_3; 135.3, ArC7″; 134.6, ArC5″; 133.2, ArC8a″; 132.2, C2′; 123.9, ArC8″; 119.0, C3′; 117.8, ArC4a″; 73.6, C2″; 54.2, C5; 52.3, OCH_3; 51.5, C2; 40.7, C8; 36.1, C1′; 32.8, C4″; 31.9, C6; 26.8, 2″-CH_3; 25.2, C7; 21.5, C3″; 18.5, 5″-CH_3; 17.5, 7″-CH_3; 12.2, 8″-CH_3. MS (ESI, +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.

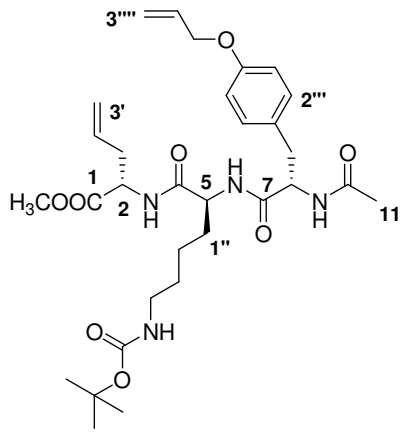
*5.7. Synthesisi of Protected Tripepetides (**9**, **32** – **37**)*

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



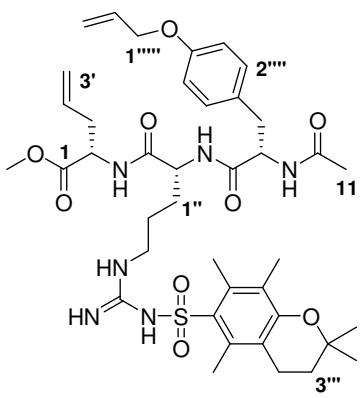
The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **8** (440 mg, 1.20 mmol) and **14** (270 mg, 1.03 mmol) to afford **9** (424 mg, 0.70 mmol, 69%) as a white solid. Mp 149-150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (d, *J* = 8.0 Hz, 1H, NH); 7.11 (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); 6.10 – 5.96 (m, 1H, H2⁗); 5.72 – 5.61 (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, $H3_b$⁗); 5.11 – 5.07 (m, 2H, H3′); 4.75 (t, *J* = 5.9 Hz, 1H, H2); 4.66 – 4.53 (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); 3.06 – 2.96 (m, 4H, H4″ and $ArCH_2$); 2.61 – 2.43 (m, 2H, H1′); 1.97 (s, 3H, H11); 1.44 (s, 9H, $C(CH_3)_3$); 1.42 – 1.32 (m, 6H, H1″, H2″ and H3″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, C7; 171.1, C1; 170.7, C4; 170.2, C10; 157.4, NCO_2; 155.9, ArC4‴; 133.0, C2′; 132.3, C2⁗; 130.1, ArCH2‴ and ArCH6‴; 128.4, ArC1‴; 118.8, C3′; 117.6, C3⁗; 114.8, ArCH3‴ and ArCH5‴; 79.0, $\underline{C}(CH_3)_3$; 68.8, C1⁗; 55.4, C5; 52.8, OCH_3; 52.4, C8; 51.8, C2; 40.1, C4″; 37.5, $ArCH_2$; 36.3, C1′; 31.6, C1″; 29.7, C3″; 28.5, $C(\underline{C}H_3)_3$; 23.1, C11; 22.3, C2″. MS (ESI, +ve) *m/z* 603.4 (40%) [MH^+], 503.4 (100%) [MH^+ - Boc)]. HRMS calcd for $C_{31}H_{47}N_4O_8$ 603.3394, found 603.3389.

5.7.2. Methyl (2S,5S,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[tert-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate (**32**)



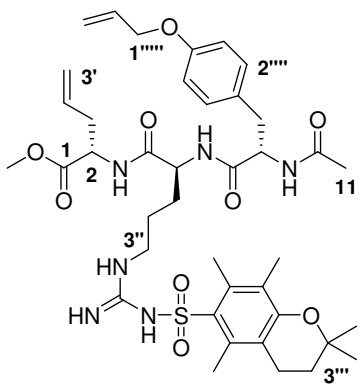
To a solution of **27** (782 mg, 2.19 mmol) and **14** (576 mg, 2.19 mmol) in CH_2Cl_2 (10 mL) was added EDCI (420 mg, 2.19 mmol) and a catalytic quantity of DMAP. The resulting mixture was allowed to stir at RT for 16 h. The reaction was diluted with CH_2Cl_2 (25 mL) and the organic layer was washed 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 CH_2Cl_2/ 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); 6.88 – 6.79 (m, 2H, ArH3‴ and ArH5‴); 6.69 (d, *J* = 8.0 Hz, 1H, NH); 6.55 (bs, 1H, NH); 6.10 – 5.97 (m, 1H, H1⁗); 5.77 – 5.60 (m, 1H, H2′); 5.42 – 5.24 (m, 4H, H3′ and H3⁗); 4.96 (bs, 1H, H2); 4.86 (bs, 1H, H8); 4.80 – 4.60 (m, 2H, H2⁗); 4.48 (dd, *J* = 3.0, 8.4 Hz, 1H, H5); 3.74/3.71 (s, 3H, OCH_3); 3.12 – 2.92 (m, 4H, H4″ and $ArCH_2$); 2.57 – 2.44 (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″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.8, C7; 171.7, C1; 171.4/171.2, C4; 170.3, C10; 157.3/157.2, NCO_2; 155.9, ArC4‴; 133.1/133.0, C2′; 130.2/130.1, ArCH2‴ and ArCH6‴; 128.8./128.7, ArC1‴; 118.6, C3′; 117.5/117.4, C3⁗; 114.4/114.3, ArCH3‴ and ArCH5‴; 78.6, $\underline{C}(CH_3)_3$; 68.5, C1⁗; 54.0, C5; 52.4, OCH_3; 52.1, C8; 52.1, C2; 39.9, C4″; 38.0, $ArCH_2$; 35.8, C1′; 32.7/32.2, C1″; 29.6/29.3, C3″; 28.3, $C(\underline{C}H_3)_3$; 22.9/22.7, C11; 22.3/22.0, C2″. MS (ESI, +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.

*5.7.3. Methyl (2S,5R,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (**33**)*



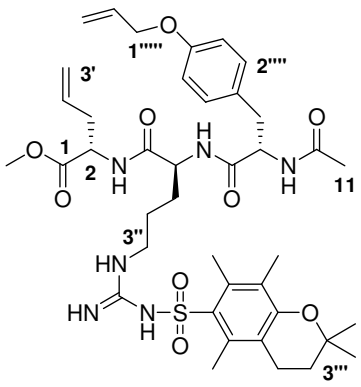
The title compound was synthesised using the general peptide coupling procedure (Procedure B) using **28** (387 mg, 0.70 mmol) and **14** (153 mg, 0.58 mmol) to afford **33** (336 mg, 0.42 mmol, 73%) as a light brown solid. IR (neat) ν_{max} 1653, 1636, 1539, 1508, 1241, 1107. Mp 172-176 °C. ^{1}H NMR ($CDCl_3$, 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); 6.05 – 5.92 (m, 1H, H2′′′′′); 5.76 – 5.62 (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$_b$′); 4.52 – 4.44 (m, 2H, H2 and H5); 4.42 (d, *J* = 4.8 Hz, 1H, H1′′′′′); 4.38 – 4.28 (m, 1H, H8); 3.69 (s, 3H, OCH_3); 3.14 – 3.00 (m, 2H, H3′′); 3.01 – 2.85 (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); 2.65 – 2.45 (m, 2H, H1′); 2.09 (s, 3H, 8′′′-CH_3); 1.93 (s, 3H, H11); 1.80 (t, *J* 6.6 Hz, 2H, H3′′′); 1.56 – 1.48 (m, 4H, H1′′ and H2′′); 1.30 (s, 6H, 2 x 2′′′-CH_3). ^{13}C NMR (DMSO, 75 MHz): δ 171.3, C4; 170.9, C1; 171.0, C11; 169.1, C7; 156.5, ArC6′′′; 155.6, ArC8a′′′; 152.4, CN_3; 134.5, ArC7′′′; 133.9, ArC5′′′; 133.3, C2′′′′′; 132.5, C2′; 132.2, ArC4′′′′; 129.5, ArCH2′′′′ and ArCH6′′′′; 128.3, ArC8′′′; 122.9, ArC1′′′′; 117.6, ArC4a′′′; 117.0, C3′′′′′; 116.8, C3′; 113.9, ArCH3′′′′ and ArCH5′′′′; 72.9, C2′′′; 68.0, C′′′′′; 55.1, C2; 51.9, C5; 51.9, OCH_3; 51.5, C8; 40.3, C3′′; 38.6, $ArCH_2$; 36.2, C4′′′; 35.2, C1′; 32.2, C7; 26.2, 2′′′-CH_3; 25.1, C6; 22.3, C11; 20.8, C3′′′; 18.0, 5′′′-CH_3; 16.9, 7′′′-CH_3; 11.6, 8′′′-CH_3. MS (ESI, +ve) *m/z* 797 (100%) [MH^+]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3913.

*5.7.4. Methyl (2S,5S,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (**34**)*



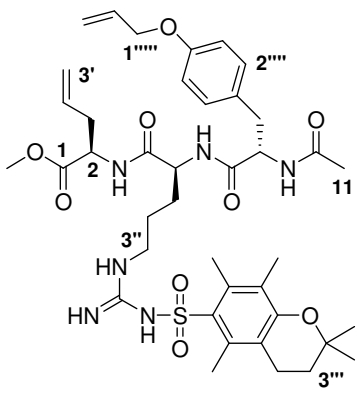
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **29** (236 mg, 0.43 mmol) and **14** (95 mg, 0.36 mmol) to afford **34** (207 mg, 0.25 mmol, 72%) as a light brown solid. $[\alpha]_D^{24}$ +27.8 (*c* 0.007, MeOH). IR (neat) ν_{max} 1653, 1541, 1512, 1244, 1109. 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* = 8.4 Hz, 2H, ArH3′′′′ and ArH5′′′′); 6.41 (bs, 2H, NH); 6.05 – 5.92 (m, 1H, H2′′′′′); 5.76 – 5.62 (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$_b$′); 4.78 – 4.71 (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′′); 3.17 – 2.79 (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); 2.62 – 2.43 (m, 2H, H1′); 2.08 (s, 3H, 8′′′-CH_3); 1.88 (s, 3H, H11); 1.78 (t, *J* = 6.3 Hz, 2H, H3′′′); 1.80 – 1.72 (m, 2H, H7); 1.61 – 1.50 (m, 2H, H6); 1.29 (s, 6H, 2 x 2′′′-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, C4; 171.8, C1; 171.5, C11; 171.0, C7; 157.2, ArC6′′′; 156.2, ArC8a′′′; 153.4, CN_3; 135.2, ArC7′′′; 134.6, ArC5′′′; 133.1, C2′′′′′; 133.1, C2′; 132.3, ArC4′′′; 130.1, ArCH2′′′′ and ArCH6′′′′; 128.6, ArC8′′′; 123.9, ArC1′′′′; 118.6, ArC4a′′′; 117.8, C3′′′′′; 117.4, C3′; 114.5, ArCH3′′′′ and ArCH5′′′′; 73.6, C2′′′; 68.6, C1′′′′′; 60.4, C2; 54.8, C5; 52.3, OCH_3; 52.2, C8; 40.7, C3′′; 37.2, $ArCH_2$; 36.0, C4′′′; 32.8, C1′; 29.7, C7; 26.8, 2′′′-CH_3; 25.3, C6; 22.9, C11; 21.5, C3′′′; 18.6, 5′′′-CH_3; 17.6, 7′′′-CH_3; 12.2, 8′′′-CH_3. MS (ESI, +ve) *m/z* 797 (100%) [MH^+]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3890.

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



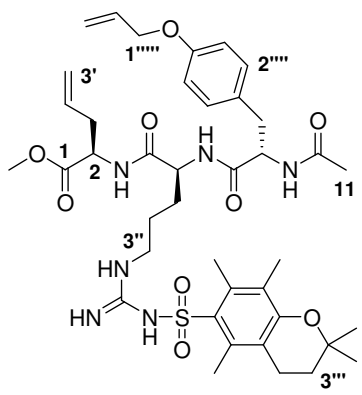
The title compound was synthesised using the general peptide coupling procedure (Procedure B) using **30** (387 mg, 0.700 mmol) and **14** (153 mg, 0.580 mmol) to afford **35** (297 mg, 0.37 mmol, 64%) as a light brown solid; $[\alpha]_D^{23}$ +0.96 (*c* 0.011, acetone). IR (neat) ν_{max} 1645, 1540, 1514, 1245, 1110, 804. 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); 6.04 – 5.97 (m, 1H, H2′′′′′); 5.73 – 5.65 (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, $H3_b$′); 4.58 – 4.54 (m, 1H, H2); 4.53 – 4.47 (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′′); 3.04 – 2.97 (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); 2.55 – 2.50 (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′′). ^{13}C NMR (DMSO, 75 MHz): δ 171.3, C4; 171.1, C1; 171.0, C11; 169.1, C7; 156.5, ArC6′′′; 155.7, ArC8a′′′; 152.1, CN_3; 135.4, ArC7′′′; 133.9, ArC5′′′; 133.7, C2′′′′′; 133.3, C2′; 130.0, ArC4′′′′; 129.5, ArCH2′′′′ and ArCH6′′′′; 129.4, ArC8′′′; 122.5, ArC1′′′′; 117.8, ArC4a′′′; 117.6, C3′′′′′; 117.1, C3′; 114.0, ArCH3′′′′ and ArCH5′′′′; 73.4, C2′′′; 68.0, C′′′′′; 54.4, C2; 51.9, C5; 51.7, OCH_3; 51.6, C8; 36.9, C3′′; 35.0, $ArCH_2$; 32.1, C4′′′; 29.3, C1′; 26.5, C7; 26.4, 2′′′-CH_3; 25.1, C6; 22.4, C11; 20.8, C3′′′; 18.2, 5′′′-CH_3; 17.1, 7′′′-CH_3; 12.0, 8′′′-CH_3. MS (ESI, +ve) *m/z* 797.4 (100%) [MH^+]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3915.

5.7.6. Methyl (2R,5S,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (**36**)



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **31** (513 mg, 0.930 mmol) and **14** (204 mg, 0.78 mmol) to afford **36** (496 mg, 0.622 mmol, 80%) as a light brown solid; $[\alpha]_D^{23}$ +21.6 (*c* 0.007, MeOH). IR (neat) ν_{max} 1653, 1558, 1541, 1508, 1248, 1109. 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); 6.05 – 5.98 (m, 1H, H2′′′′′); 5.73 – 5.65 (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, $H3_b$′); 4.68 – 4.64 (m, 1H, H2); 4.57 – 4.52 (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′′); 3.13 – 2.81 (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); 2.50 – 2.45 (m, 2H, H1′); 2.09 (s, 3H, 8′′′-CH_3); 1.88 (s, 3H, H11); 1.79 (t, *J* = 7.0 Hz, 2H, H3′′′); 1.75 – 1.73 (m, 2H, H7); 1.60 – 1.52 (m, 2H, H6); 1.30 (s, 6H, 2 x 2′′′-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.2, C4; 171.9, C1; 171.3, C11; 170.9, C7; 157.3, ArC6′′′; 156.2, ArC8a′′′; 153.5, CN_3; 135.3, ArC7′′′; 134.7, ArC5′′′; 133.2, C2′′′′′; 133.1, C2′; 132.4, ArC4′′′; 130.0, ArCH2′′′′ and ArCH6′′′′; 128.7, ArC8′′′; 124.0, ArC1′′′′; 118.8, ArC4a′′′; 117.9, C3′′′′′; 117.4, C3′; 114.1, ArCH3′′′′ and ArCH5′′′′; 73.6, C2′′′; 68.7, C1′′′′′ 55.3, C2; 52.9, C5; 52.3, OCH_3; 52.2, C8; 40.7, C3′′; 37.0, $ArCH_2$; 36.1, C4′′′; 32.8, C1′; 29.3, C7; 26.8, 2′′′-CH_3; 25.3, C6; 22.9, C11; 21.5, C3′′′; 18.6, 5′′′-CH_3; 17.6, 7′′′-CH_3; 12.2, 8′′′-CH_3. MS (ESI, +ve) *m/z* 819 (100%) [MNa^+]. HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3873.

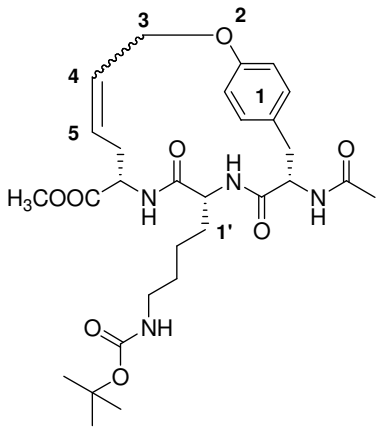
*5.7.7. Methyl (2S,5S,8R)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-4,7,10-trioxoundecanoate (**37**)*



The title compound was synthesised using the general peptide coupling procedure (Procedure B), from **29** (654 mg, 1.19 mmol) and **19** (260 mg, 0.99 mmol) to afford **37** (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); 6.08 – 5.94 (m, 1H, H2′′′′′); 5.79 – 5.60 (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, $H3_b$′); 4.57 – 4.42 (m, 5H, H2, H5, H8 and H1′′′′′); 3.70 (s, 3H, OCH_3); 3.20 – 3.10 (m, 2H, H3′′); 3.01 – 2.98 (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); 2.65 – 2.53 (m, 2H, H1′); 2.11 (s, 3H, 8′′′-CH_3); 1.96 (s, 3H, H11); 1.80 (t, *J* = 6.3 Hz, 2H, H3′′′); 1.60 – 1.48 (m, 2H, H6); 1.30 (s, 6H, 2 x 2′′′-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.6, C4; 171.5, C1; 171.3, C11; 169.4, C7; 156.7, ArC6′′′; 156.0, ArC8a′′′; 152.4, CN_3; 134.6, ArC7′′′; 134.1, ArC5′′′; 133.8, C2′′′′′; 133.7, C2′; 133.6, ArC4′′′; 130.2, ArCH2′′′′ and ArCH6′′′′; 129.7, ArC8′′′; 122.7, ArC1′′′′; 118.0, ArC4a′′′; 117.7, C3′′′′′; 117.2, C3′; 114.1, ArCH3′′′′ and ArCH5′′′′; 73.4, C2′′′; 68.0, C1′′′′′; 54.5, C2; 52.0, C5; 51.7, OCH_3; 51.6, C8; 40.1, C3′′; 39.8, $ArCH_2$; 37.0, C4′′′; 32.1, C1′; 29.2, C7; 26.4, 2′′′-CH_3; 25.1, C6; 22.4, C11; 20.8, C3′′′; 18.2, 5′′′-CH_3; 17.1, 7′′′-CH_3; 11.9, 8′′′-CH_3. MS (ESI, +ve) *m/z* 797 (40%) [MH^+], 106 (100%). HRMS calcd for $C_{40}H_{57}N_6O_9S$ 797.3908, found 797.3926.

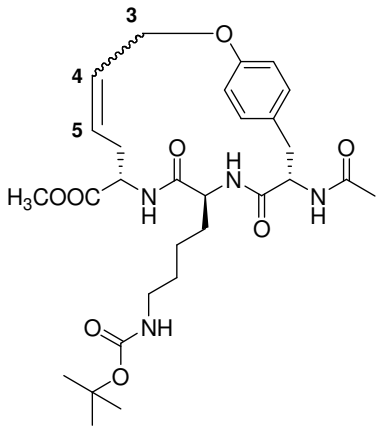
*5.8. Synthesis of Protected Cyclic Tripeptides (**10, 38 – 43**)*

*5.8.1. (7S,10R,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(4-[tert-butoxycarboxamido]butyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**10**)*



The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **9** (277 mg, 0.46 mmol) to yield **10** (199 mg, 0.35 mmol, 75%) as a brown solid. Mp 178-180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 – 7.72 (m, 2H, NH); 7.13 – 7.03 (m, 2H, ArH); 6.90 – 6.65 (m, 2H, ArH); 5.87 – 5.39 (m, 2H, H4 and H5); 4.65 – 4.36 (m, 4H, H7, H13 and H3); 4.20 – 4.06 (m, 2H, NH and H10); 3.61 – 3.57 (m, 3H, OCH_3); 2.87 – 2.69 (bs, 4H, H4′ and H14); 2.58 – 2.38 (m, 2H, H6); 1.82 – 1.75 (m, 3H, $NCOCH_3$); 1.31 – 0.79 (m, 6H, H1′, H2′ and H3′); 1.35 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.8, C9; 172.3, 7-CO; 171.7, 13-NCO; 171.6, C12; 157.2, NCO_2; 156.5, 1-ArC1; 130.3, 1-ArCH2 and 1-ArCH6; 130.2, C4; 128.6, C5; 127.6, 1-ArCH4; 117.7, 1-ArCH3 and 1-ArCH5; 78.7, $\underline{C}(CH_3)_3$; 66.9, C3; 55.7, C13; 54.4, C10; 54.1, C4′; 51.8, C4′; 40.1, C7; 36.0, C14; 29.4, C1′; 27.8, C6; 26.8, C3′; 26.2, $C(\underline{C}H_3)_3$; 22.6, $NCO\underline{C}H_3$; 21.7, C2′. MS (ESI, +ve) *m/z* 575.3 (20%) [MH^+], 475.3 (100%) [MH^+ - Boc)]. HRMS calcd for $C_{29}H_{43}N_4O_8$ 575.3081, found 575.3091.

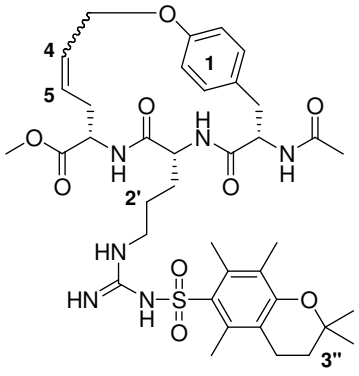
*5.8.2. (7S,10S,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(4-[tert-butoxycarboxamido]butyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**38**)*



The title compound was prepared using the general procedure for olefin metathesis (Procedure D) using **32** (311 mg, 0.52 mmol) to yield **38** 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 7.62 – 7.46 (m, 2H, NH); 7.34 (bs, 1H, NH); 7.11 – 7.01 (m, 2H, ArH); 6.81/6.73 (d, *J* = 8.0 Hz, 2H, ArH); 5.66 (d, *J* =

16.4 Hz, 1H, H4-*trans*); 5.57 – 5.36 (m, 1H, H5); 5.52 – 4.84 (m, 2H, H7 and H13); 4.76 – 4.56 (m, 3H, H2 and H10); 3.80/3.77 (s, 3H, OCH_3); 3.15 – 2.98 (m, 4H, H6 and H4′); 2.80 – 2.58 (m, 2H, H14); 2.10 (s, 3H, $NCOC\underline{H}_3$); 1.50 – 1.19 (m, 6H, H1′, H2′ and H3′); 1.44/1.40 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.5, C9; 171.5/171.3, 7-CO; 170.8/170.7, 13-NCO; 170.0, C12; 156.9, NCO_2; 156.3, 1-ArC1; 130.1, 1-ArCH2 and 1-ArCH6; 128.5, C4; 128.1, C5; 127.7, 1-ArCH4; 117.0/115.4, 1-ArCH3 and 1-ArCH5; 79.1, $\underline{C}(CH_3)_3$; 66.2, C3; 55.0, C13; 53.2/53.0, C10; 52.4, C4′; 40.5/39.7, C7; 35.9/35.1, C14; 29.8/29.4, C1′; 28.6, C6; 27.2/27.0, C3′; 26.6, $C(\underline{C}H_3)_3$; 23.7/23.4, $NCO\underline{C}H_3$; 22.7, C2′. MS (ESI, +ve) *m/z* 575.3 (25%) [MH^+], 475.3 (40%) [MH^+ - Boc)]. HRMS calcd for $C_{29}H_{43}N_4O_8$ 575.3081, found 575.3092.

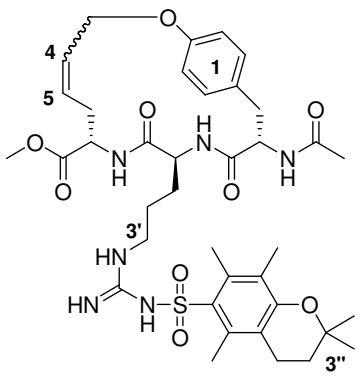
*5.8.3. (7S,10R,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3[{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**39**)*



The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **33** (104 mg, 0.13 mmol) to yield **39** (103 mg, 0.13 mmol, 100%) as a grey solid. Mp 172-175 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.18 – 6.98 (m, 2H, ArH); 6.88 – 6.62 (m, 2H, ArH); 6.37 (bs, 1H, NH); 5.88 – 5.35 (m, H4 and H5); 4.95 – 4.62 (m, 2H, H3); 4.62 – 4.22 (m, 3H, H7, H10 and H13); 3.63 (s, 3H, OCH_3); 3.22 – 2.80 (m, 4H, H3′ and H6); 2.70 – 2.22 (m, 10H, H14, 7″-CH_3, 5″-CH_3 and H4″); 2.06 (s, 3H, 8″-CH_3); 1.90 (s, 3H, $NCOC\underline{H}_3$); 1.95 – 1.76 (m, 2H, H1′); 1.70 – 1.30 (m, 2H, H3″); 1.27 (s, 6H, 2 x 2″-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, $\underline{C}OOCH_3$; 171.2, C11; 170.5, C9; 170.3, $N\underline{C}OCH_3$; 157.1, ArC6″; 156.2, CN_3; 155.4, 1-ArC4; 153.3, ArC8a″; 135.2, ArC5″; 134.6, ArC7″; 133.3, 1-ArCH2 and 1-ArCH6; 130.2, 1-ArC1; 128.4, C4; 128.3, C5; 123.9, ArC8″; 117.8, ArC4a″; 114.7, 1-ArCH3 and 1-ArCH5; 73.6, C2″; 67.7, C3; 65.9, C7; 56.2, C10; 52.5, C13; 52.2, C3′; 51.7, OCH_3; 40.1, C6; 34.9, C14; 32.8, $NCO\underline{C}H_3$; 26.8, 2″-CH_3; 21.5, C3″; 18.6, C4″; 17.6,

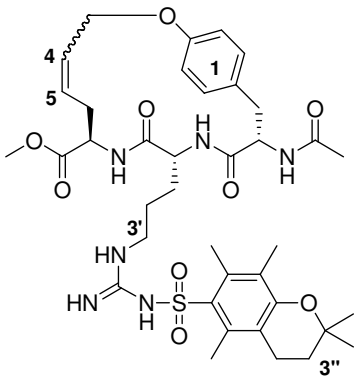
5″-CH_3; 17.2, 7″-CH_3; 15.2, C2′; 12.2, 8″-CH_3. MS (ESI, -ve) *m/z* 767 (100%) [MH^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3558.

*5.8.4. (7S,10S,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**40**)*



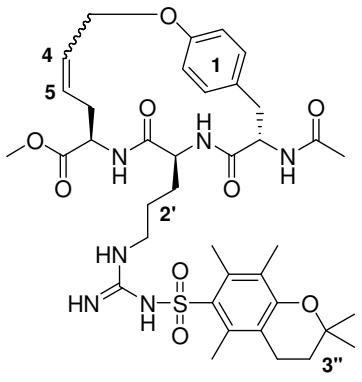
The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **34** (127 mg, 0.16 mmol) to yield **40** (117 mg, 0.15 mmol, 95%) as a grey solid. Mp 224-228 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 – 6.82 (m, 2H, ArH); 6.77 – 6.60 (m, 2H, ArH); 6.41 (bs, 1H, NH); 5.77 – 5.53 (m, H4 and H5); 4.68 – 4.46 (bs, 5H, H3, H7, H10 and H13); 3.67 (s, 3H, OCH_3); 3.30 – 3.05 (m, 2H, H3′); 2.70 – 2.40 (m, 10H, H14, 7″-CH_3, 5″-CH_3 and H4″); 2.08 (s, 3H, 8″-CH_3); 1.78 (s, 3H, NCOC<u>H</u>$_3$); 1.65 – 1.30 (m, 2H, H1′); 1.40 – 1.21 (m, 2H, H3″); 1.30 (s, 6H, 2 x 2″-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, <u>C</u>OOCH$_3$; 171.2, C11; 170.6, C9; 170.2, N<u>C</u>OCH$_3$; 156.3, ArC6″; 156.2, CN_3; 155.4, 1-ArC4; 153.3, ArC8a″; 135.3, ArC5″; 134.7, ArC7″; 130.4, 1-ArCH2 and 1-ArCH6; 129.7, 1-ArC1; 128.4, C4; 127.7, C5; 123.9, ArC8″; 117.8, ArC4a″; 115.2, 1-ArCH3 and 1-ArCH5; 73.6, C2″; 67.7, C3; 65.9, C7; 56.2, C10; 52.6, C13; 52.2, C3′; 51.7, OCH_3; 40.1, C6; 34.9, C14; 33.6, NCO<u>C</u>H$_3$; 26.8, 2″-CH_3; 21.5, C3″; 18.7, C4″; 17.6, 5″-CH_3; 17.2, 7″-CH_3; 15.2, C2′; 12.2, 8″-CH_3. MS (ESI, +ve) *m/z* 769 (100%) [MH^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3574.

*5.8.5. (7R,10R,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3-imino[{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**41**)*



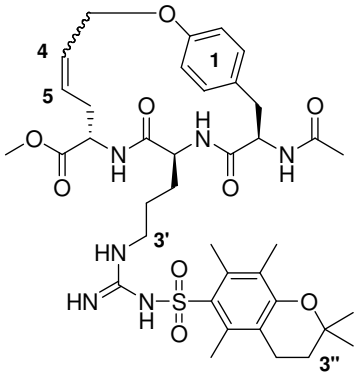
The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **35** (170 mg, 0.210 mmol) to yield **41** (160 mg, 0.210 mmol, 99%) as a grey solid. Mp 205-207 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.10 – 8.00 (m, 2H, NH); 7.10 – 6.95 (m, 2H, ArH); 6.80 – 6.60 (m, 2H, ArH); 6.48 (bs, 1H, NH); 5.90 – 5.60 (m, 2H, NH); 5.60 – 5.30 (m, H4 and H5); 4.62 (bs, 2H, H3); 4.60 – 4.25 (m, 3H, H7, H10 and H13); 3.66 (s, 3H, OCH_3); 3.30 – 2.80 (m, 4H, H3′ and H14); 2.70 – 2.50 (m, 6H, 5″-CH_3 and 7″-CH_3); 2.50 – 2.30 (m, 2H, H4″); 2.00 (s, 3H, 8″-CH_3); 1.75 (s, 3H, NCOC<u>H</u>$_3$); 1.60 – 1.40 (m, 2H, H1′); 1.34 (bs, 2H, H3″); 1.27 (s, 6H, 2 x 2″-CH_3). ^{13}C NMR (CD_3OD, 125 MHz): δ 171.8, <u>C</u>OOCH$_3$; 171.7, C11; 171.4, C9; 171.1, N<u>C</u>OCH$_3$; 157.0, ArC6″; 155.9, CN_3; 155.5, 1-ArC4; 152.4, ArC8a″; 134.2, ArC5″; 134.0, ArC7″; 130.4, 1-ArCH2 and 1-ArCH6; 129.6, 1-ArC1; 128.7, C4; 127.5, C5; 122.8, ArC8″; 117.7, ArC4a; 114.2, 1-ArCH3 and 1-ArCH5; 73.5, C2″; 66.4, C3; 55.0, C7; 53.3, C10; 52.9, C13; 52.3, C3′; 51.9, OCH_3; 40.6, C6; 37.4, C14; 32.2, NCO<u>C</u>H$_3$; 26.7, 2″-CH_3; 22.5, C3″; 21.0, C4″; 18.2, 5″-CH_3; 17.2, 7″-CH_3; 15.2, C2′; 12.0, 8″-CH_3. MS (ESI, -ve) *m/z* 769.5 (85%) [MH^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3631.

*5.8.6. (7R,10S,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3-imino[{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-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 **36** (262 mg, 0.330 mmol) to yield **42** (217 mg, 0.280 mmol, 86%) as a grey solid. Mp 174-176 °C. ^{1}H NMR (d_6DMSO, 500 MHz): δ 8.28 – 8.09 (m, 2H, NH); 7.11 – 7.01 (m, 2H, ArH); 6.77 – 6.72 (m, 2H, ArH); 6.54 - 6.44 (bs, 1H, NH); 5.72 – 5.68 (m, 2H, NH); 5.41 – 5.34 (m, H4 and H5); 4.62 (bs, 2H, H3); 4.52 – 4.04 (m, 3H, H7, H10 and H13); 3.55 (s, 3H, OCH_3); 3.06 – 2.96 (m, 2H, H3′); 2.92 – 2.67 (m, 2H, H14); 2.60 – 2.50 (m, 6H, 5″-CH_3 and 7‴-CH_3); 2.35 – 2.20 (m, 2H, H4″); 2.00 (s, 3H, 8″-CH_3); 1.73 (s, 3H, NCOC<u>H</u>$_3$); 1.67 – 1.44 (m, 2H, H1′); 1.35 (bs, 2H, H3″); 1.23 (s, 6H, 2 x 2″-CH_3). ^{13}C NMR (d_6DMSO, 125 MHz): δ 171.7, <u>C</u>OOCH$_3$; 171.5, C11; 171.3, C9; 171.1, N<u>C</u>OCH$_3$; 156.6, ArC6″; 155.8, CN_3; 155.4, 1-ArC4; 152.2, ArC8a″; 134.4, ArC5″; 133.9, ArC7″; 130.0, 1-ArCH2 and 1-ArCH6; 129.5, 1-ArC1; 128.8, C4; 127.5, C5; 122.6, ArC8″; 117.6, ArC4a″; 114.1, 1-ArCH3 and 1-ArCH5; 73.4, C2″; 66.4, C3; 54.9, C7; 53.3, C10; 52.6, C13; 52.2, C3′; 51.9, OCH_3; 40.6, C6; 37.2, C14; 32.2, NCO<u>C</u>H$_3$; 26.5, 2″-CH_3; 22.5, C3″; 20.8, C4″; 18.2, 5″-CH_3; 17.2, 7″-CH_3; 15.2, C2′; 12.0, 8″-CH_3. MS (ESI, +ve) *m/z* 767 (65%) [MH^+]. HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3630.

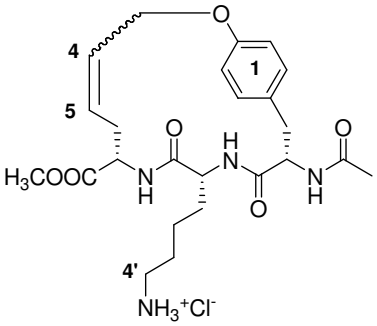
*5.8.7. (7R,10S,13R,4E/Z)-13-Acetamido-8,11-diaza-10-(3-[{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**43**)*



The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **37** (366 mg, 0.46 mmol) to yield **43** (307 mg, 0.40 mmol, 87%) as a grey solid. Mp 186-190 °C. ^{1}H NMR (d_6DMSO, 500 MHz): δ 8.20 – 7.85 (m, 3H, NH); 7.15 – 6.98 (m, 2H, ArH); 6.85 – 6.60 (m, 2H, ArH); 6.41 (bs, 1H, NH); 6.00 – 5.60 (m, 1H H5); 5.60 – 5.38 (m, 1H, H4); 4.65 – 4.10 (m, 5H, H3, H7, H10 and H13); 3.69 (s, 3H, OCH_3); 3.30 – 3.10 (m, 2H, H3′); 2.90 – 2.62 (m, 2H, H4″); 2.60 – 2.50 (m, 8H, H14, 7″-CH_3, and 5″-CH_3); 2.08 (s, 3H, 8″-CH_3); 1.85 (s, 3H, NCOC<u>H</u>$_3$); 1.70 – 1.60 (m, 2H, H1′); 1.50 – 1.30 (m, 2H, H3″); 1.26 (s, 6H, 2 x 2″-CH_3). ^{13}C NMR (d_6DMSO, 125 MHz): δ 171.8, <u>C</u>OOCH$_3$; 171.6, C11; 170.8, C9; 169.5, N<u>C</u>OCH$_3$; 156.8, ArC6″; 156.4, CN_3; 156.0, 1-ArC4; 152.4, ArC8a″; 134.6, ArC5″; 134.5, ArC7″; 130.2, 1-ArCH2 and 1-ArCH6; 129.4, 1-ArC1; 128.3, C4; 127.9, C5; 122.7, ArC8″; 117.8, ArC4a; 114.9, 1-ArCH3 and 1-ArCH5; 73.5, C2″; 67.0, C3; 66.9, C7; 54.8, C10; 54.5, C13; 51.9, C3′; 51.8, OCH_3; 40.1, C6; 36.8, C14; 32.1, NCO<u>C</u>H$_3$; 26.5, 2″-CH_3; 22.4, C3″; 20.8, C4″; 18.2, 5″-CH_3; 17.2, 7″-CH_3; 15.2, C2′; 12.0, 8″-CH_3. MS (ESI, +ve) *m/z* 769 (40%) [MH^+], 106 (100%). HRMS calcd for $C_{38}H_{53}N_6O_9S$ 769.3595, found 769.3600.

*5.9. Synthesis of Tripeptide hydrochloride salts (**11**, **44** – **49**)*

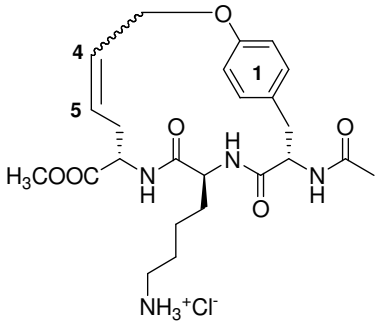
*5.9.1. (7S,10R,13S,4E/Z)-13-Acetamido-10-(4-aminobutyl)-8,11-diaza-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (**11**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **10** (49 mg, 0.084 mmol) to yield **11** (17 mg, 0.033 mmol, 49%) as a highly hygroscopic yellow solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.14 – 7.03 (m, 3H, ArH and

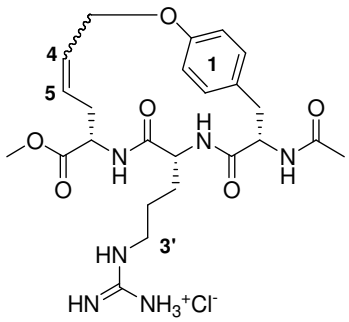
NH); 6.85 (bs, 1H, NH); 6.71 (d, J = 7.5 Hz, 2H, ArH); 6.03 – 5.68 (m, 2H, H4 and H5); 4.50 – 4.02 (m, 5H, H3, H7, H10 and H13); 3.68 (s, 3H, OCH_3); 2.93 – 2.48 (m, 4H, H6 and H4′); 1.93 (s, 3H, $NCOCH_3$); 1.80 – 0.83 (m, 6H, H1′, H2′ and H3′). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.5, C9; 173.1, 7-CO; 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<u>C</u>H_3; 22.6, C2′. MS (ESI, +ve) *m/z* 475.3 (100%) [MH^+]. HRMS calcd for $C_{24}H_{35}N_4O_6$ 475.2557, found 475.2534.

*5.9.2. (7S,10S,13S,4E/Z)-13-Acetamido-10-(4-aminobutyl)-8,11-diaza-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (**44**)*



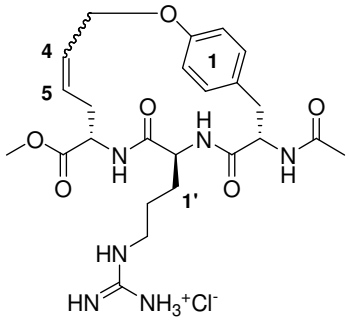
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **38** (220 mg, 0.380 mmol) to yield **44** as a mixture of epimers and *E/Z* iosomers (152 mg, 0.300 mmol, 79%) as a highly hygroscopic yellow solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.19 (d, J = 8.4 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*); 5.46 – 5.35 (m, 1H, H5); 4.56 – 4.37 (m, 4H, H7, H13 and H2); 4.26 – 4.19 (m, 1H, H10); 3.93 (bs, 1H, NH); 3.63/3.60 (s, 3H, OCH_3); 2.89 – 2.57 (m, 6H, H6, H4′ and H14); 1.99/1.89 (s, 3H, NCOC<u>H</u>$_3$); 1.73 – 1.58 (m, 2H, H2′); 1.58 – 1.42 (bs, 2H, H3′); 1.35 – 1.16 (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<u>C</u>H_3; 22.5, C2′. MS (ESI, +ve) *m/z* 475.4 (100%) [MH^+]. HRMS calcd for $C_{24}H_{35}N_4O_6$ 475.2557, found 475.2581.

*5.9.3. (7S,10R,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**45**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **39** (60 mg, 0.078 mmol) to yield **45** (38 mg, 0.071 mmol, 91%) as a white solid. Mp 218-224 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.14 – 7.05 (m, 2H, ArH); 6.85 – 6.68 (m, 2H, ArH); 5.86 – 5.70 (m, 1H, H5); 5.11 – 4.95 (m, 1H, H4); 4.68 – 4.44 (m, 5H, H3, H7, H10 and H13); 3.73 – 3.69 (m, 3H, OCH_3); 3.30 – 3.10 (m, 2H, H3′); 3.04 – 2.94 (m, 2H, H14); 2.81 – 2.48 (m, 2H, H6); 1.94 (s, 3H, NCOC$\underline{H}_3$); 1.71 – 1.91 (m, 2H, H1′); 1.41 - 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′. MS (ESI, +ve) *m/z* 503 (100%) [MH^+]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2626.

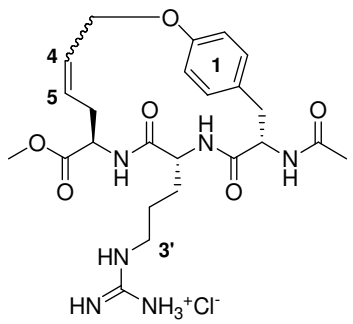
*5.9.4. (7S,10S,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (**46**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **40** (91 mg, 0.12 mmol) to yield **46** as a white solid (38 mg, 0.076 mmol, 59%). Mp 218-220 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.14 – 7.04 (m, 2H, ArH); 6.85 – 6.68 (m, 2H, ArH); 5.80 – 5.65 (m, 1H, H5); 5.55 – 5.35 (m, 1H, H4); 4.65 – 4.10 (m, 5H, H3, H7, H10 and H13); 3.68 (bs, 3H, OCH_3); 3.18 – 3.00 (m, 2H, H3′); 3.00 – 2.85 (m, 2H, H14); 2.70 – 2.40 (m, 2H, H6); 1.99 (s, 3H, NCOC$\underline{H}_3$); 1.80 – 1.65 (m, 2H, H1′); 1.65 – 1.40 (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,

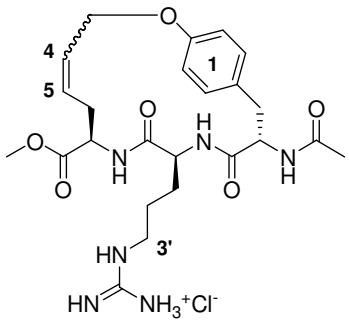
1-ArC1; 116.2, 1-ArCH3 and 1-ArCH5; 66.8, C3; 57.6, C7; 56.0, C10; 54.1, C10; 53.6, C3′; 52.9, OCH_3; 42.0, C6; 38.0, C14; 35.3, NCO<u>C</u>H_3; 26.2, C1′; 22.6, C2′. MS (ESI, +ve) *m/z* 503 (100%) [MH^+]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2603.

*5.9.5. (7R,10R,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (**47**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **41** (108 mg, 0.140 mmol) to yield **47** (25 mg, 0.049 mmol, 35%) as a white solid. Mp 170-176 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.14 – 7.04 (m, 2H, ArH); 6.83 – 6.70 (m, 2H, ArH); 6.08 – 5.79 (m, 1H, H5); 5.54 – 5.45 (m, 1H, H4); 4.66 – 4.12 (m, 5H, H3, H7, H10 and H13); 3.70 – 3.68 (m, 3H, OCH_3); 3.13 – 3.02 (m, 2H, H3′); 3.00 – 2.85 (m, 2H, H14); 2.57 – 2.37 (m, 2H, H6); 1.94 (s, 3H, NCOC<u>H</u>$_3$); 1.80 – 1.45 (m, 2H, H1′); 1.42 – 1.28 (m, 2H, H2′). ^{13}C NMR (CD_3OD, 75 MHz): δ 173.8, <u>C</u>$OOCH_3$; 173.5, C11; 173.2, C9; 172.6, N<u>C</u>OCH_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, NCO<u>C</u>H_3; 26.1, C1′; 22.6, C2′. MS (ESI, +ve) *m/z* 503 (35%) [MH^+]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2644.

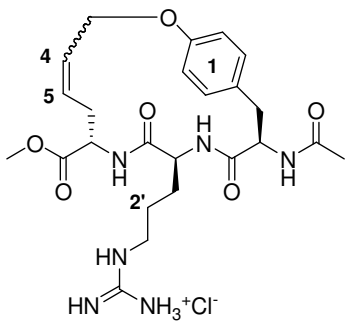
*5.9.6. (7R,10S,13S,4E/Z)-13-Acetamido-8,11-diaza-10-(3-[guanidino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (**48**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **42** (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 7.18 – 7.04 (m, 2H, ArH); 6.88 – 6.67 (m, 2H, ArH); 6.00 – 5.70 (m, 1H, H5); 5.51 – 5.36(m, 1H, H4);

4.65 – 4.26 (m, 5H, H3, H7, H10 and H13); 3.72/3.69 (2 x s, 3H, OCH_3, 2 rotomers 1:3); 3.31 – 3.29 (m, 2H, H3′); 2.25 – 2.82 (m, 2H, H14); 2.70 – 2.40 (m, 2H, H6); 1.94 (s, 3H, NCOC<u>H</u>$_3$); 1.90 – 1.74 (m, 2H, H1′); 1.69 – 1.53 (m, 2H, H2′). ^{13}C NMR (CD_3OD, 75 MHz): δ 174.0, <u>C</u>OOCH$_3$; 173.6, C11; 173.3, C9; 173.0, N<u>C</u>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<u>C</u>H$_3$; 26.5, C1′; 22.3, C2′. MS (ESI, +ve) *m/z* 503.4 (100%) [MH$^+$]. HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2666.

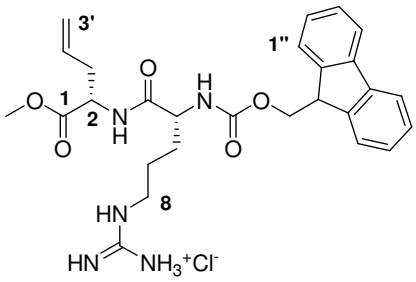
*5.9.7. (7S,10S,13R,4E/Z)-13-Acetamido-8,11-diaza-10-(3-[amino{imino}methylamino]propyl)-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene (**49**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **43** (128 mg, 0.17 mmol) to yield **49** as a highly hygroscopic solid (29 mg, 0.058 mmol, 34%). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.39 – 8.06 (m, 3H, NH); 7.63 (bs, 1H, NH); 7.16 – 7.00 (m, 2H, ArH); 6.83 – 6.64 (m, 2H, ArH); 5.88 – 5.78 (m, 1H, H5); 5.39 – 5.08 (m, 1H, H4); 4.67 – 4.19 (m, 5H, H3, H7, H10 and H13); 3.58 (bs, 3H, OCH$_3$); 3.15 – 2.98 (m, 2H, H3′); 2.92 – 2.60 (m, 2H, H14); 2.59 – 2.30 (m, 2H, H6); 1.77 (s, 3H, NCOC<u>H</u>$_3$); 1.84 – 1.66 (m, 2H, H1′); 1.39 – 1.26 (m, 2H, H2′). ^{13}C NMR (CD_3OD, 75 MHz): δ 171.3, <u>C</u>OOCH$_3$; 171.6, C11; 171.3, C9; 169.4, N<u>C</u>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<u>C</u>H$_3$; 29.0, C1′; 22.4, C2′. MS (ESI, +ve) *m/z* 503 (30%) [MH$^+$], 102 (100%). HRMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2638.

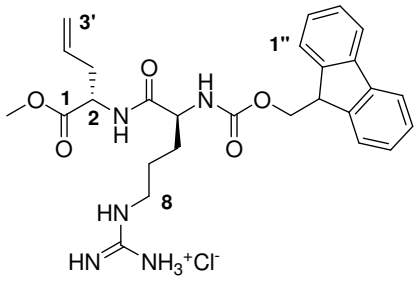
*5.10 Synthesis of Dipeptide Hydrocholride Salts (Scheme 5, **50** – **53**)*

*5.10.1. Methyl (2S,5R)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (**50**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **23** (81 mg, 0.105 mmol) giving **50** (43 mg, 0.079 mmol, 75%). as a highly hygroscopic solid; $[\alpha]_D^{23}$ +17.7 (*c* 0.008, MeOH). IR (neat) ν_{max} 1662, 1540, 1210, 1178, 1098, 1030, 1004, 742. Mp 203-208 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.88 – 7.85 (m, 2H, ArH1″ and ArH8″); 7.66 – 7.77 (m, 2H, ArH4″ and ArH5″); 7.45 – 7.27 (m, 4H, ArH3″ and ArH6″ and ArH2″ and ArH7″); 5.81 – 5.71 (m, 1H, H2′); 5.16 – 5.03 (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″); 4.35 – 4.29 (m, 1H, H5); 4.2 – 4.15 (m, 1H, H9″); 3.68 (s, 3H, OCH_3); 3.17 (bs, 2H, H8); 2.61 – 2.41 (m, Hz, 2H, H1′); 1.88 – 1.75 (m, 2H, H7); 1.75 – 1.55 (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. MS (ESI, +ve) *m/z* 508 (100%) [MH^+]. HRMS calcd for $C_{27}H_{34}N_5O_5$ 508.2526, found 508.2570.

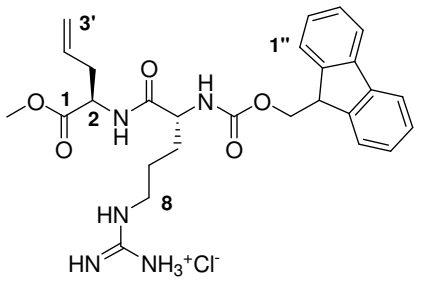
*5.10.2. Methyl (2S,5S)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (**51**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **24** (81 mg, 0.105 mmol) giving **51** (27 mg, 0.05 mmol, 47%) as a highly hygroscopic solid; $[\alpha]_D^{23}$ +6.4 (*c* 0.005, MeOH). IR (neat) ν_{max} 1663, 1528, 1210, 1179, 1098, 1030, 741. Mp 176-182 °C. ^{1}H

NMR (CD_3OD, 500 MHz): δ 7.79 (d, *J* = 7.5 Hz, 2H, ArH1″ and ArH8″); 7.68 – 7.56 (m, 2H, ArH4″ and ArH5″); 7.44 – 7.27 (m, 4H, ArH3″ and ArH6″ and ArH2″ and ArH7″); 5.81 – 5.65 (m, 1H, H2′); 5.15 – 5.02 (m, 2H, H3′); 4.46 (dd, *J* = 6.0, 8.1 Hz, 1H, H2); 4.34 (d, *J* = 7.2 Hz, 2H, OC$\underline{H}_2$-H9″); 4.34 – 4.28 (m, 1H, H5); 4.22 – 4.12 (m, 1H, H9″); 3.71/3.69 (2 x s, 3H, OCH_3, 2 rotomers 1:3); 3.28 – 3.08 (m, 2H, H8); 2.59 – 2.40 (m, 2H, H1′); 1.95 – 1.72 (m, 2H, H7); 1.75 – 1.52 (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, $\underline{C}H_2$-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. MS (ESI, +ve) *m/z* 508 (100%) [MH^+]. HRMS calcd for $C_{37}H_{34}N_5O_5$ 508.2560, found 508.2574.

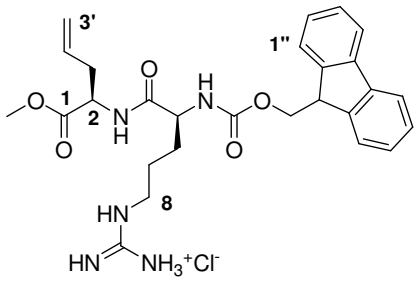
*4.10.3. Methyl (2R,5R)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (**52**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **25** (80 mg, 0.10 mmol) to yield **52** (45 mg, 0.083 mmol, 80%) as a highly hygroscopic white solid; $[\alpha]_D^{23}$ -50.6 (*c* 0.002, MeOH). IR (neat) ν_{max} 1715, 1653, 1558, 1540, 1212, 1046, 738. ^1H 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″); 5.62 – 5.54 (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$\underline{H}_2$-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); 2.41 – 2.26 (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, $\underline{C}H_2$-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. MS (ESI, +ve) *m/z* 508 (45%) [MH^+]. HRMS calcd for $C_{27}H_{34}N_5O_5$ 508.2560, found 508.2592.

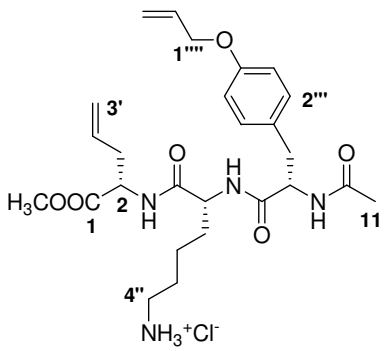
*5.10.4. Methyl (2R,5S)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-8-(guanidino)-4-oxooctanoate hydrochloride (**53**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A) using **26** (94 mg, 0.12 mmol) to yield **53** (33 mg, 0.061 mmol, 51%) as a highly hygroscopic white solid; $[\alpha]_D^{22}$ -19.6 (*c* 0.005, MeOH). IR (neat) ν_{max} 1662, 1537, 1213, 1107, 1050, 1031, 738. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.79 (d, *J* = 7.5 Hz, 2H, ArH1″ and ArH8″); 7.67 – 7.63 (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″); 5.78 – 5.65 (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); 4.24 – 4.13 (m, 1H, H9″); 3.69 (s, 3H, OCH_3); 3.17 (t, *J* = 6.6 Hz, 2H, H8); 2.60 – 2.40 (m, 2H, H1′); 1.86 – 1.78 (m, 2H, H7); 1.67 – 1.50 (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, $\underline{C}H_2$-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. MS (ESI, +ve) *m/z* 508 (25%) [MH^+], 179 (100%) [Sodium allylglycinamide]. HRMS calcd for $C_{27}H_{34}N_5O_5$ 508.2560, found 508.2555.

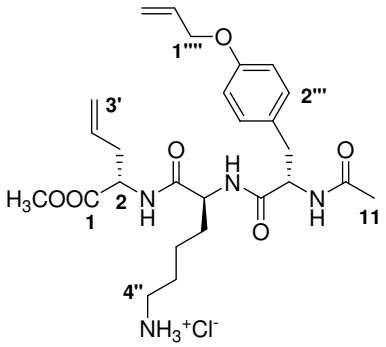
*5.11. Synthesis of Acyclic Tripeptide hydrochloride salts (Scheme 6: **54** – **59**)*

*5.11.1. Methyl (2S,5R,8S)-2-allyl-8-(4-allyloxyphenyl)-5-(4-aminobutyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (**54**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **9** (64 mg, 0.11 mmol) to yield **54** (22 mg, 0.041 mmol, 37%) as a cream coloured highly hygroscopic 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‴); 6.09 – 6.01 (m, 1H, H2⁗); 5.77 – 5.69 (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⁗); 4.43 – 4.37 (m, 2H, H2 and H5); 4.15 (d, *J* = 6.5 Hz, 1H, H8); 3.69 (s, 3H, OCH_3); 2.96 – 2.90 (m, 2H, H1′); 2.83 (bs, 2H, H4″); 2.60 – 2.48 (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″. MS (ESI, +ve) *m/z* 503.7 (100%) [MH^+]. HRMS calcd for $C_{26}H_{39}N_4O_6$ 503.2870, found 503.2881.

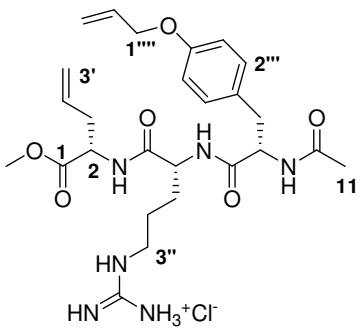
*5.11.2. Methyl (2S,5S,8S)-8-acetamido-2-allyl-9-(4-allyloxyphenyl)-5-(4-aminobutyl)-3,6-diaza-4,7-dioxononanoate hydrochloride (**55**)*



The title compound was synthesized using the general procedure (Procedure A), by deprotection of **32** (104 mg, 0.170 mmol) to yield **55** as a 1:1 mixture of epimers (55 mg, 0.10 mmol, 60%) as a highly hygroscopic 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‴); 6.08 – 5.99 (m, 1H, H2⁗); 5.81 – 5.73 (m, 1H, H2′); 5.37 (d, J = 17.3 Hz, 1H, $H3_a$⁗); 5.22 (d, J = 9.7 Hz, 1H, $H3_b$⁗); 5.15 – 5.04 (m, 2H, H3′); 4.52 – 4.36 (m, 5H, H2, H5, H8 and H1⁗); 3.69/3.67 (s, 3H, OCH_3); 3.08 – 2.76 (m, 4H, H1′ and H4″); 2.62 – 2.40 (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″. MS (ESI, +ve) *m/z* 503.3 (100%) [MH^+]. HRMS calcd for $C_{26}H_{39}N_4O_6$ 503.2870, found 503.2894.

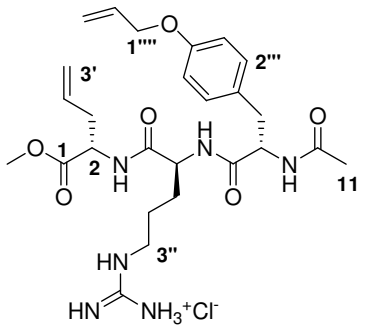
*5.11.3. Methyl (2S,5R,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino]propyl)-4,7,10-oxoundecanoate hydrochloride (**56**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **33** (70 mg, 0.088 mmol) to yield **56** (37 mg, 0.065 mmol, 74%) as a highly hygroscopic solid; $[\alpha]_D^{24}$ +17.4 (*c* 0.007, MeOH). IR (neat) ν_{max} 1734, 1652, 1543, 1507, 1445, 1217, 1052, 1000, 767. ^1H 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‴); 6.05 – 5.96 (m, 1H, H2⁗); 5.76 – 6.64 (m, 1H, H2′); 5.35 (d, J = 17.4 Hz, 1H, $H3_a$⁗); 5.19 (d, J = 9.9 Hz, 1H, $H3_b$⁗); 5.08 – 5.02 (m, 2H, H3′); 4.48 – 4.47 (m, 2H, H2⁗); 4.42 – 4.342 (m, 2H, H2 and H5); 4.18 – 4.14 (m, 1H, H8); 3.65 (s, 3H, OCH_3); 3.36 – 3.26 (m, 2H, H3″); 3.06 – 2.96 (m, 2H, $ArCH_2$); 2.54 – 2.46 (m, 2H, H1′); 1.92 (s, 3H, H11); 1.85 – 1.64 (m, 2H, H1″); 1.40 – 1.16 (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;

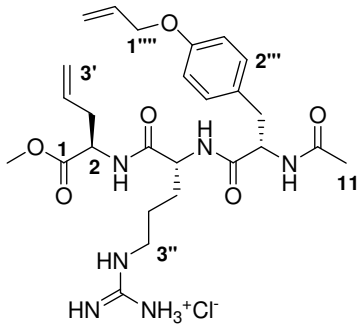
50.1, C3″; 37.5, $ArCH_2$; 36.4, C1′; 29.5, C2″; 24.0, C11; 22.3, C1″. MS (ESI, +ve) *m/z* 531 (100%) [MH^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2939.

*5.11.4. Methyl (2S,5S,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino]propyl)-4,7,10-oxoundecanoate hydrochloride (**57**)*



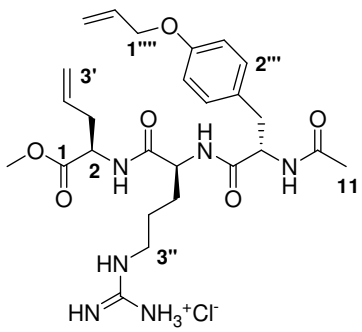
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **34** (63 mg, 0.079 mmol) to yield **57** (38 mg, 0.036 mmol, 85%) as a highly hygroscopic solid; $[\alpha]_D^{21}$ +46.1 (*c* 0.001, MeOH). IR (neat) ν_{max} 1740, 1631, 1543, 1512, 1254, 1093. ^{1}H 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‴); 6.09 – 5.97 (m, 1H, H2⁗); 5.84 – 5.70 (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, $H3_b$′); 4.50 – 4.48 (m, 3H, H1⁗ and H5); 4.42 – 4.36 (m, 2H, H2 and H8); 3.69 (s, 3H, OCH_3); 3.21 – 3.15 (m, 2H, H3″); 3.02 (dd, *J* = 5.7, 13.8 Hz, 1H, ArC<u>H</u>H); 2.82 (dd, *J* = 9.0, 14.1 Hz, 1H, ArCH<u>H</u>); 2.60 – 2.41 (m, 2H, H1′); 1.92 (s, 3H, H11); 1.88 – 1.81 (m, 2H, H1″); 1.70 – 1.58 (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″. MS (ESI, +ve) *m/z* 531.1 (100%) [MH^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2916.

*5.11.5. Methyl (2R,5R,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino]propyl)-4,7,10-oxoundecanoate hydrochloride (**58**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **35** (48 mg, 0.60 mmol) to yield **58** (32 mg, 0.060 mmol, 100%) as a highly hygroscopic solid; $[\alpha]_D^{22}$ +16.0 (*c* 0.008, MeOH). IR (neat) ν_{max} 1652, 1543, 1512, 1222, 1181, 1047, 1005, 834, 752. ^{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‴); 6.08 – 6.00 (m, 1H, H2⁗); 5.78 – 5.70 (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, $H3_b$′); 4.45 – 4.40 (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″); 2.89 – 2.82 (m, 2H, $ArCH_2$); 2.59 – 2.42 (m, 2H, H1′); 1.95 (s, 3H, H11); 1.75 – 1.59 (m, 2H, H1″); 1.11 – 1.08 (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″. MS (ESI, +ve) *m/z* 531.5 (80%) [MH^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2936.

*5.11.6. Methyl (2R,5S,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(3-[guanidino]propyl)-4,7,10-oxoundecanoate hydrochloride (**59**)*

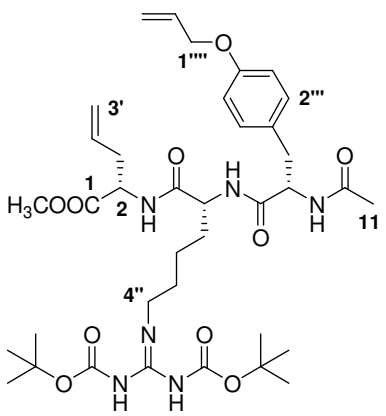


The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **36** (87 mg, 0.11 mmol) to yield **59** (35 mg, 0.062 mmol, 56%) as a highly hygroscopic solid; $[\alpha]_D^{22}$ +16.0 (*c* 0.008, MeOH). IR (neat) ν_{max} 1652, 1543, 1512, 1222, 1181, 1047, 1005, 834, 752. ^{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‴); 6.10 – 5.98 (m, 1H, H2⁗); 5.84 – 5.70 (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⁗); 4.42 – 4.37 (m, 3H, H2, H5 and H8); 3.71 (s, 3H, OCH_3); 2.97 (t, J = 7.5 Hz, 2H, H3″); 3.02 – 2.85 (m, 2H, $ArCH_2$); 2.63 – 2.45 (m, 2H, H1′); 1.93 (s, 3H, CH_3, H11); 1.84 – 1.73 (m, 2H, H1″); 1.63 – 1.60 (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″. MS (ESI, +ve) *m/z* 531.1 (85%) [MH^+]. HRMS calcd for $C_{26}H_{39}N_6O_6$ 531.2931, found 531.2952.

5.12. Synthesis of Acyclic GuanidineLysine Derivatives (Scheme 7)

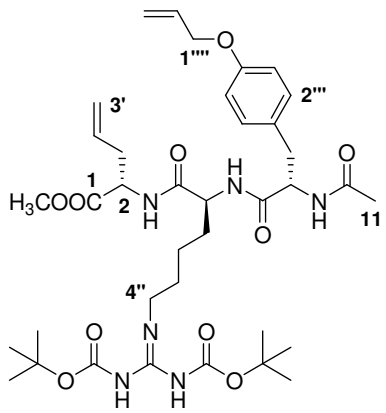
*5.12.1. Methyl (2S,5R,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4[{N,N-di-tert-butoxycarbonyl}guanidino]butyl)-4,7,10-trioxoundecanoate (**60**)*



To a solution of **9** (56 mg, 0.093 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (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, CH_2Cl_2/ MeOH) to yield the title compound as a 1:1 mixture of epimers (70 mg, 0.093 mmol, 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); 7.11 – 7.04 (m, 2H, ArH2‴ and ArH6‴); 6.94 (d,

J = 7.6 Hz, 1H, NH); 7.11 – 6.79 (m, 2H, ArH3‴ and ArH5‴); 6.72 (d, J = 7.2 Hz, 1H, NH); 6.60 (d, J = 7.6 Hz, 1H, NH); 6.07 – 5.96 (m, 1H, H2⁗); 5.71 – 5.61 (m, 1H, H2′); 5.38 (d, J = 17.3 Hz, 1H, $H3_a$⁗); 5.26 (d, J = 10.5 Hz, 1H, $H3_b$⁗); 5.14 – 5.06 (m, 2H, H3′); 4.70 – 4.34 (m, 5H, H2, H5, H8 and H2⁗); 3.74/3.70 (s, 3H, OCH_3); 3.32 (d, J = 6.7 Hz, 2H, H4″); 3.00 – 2.86 (m, 2H, $ArCH_2$); 2.56 – 2.43 (m, 2H, H1′); 1.97/1.96 (s, 3H, H11); 1.40 – 1.05 (m, 6H, H1″, H2″ and H3″); 1.49 (s, 18H, 2 x $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1/171.7, C7; 171.4/171.3, C1; 170.9, C4; 170.7, C10; 163.1, CN_3; 157.5/157.4, ArC4‴; 156.0/155.9, NCO_2; 153.0, NCO_2; 133.1/133.0, C2′; 132.1/131.9, C2⁗; 130.0, ArCH2‴ and ArCH6‴; 128.2/128.0, ArC1‴; 119.1/118.9, C3′; 117.5/117.3, C3⁗; 114.8/114.7, ArCH3‴ and ArCH5‴; 83.2/83.1, $\underline{C}(CH_3)_3$; 79.5/79.4, $\underline{C}(CH_3)_3$; 68.7, C1⁗; 55.4/54.6, C5; 52.9, OCH_3; 52.5/52.8, C8; 51.9/51.8, C2; 40.7/40.5, C4″; 37.2, $ArCH_2$; 36.3, C1′; 36.1, C1″; 31.9/31.5, C3″; 28.6/28.3, $C(CH_3)_3$; 22.9/22.7, C11; 22.5, C2″. MS (ESI, +ve) *m/z* 745.4 (100%) [MH^+]. HRMS calcd for $C_{37}H_{57}N_6O_{10}$ 745.4136, found 745.4138.

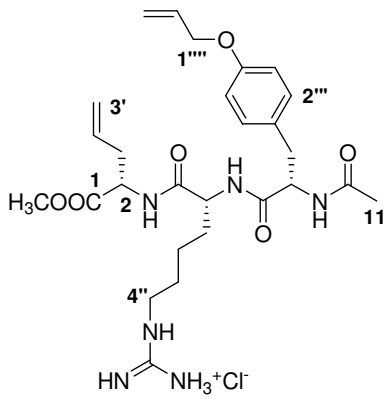
*5.12.2. Methyl (2S,5S,8S)-2-allyl-8-(4-allyloxybenzyl)-3,6,9-triaza-5-(4[{N,N-di-tert-butoxycarbonyl}guanidino]butyl)-4,7,10-trioxoundecanoate (**61**)*



To a solution of **32** (41 mg, 0.081 mmol) in CH_2Cl_2 (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, CH_2Cl_2/ MeOH) to yield the title compound as a 1:1 mixture of epimers (45 mg, 0.060 mmol, 74%) as an orange/yellow solid. Mp 114-118 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.26 (bs, 1H, NH); 7.08 (t, J = 8.4 Hz, 2H, ArH2‴ and ArH6‴); 6.99 – 6.94 (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); 6.09 – 5.96 (m, 1H, H2⁗); 5.74 – 5.59 (m, 1H,

H2′); 5.39 (d, J = 17.3 Hz, 1H, H3$_a$′′′′); 5.26 (d, J = 10.1 Hz, 1H, H3$_b$′′′′); 5.14 – 5.06 (m, 2H, H3′); 4.70 – 4.33 (m, 5H, H2, H5, H8 and H1′′′′); 3.74/3.71 (s, 3H, OCH_3); 3.33 (bs, 2H, H4′′); 3.05 – 2.88 (m, 2H, H1′); 2.59 – 2.46 (m, 2H, $ArCH_2$); 1.97 (s, 3H, H11); 1.50 – 1.20 (m, 6H, H1′′, H2′′ and H3′′);1.49 (s, 18H, C(C$\underline{H}_3$)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.7/171.6, C7; 171.3/171.2, C1; 170.9/170.7, C4; 170.6, C10; 163.2/163.1, CN_3; 157.5/157.4, ArC4′′′; 156.0, NCO_2; 153.1/151.4, NCO_2; 133.1/133.0, C2′; 132.0/131.9, C2′′′′; 130.1, ArCH2′′′ and ArCH6′′′; 128.2/128.1, ArC1′′′; 119.2/119.0, C3′; 117.5, C3′′′′; 114.8/114.7, ArCH3′′′ and ArCH5′′′; 83.2/83.1, NCO_2; 79.5/79.4, NCO_2; 68.7, C1′′′′; 55.2/54.5, C5; 53.1/53.0, OCH_3; 52.4, C8; 52.4/51.9, C2; 40.7/40.5, C4′′; 37.2, $ArCH_2$; 36.1, C1′; 32.0/31.6, C1′′; 28.6/28.3, C($\underline{C}H_3$)$_3$; 28.1/27.8, C($\underline{C}H_3$)$_3$; 22.9, C11; 22.6, C2′′. MS (ESI, +ve) *m/z* 745.2 (100%) [MH^+]. HRMS calcd for $C_{37}H_{57}N_6O_{10}$ 745.4136, found 745.4105.

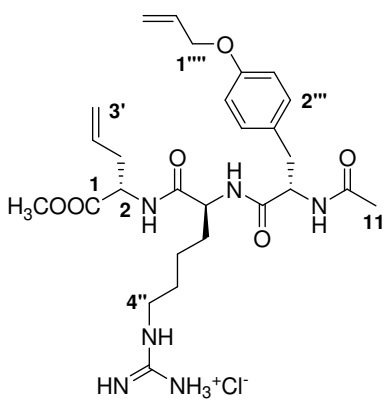
*5.12.3. Methyl (2S,5R,8S)-2-allyl-9-(4-allyloxybenzyl)-5-(4-[guanidino]butyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (**62**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **60** (71 mg, 0.095 mmol) to yield **62** (43 mg, 0.074 mmol, 78%) as a yellow hygroscopic solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.25 – 8.15 (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′′′); 6.10 – 5.96 (m, 1H, H2′′′′); 5.80 – 5.66 (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$_b$′); 4.52 – 4.37 (m, 4H, H2, H5 and H1′′′′); 4.17 (dd, J = 4.0, 8.7 Hz, 1H, H8); 3.72 (s, 3H, OCH_3); 3.18 – 2.80 (m, 4H, H1′ and H4′′); 2.62 – 2.42 (m, 2H, $ArCH_2$); 1.94 (s, 3H, H11); 1.83 – 1.39 (m, 4H, H2′′ and H3′′); 1.05 – 0.97 (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″. MS (ESI, +ve) *m/z* 545.4 (100%) [MH^+]. HRMS calcd for $C_{27}H_{41}N_6O_6$ 545.3088, found 545.3073.

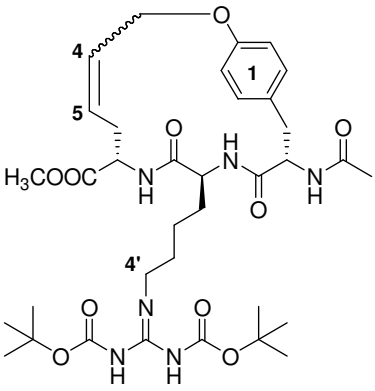
*5.12.4. Methyl (2S,5S,8S)-2-allyl-9-(4-allyloxyphenyl)-5-(4-[guanidino]butyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (**63**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **61** (40 mg, 0.054 mmol) to yield **63** (11 mg, 0.019 mmol, 35%) as a highly hygroscopic yellow solid. ^1H NMR (CD_3OD, 300 MHz): δ 7.10 (bs, 2H, ArH2‴ and ArH6‴); 6.79 (bs, 2H, ArH3‴ and ArH5‴); 6.10 – 5.90 (m, 1H, H2⁗); 5.84 – 5.62 (m, 1H, H2′); 5.36 – 4.99 (m, 4H, H3⁗ and H3′); 4.45 – 4.10 (m, 5H, H2, H5, H8 and H1⁗); 3.65 (s, 3H, OCH_3); 3.11 – 2.70 (m, 4H, H1′ and H4″); 2.49 (bs, 2H, $ArCH_2$); 1.87 (s, 3H, H11); 1.47 – 1.23 (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″. MS (ESI, +ve) *m/z* 545.3 (100%) [MH^+]. HRMS calcd for $C_{27}H_{41}N_6O_6$ 545.3088, found 545.3066.

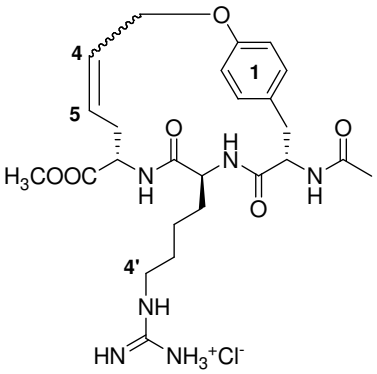
5.13. Synthesis of Cyclic GuanidineLysine Derivatives (Scheme 8)

*5.13.1.(7S,10S,13S,4E/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 (**64**)*



To a solution of **10** (75 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added *N-tert*-butoxycarboxamido(trifluoromethylsulfonylimino)methyl propanamide (115 mg, 0.29 mmol), triethylamine (0.1 mL) and CH_2Cl_2 (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, CH_2Cl_2/MeOH) to yield **64** as a 1:1 mixture of epimers (96 mg, 0.13 mmol, 87%) as an orange/yellow solid. Mp 104-102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.28 – 8.24 (m, 1H, NH); 7.14 – 6.71 (m, 4H, ArH); 6.00 – 5.50 (m, 2H, H4 and H5); 4.77 – 4.55 (m, 5H, H2, H7, H10 and H13); 3.79/3.78 (s, 3H, OCH_3); 3.34 – 3.23 (m, 2H, H4′); 2.99 – 2.87 (m, 2H, H6); 2.77 – 2.637 (m, 2H, H14); 2.09/2.07 (s, 3H, $NCOC\underline{H}_3$); 1.60 – 1.50 (m, 6H, H1′, H2′ and H3′); 1.49/1.48 (s, 18H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1/171.8, C9; 170.8/170.7, 7-CO; 170.3, 13-NCO; 169.9, C12; 163.6, CN_3; 156.7, 1-ArC1; 156.3/156.2, NCO_2; 153.4/153.3, NCO_2; 130.4, 1-ArCH2 and 1-ArCH6; 129.9, C4; 128.4, C5; 127.6, 1-ArC4; 116.8, 1-ArCH3 and 1-ArCH5; 83.4/83.3, $\underline{C}(CH_3)_3$; 79.5/79.4, $\underline{C}(CH_3)_3$; 66.2, C3; 54.8, C13; 53.8, C10; 52.1, OCH_3; 41.1, C4′; 33.9, C7; 31.3, C14; 30.0, C6; 29.2, $C(\underline{C}H_3)_3$; 27.5, C3′; 23.5, 13-$NCO\underline{C}H_3$; 22.6, C2′. MS (ESI, +ve) *m/z* 717.4 (100%) [MH^+]. HRMS calcd for $C_{35}H_{53}N_6O_{10}$ 717.3823, found 717.3806.

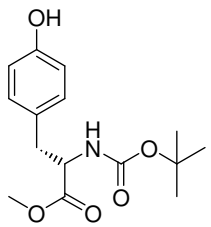
*5.13.2. (7S,10S,13S,4E/Z)-13-Acetamido-10-(4-[guanidino]butyl)-8,11-diaza-7-methoxycarbonyl-2-oxa-9,12-dioxo-1(1,4)phenylenacyclotetradecaphane-4-ene hydrochloride (**65**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **64** (86 mg, 0.12 mmol) to yield **65** (50 mg, 0.097 mmol, 81%) as a highly hygroscopic yellow solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 10.34 (bs, 1H, NH); 7.55 – 7.36 (m, 2H, ArH); 7.18 – 7.07 (m, 2H, ArH); 5.97 – 5.80 (m, 2H, H4 and H5); 4.98 – 4.68 (m, 5H, H2, H7, H10 and H13); 3.65 (s, 3H, OCH_3); 3.32 – 3.31 (m, 2H, H4′); 3.10 – 3.00 (m, 2H, H6); 2.42 – 2.40 (m, 2H, H14); 2.10 (s, 3H, NCOC<u>H</u>$_3$); 2.10 – 2.00 (m, 2H, H3′); 1.90 – 1.80 (m, 2H, H1′); 1.54 – 1.42 (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<u>C</u>H$_3$; 22.5, C2′. MS (ESI, +ve) *m/z* 517.4 (100%) [MH^+]. HRMS calcd for $C_{25}H_{37}N_6O_6$ 517.2775, found 517.2765.

5.14. Synthesis of Dityrosine Cyclic Peptides (Scheme 9)

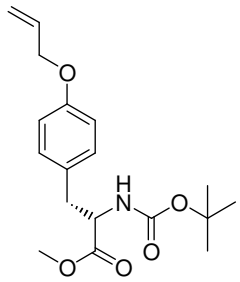
*5.14.1. Methyl (2S)-(4-hydroxyphenyl)-2-tert-butoxycarboxamido propanoate (**67**)*



To a solution of (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid **66** (5.23 g, 28.9 mmol) in anhydrous MeOH (20 mL) at 0 °C 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 extracts were washed with water (5 x 20 mL), dried and evaporated. The crude product was purified by flash

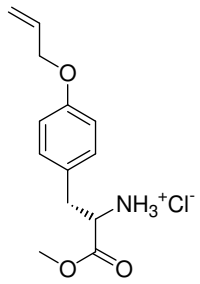
column chromatography (25 : 1, CH_2Cl_2/MeOH) to yield the title compound (1.32 g, 4.48 mmol, 16%) as a yellow oil, which was spectroscopically identical to that reported.[20] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.95 (d, *J* = 8.4 Hz, 2H, ArH2′ and ArH6′); 6.73 (d, *J* = 8.4 Hz, 2H, ArH3′ and ArH5′); 6.51 (bs, 1H, OH); 5.05 (d, *J* = 8.4 Hz, 1H, NH); 4.57 – 4.50 (m, 1H, H2), 3.71 (s, 3H, OCH_3); 3.06 – 2.91 (m, 2H, H3); 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.5, C1; 155.2, NCO; 155.1, ArC4′; 130.2, ArCH2′ and ArCH6′; 127.2, ArCH3′ and ArCH5′; 115.4, ArC1′; 80.2, $\underline{C}(CH_3)_3$; 54.6, C2; 52.3, OCH_3; 37.6, C3; 28.3, $C(\underline{C}H_3)_3$. MS (CI, +ve) *m/z* 196 (100%) [MH^+ (less Boc)]. HRMS calcd for $C_{16}H_{22}NO_5$ 296.1498, found 296.1503.

*5.14.2. Methyl (2S)-3-(4-allyloxyphenyl)-2-tert-butoxycarboxamidopropanoate (**68**)*



To a solution of **67** (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 40 mL). The combined extracts 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 colourless solid, which was identical to that reported.[23] Mp 142-144 °C (lit. 145 °C).[23]

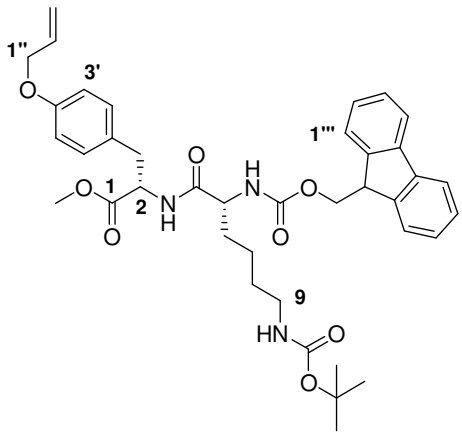
*5.14.3. Methyl (2S)-2-(4-allyloxyphenyl)-2-aminopropanoate hydrochloride (**69**)*



To a solution of **68** (1.10 g, 3.28 mmol) in CH_2Cl_2 (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 (CH_2Cl_2/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′); 6.11 – 5.98 (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, $H3_b$″); 4.55 – 4.53 (m, 2H, H1″); 4.26 (t, *J* = 7.2 Hz 1H, H2); 3.81 (s, 3H, OCH_3); 3.23 – 3.06 (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. MS (CI, +ve) *m/*z 236 (90%) [MH^+]. HRMS calcd for $C_{13}H_{18}NO_3$ 236.1287, found 236.1276.

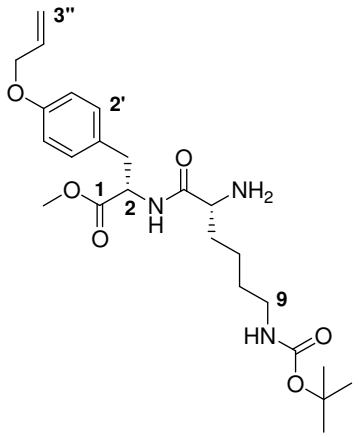
*5.14.4. Methyl (2S,5R)-2-(4-allyloxybenzyl)-3-aza-9-(tert-butoxycarboxamido)-5-(9H-9-fluorenylmethylcarboxamido)-4-oxononanoate (**70**)*



The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **69** (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 **70** (317 mg, 0.47 mmol, 75%) as a pale yellow solid. IR (neat) ν_{max} 11734, 1684, 1653, 1539, 1510, 1250, 1174, 738. 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′); 5.99 – 5.95 (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); 4.38 – 4.34 (m, 3H, OCH_2 and $OC\underline{H_2}$-H9‴); 4.20 – 4.18 (m, 2H, H1″); 3.68 (s, 3H, OCH_3); 3.05 – 3.04 (m, 4H, H9 and $ArCH_2$); 1.76 – 1.70 (m, 2H, H6); 1.60 – 1.50 (m, 2H, H7); 1.42 (s, 9H $C(CH_3)_3$); 1.23 – 1.21 (m, 2H, H8). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.7, C4; 171.2, C1; 157.4 , NCO; 155.9, NCO‴; 143.6, ArC4′; 143.3, ArC8a‴ and ArC9a‴; 141.0, ArC4a‴ and ArC4b‴;

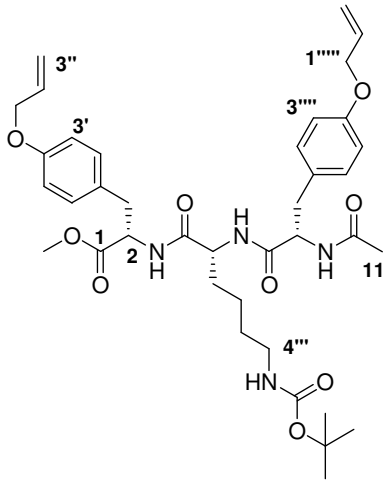
133.0, C2″; 130.0, ArCH2′ and ArCH6′; 127.7, ArCH3‴ and ArCH6‴; 127.5, ArCH2‴ and ArCH7‴; 126.9, ArCH1‴ and ArCH8‴; 124.9, ArCH4‴ and ArCH5‴; 119.8, ArC1′; 117.4, C3″; 114.6, ArCH3′ and ArCH5′; 79.0, $\underline{C}(CH_3)_3$; 68.6, $\underline{C}H_2$-C9‴; 67.1, C1″; 54.6, C5; 53.2, C2; 52.3, OCH_3; 47.0, C9‴; 39.9, C9; 37.0, $ArCH_2$; 32.2, C6; 29.6, C8; 28.4, $C(\underline{C}H_3)_3$; 22.3, C7. MS (ESI, +ve) *m/z* 708.4 (100%) [MNa^+]. HRMS calcd for $C_{39}H_{48}N_3O_8$ 686.3439, found 686.3441.

*5.14.5. Methyl (2S,5R)-2-(4-allyloxybenzyl)-5-amino-3-aza-9-(tert-butoxycarboxamido)-4-oxononanoate (**71**)*



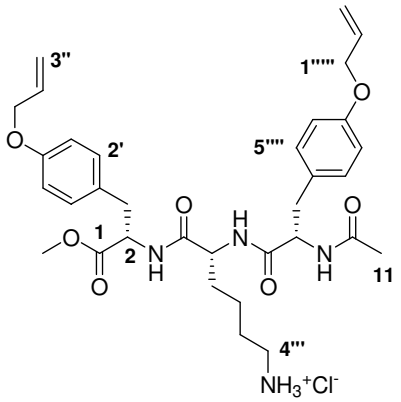
The title compound was synthesized using the general *N*-Fmoc deprotection procedure (Procedure C), from **70** (198 mg, 0.290 mmol) to yield **71** (131 mg, 0.280 mmol, 97%) as a cream oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.63 (d, *J* = 8.4 Hz, 1H, NH); 7.04 (d, *J* = 8.4 Hz, 2H, ArH2′ and ArH6′); 6.83 (d, *J* = 8.4 Hz, 2H, ArH3′ and ArH5′); 6.11 – 5.98 (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, $H3_b$″); 4.81 – 4.75 (m, 1H, H2); 4.66 (bs, 1H, NH); 4.51 – 4.49 (m, 2H, H1″); 3.71 (s, 3H, OCH_3); 3.32 (dd, *J* = 4.2, 7.6 Hz, 1H, H5); 2.60 – 2.54 (m, 4H, $ArCH_2$ and H8); 1.81 – 1.25 (m, 6H, H6, H7 and H8); 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.0, C4; 172.3, C1; 157.9, NCO_2; 156.3, ArC4′; 133.5, C2″; 130.4, ArCH2′ and ArCH6′; 128.5, ArC1′; 118.0, C3″; 115.0, ArCH3′ and ArCH5′; 79.4, $\underline{C}(CH_3)_3$; 69.1, C1″; 55.3, C2; 54.4, C5; 52.7, OCH_3; 40.6, C9; 37.5, $ArCH_2$; 34.8, C6; 30.3, C8; 28.9, $C(\underline{C}H_3)_3$; 23.1, C7. MS (ESI, +ve) *m/z* 464.3 (100%) [MH^+]. HRMS calcd for $C_{24}H_{38}N_3O_6$ 464.2761, found 464.2749.

*5.14.6. Methyl (2S,5R,8S)-2,8-di(4-allyloxybenzyl)-3,6,9-triaza-5-(4-[tert-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate (**72**)*



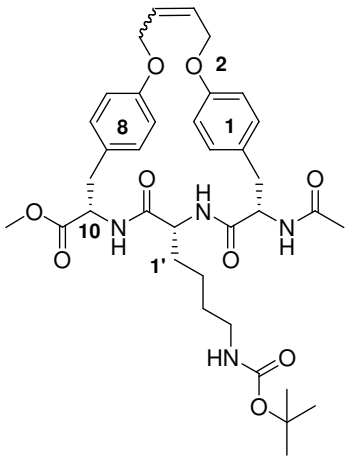
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **71** (220 mg, 0.600 mmol) and **14** (132 mg, 0.500 mmol) to yield **72** (130 mg, 0.180 mmol, 37%) as a white solid. Mp 185-186 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (d, *J* = 7.6 Hz, 2H, NH); 7.08 (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); 6.10 – 5.94 (m, 2H, H2″ and H2′′′′′); 5.43 – 5.24 (m, 4H, H3″ and H3′′′′′); 4.82 – 4.75 (m, 2H, H2 and H8); 4.62 – 4.58 (m, 1H, H5); 4.91 – 4.44 (m, 4H, H1″ and H1′′′′′); 3.67 (s, 3H, OCH_3); 3.04 – 2.89 (m, 6H, Ar′-CH_2, Ar′′′′-CH_2 and H4‴); 1.93 (s, 3H, H11); 1.43 (s, 9H, $C(CH_3)_3$); 1.37 – 1.26 (m, 6H, H1‴, H2‴ and H3‴). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.2, C7; 170.8, C4; 170.6, C1; 170.1, C10; 157.4, NCO_2; 157.3, ArC4′′′′; 155.8, ArC4′; 133.0, C2″ and C2′′′′′; 130.1, ArCH2′ and ArCH6′; 130.1, ArCH2′′′′ and ArCH6′′′′; 128.4, ArC1′′′′; 128.0, ArC1′; 117.5, C3″ and C3′′′′′; 114.7, ArCH3′ and ArCH5′; 114.6, ArCH3′′′′ and ArCH5′′′′; 78.9, $\underline{C}(CH_3)_3$; 68.7, C1″; 68.7, C1′′′′′; 55.1, C2; 53.3, C5; 52.6, OCH_3; 52.3, C8; 40.1, C4‴; 37.5, Ar′CH_2; 37.2, Ar′′′′CH_2; 31.9, C1‴; 29.7, C3‴; 28.5, $C(\underline{C}H_3)_3$; 23.0, C11; 22.1, C2‴. MS (ESI, +ve) *m/z* 709.3 (100%) [MH^+]. HRMS calcd for $C_{38}H_{52}N_4O_9$ 709.3813, found 709.3793.

*5.14.7. Methyl (2S,5R,8S)-2,8-di(4-allyloxybenzyl)-5-(4-aminobutyl)-3,6,9-triaza-4,7,10-trioxoundecanoate hydrochloride (**73**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **72** (33 mg, 0.051 mmol) to yield **73** (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 (bs, 4H, ArH); 7.26 – 7.10 (m, 4H, ArH); 6.46 – 6.30 (m, 2H, H2″ and H2′′′′′); 5.80 – 5.64 (m, 4H, H3″ and H3′′′′′); 4.99 – 4.70 (m, 6H, H2, H8, H1″ and H1′′′′′); 4.55 – 4.42 (m, 1H, H5); 3.70 (s, 3H, OCH_3); 3.42 – 3.18 (bs, 6H, H4‴, Ar′-CH_2 and Ar′′′′-CH_2); 2.27 (s, 3H, H11); 2.05 – 1.65 (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‴. MS (ESI, +ve) *m/z* 609.7 (100%) [MH^+]. HRMS calcd for $C_{33}H_{45}N_4O_7$ 609.3288, found 609.3301.

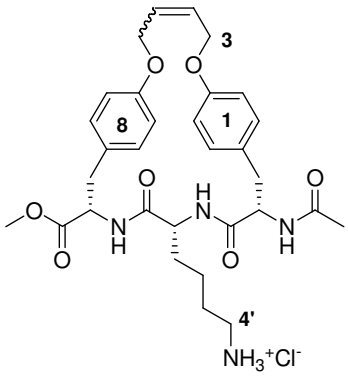
*5.14.8. (10S,13R,16S,4E/Z)-16-Acetamido-11,14-diaza-13-([tert-butoxycarboxamido]butyl)-10-methoxycarbonyl-2,7-dioxa-12,15-dioxo-1(1,4),8(4,1)-diphenylenecycloheptadecaphane-4-ene (**74**)*



The title compound was prepared using the general procedure for olefin metathesis (Procedure D), from **72** (56 mg, 0.079 mmol) to yield **74** (22 mg, 0.032 mmol, 41%) as a brown solid. Mp 190-194 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.13 – 6.73 (m, 8H, ArH); 6.02 – 5.83 (m, 2H, H4 and H5); 5.02 – 4.94 (m, 1H, H10); 4.86 – 4.76 (m, 1H, H16); 4.61 – 4.50 (m, 4H, H3 and H6); 4.18 – 4.10 (m, 1H, H13); 3.74 (s, 3H, OCH_3); 3.30 – 3.25 (m, 2H, H4′); 3.01 – 2.52 (m, 4H, H9 and H17);

1.97 (s, 3H, $NCOCH_3$); 1.25 (s, 9H, $C(CH_3)_3$); 1.93 – 0.88 (m, 6H, H1′, H2′ and H3′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.8, C12; 170.0, $NCOCH_3$; 169.8, 10-CO; 169.2, C15; 157.3, 1-ArC1; 157.3, 8-ArC1; 156.1, NCO_2; 130.8, 8-ArC4; 130.4, 8-ArCH2 and 8-ArCH6; 130.3, 1-ArCH2 and 1-ArCH6; 128.7, C4; 128.5, C5; 126.3, 1-ArCH4; 115.1, 8-ArCH3 and 8-ArCH5; 114.7, 1-ArCH3 and 1-ArCH5; 79.3, $\underline{C}(CH_3)_3$; 68.2, C3; 67.9, C6; 54.8, C16; 52.5, C13; 52.3, OCH_3; 52.1, C10; 39.5, C4′; 38.0, C9; 35.8, C17; 34.9, C1′; 31.9, C3′; 28.5, $C(\underline{C}H_3)_3$; 26.2, 16-$NCO\underline{C}H_3$; 23.3, C2′. MS (ESI, -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.

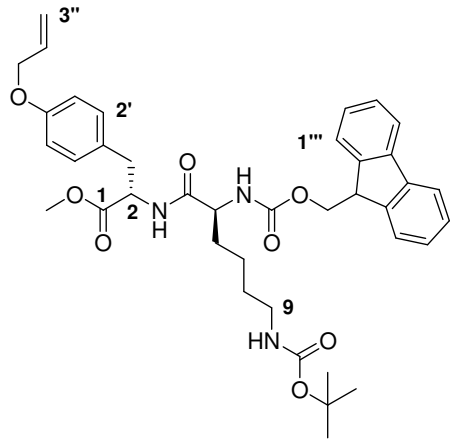
*5.14.9. (10S,13R,16S,4E/Z)-16-Acetamido-13-(4-aminobutyl)-11,14-diaza-10-methoxycarbonyl-2,7-dioxa-12,15-dioxo-1(1,4),8(4,1)-diphenylenecycloheptadecaphane-4-ene (**75**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **74** (22 mg, 0.038 mmol) to yield **75** (20 mg, 0.034 mg, 89%) as a yellow solid. Mp >260 °C. ^1H NMR (CD_3OD, 300 MHz): δ 8.16 – 8.03 (m, 3H, NH); 7.13 – 7.02 (m, 4H, ArH); 6.83 – 6.70 (m, 4H, ArH); 6.04 – 5.93 (m, 2H, H4 and H5); 4.66 (bs, 4H, H3 and H6); 4.60 – 4.50 (m, 1H, H10); 4.42 – 4.36 (m, 1H, H16); 4.16 – 4.06 (m, 1H, H13); 3.75 – 3.67 (m, 3H, OCH_3); 3.09 – 2.73 (m, 6H, H9, H17 and H4′); 1.92 (s, 3H, $NCOCH_3$); 1.52 – 1.28 (m, 4H, H1′ and H2′); 0.98 – 0.75 (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′. MS (ESI, -ve) *m/z* 581.6 (100%) [MH^+]. HRMS calcd for $C_{31}H_{41}N_3O_7$ 581.2975, found 581.2980.

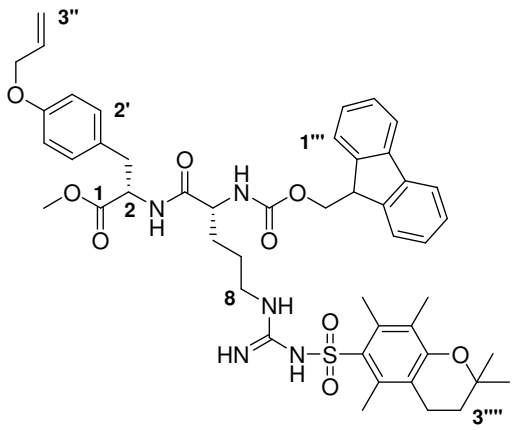
5.15. Synthesis of L-Tyrosine Acyclic Dipeptides Hydrochloride Salts (Scheme 10)

*5.15.1. Methyl (2S,5S)-2-(4-allyloxybenzyl)-3-aza-9-(tert-butoxycarboxamido)-5-(9H-9-fluorenylmethylcarboxamido)-4-oxononanoate (**76**)*



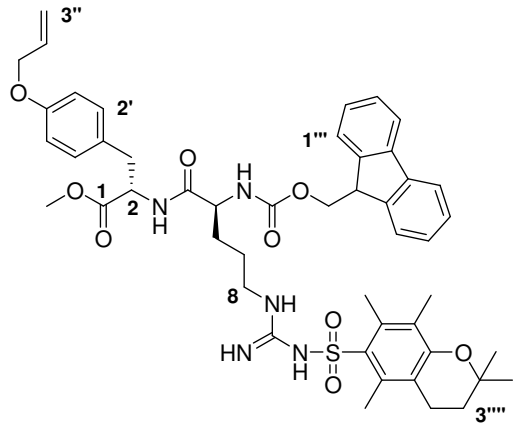
The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **69** (200 mg, 0.74 mmol) and (2*S*)-6-*tert*-butoxycarboxamido-2-[(9*H*-9-fluorenylmethyloxy)carboxamido]hexanoic acid (291 mg, 0.62 mmol) to afford **76** (328 mg, 0.48 mmol, 77%) as a pale yellow solid. 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); 6.02 – 5.92 (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); 4.43 – 4.35 (m, 4H, H1″ and $OC\underline{H}_2$-H9‴); 4.20 (d, *J* = 7.2 Hz, 2H, H1″); 3.70 (s, 3H, OCH_3); 3.10 – 3.02 (m, 4H, H9 and $ArCH_2$); 1.83 – 1.78 (m, 2H, H6); 1.66 – 1.64 (m, 2H, H7); 1.43 (s, 9H $C(CH_3)_3$); 1.36 – 1.33 (m, 2H, H8). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.7, C4; 171.3, C1; 157.7, NCO_2; 156.1, NCO_2‴; 143.7, ArC4′; 141.2, ArC8a‴ and ArC9a‴; 141.0, ArC4a‴ and ArC4b‴; 133.1, C2″; 130.1, ArCH2′ and ArCH6′; 127.7, ArCH3‴ and ArCH6‴; 127.5, ArCH2‴ and ArCH7‴; 127.0, ArCH1‴ and ArCH8‴; 125.0, ArCH4‴ and ArCH5‴; 119.9, ArC1′; 117.6, C3″; 114.7, ArCH3′ and ArCH5′; 79.0, $\underline{C}(CH_3)_3$; 68.6, $\underline{C}H_2$-C9‴; 67.1, C1″; 54.6, C5; 53.3, C2; 52.3, OCH_3; 47.0, C9‴; 39.8, C9; 36.8, $ArCH_2$; 32.0, C6; 29.5, C8; 28.4, $C(\underline{C}H_3)_3$; 22.2, C7. MS (ESI, +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.

*5.15.2. Methyl (2S,5R)-2-(4-allyloxybenzyl)-3-aza-5-(9H-9-fluorenylmethylcarboxamido)-4-oxo-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]nonanoate (**77**)*



The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **69** (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 **77** (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‴); 7.23 – 7.16 (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); 5.97 – 5.84 (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); 4.31 – 4.24 (m, 5H, H1″, $O\underline{CH_2}$-H9‴ and H5); 4.15 – 4.04 (m, 1H, H9‴); 3.62 (s, 3H, OCH_3); 3.23 - 313 (m, 2H, H8); 3.09 – 2.95 (m, 2H, $ArCH_2$); 2.58 (s, 3H, 7⁗-CH_3); 2.58 – 2.52 (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⁗); 1.62 – 1.57 (m, 2H, H6); 1.50 – 1.42 (m, 2H, H7); 1.24 (s, 6H, 2 x 2⁗-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, C1; 172.0, C4; 157.4, ArC6⁗; 156.8, NCO_2; 156.2, ArC8a⁗; 153.6, CN_3; 143.7, ArC4′; 141.2, ArC8a‴ and ArC9a‴; 141.0, ArC4a‴ and ArC4b‴; 135.4, ArC7⁗; 134.8, ArC5⁗; 133.1, C2″; 130.1, ArCH2′ and ArCH6′; 128.7, ArC8⁗; 128.3, ArCH3‴ and ArCH6‴; 127.6, ArCH2‴ and ArCH7‴; 127.0, ArCH1‴ and ArCH8‴; 125.1, ArCH4‴ and ArCH5‴; 119.8, ArC1′; 117.9, ArC4a⁗; 117.5, C3″; 114.6, ArCH3′ and ArCH5′; 73.6, C2⁗; 68.6, C1″; 67.2, $\underline{C}H_2$-C9‴; 60.4, C9‴; 53.7, C5; 52.3, OCH_3; 46.9, C2; 40.3, C8; 36.6, $ArCH_2$; 32.6, C4⁗; 26.7, 2⁗-CH_3; 21.3, C6; 21.0, C3⁗; 18.5, C7; 17.5, 7⁗-CH_3; 14.2, 5⁗-CH_3; 12.0, 8⁗-CH_3. MS (ESI, +ve) *m/z* 880 (100%), [MH^+]. HRMS calcd for $C_{48}H_{58}N_5O_9S$ 880.3955, found 880.3944.

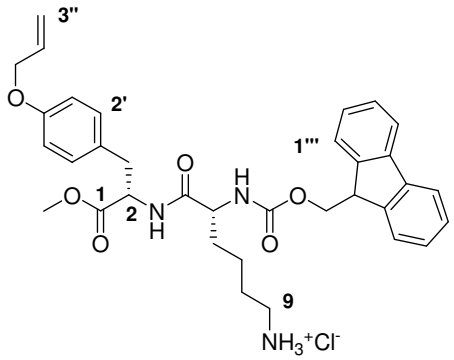
*5.15.3. Methyl (2S, 5S)-2-(4-allyloxybenzyl)-3-aza-5-(9H-9-fluorenylmethylcarboxamido)-4-oxo-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]nonanoate (**78**)*



The title compound was synthesized using the general peptide coupling procedure (Procedure B), from **69** (200 mg, 0.74 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 (411 mg, 0.62 mmol) to afford **78** (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‴); 7.40 – 7.25 (m, 2H, ArH3‴ and ArH6‴); 7.21 – 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); 5.99 – 5.87 (m, 1H, H2″); 5.30 (dd, *J* = 1.5, 17.1, 1H, $H3_a$″); 5.19 (d, *J* = 1.5, 10.5 Hz, 1H, $H3_b$″); 4.72 – 4.65 (m, 1H, H2); 4.35 – 4.26 (m, 5H, H1″, $OC\underline{H}_2$-H9‴and H5); 4.15 – 4.06 (m, 1H, H9‴); 3.60 (s, 3H, OCH_3); 3.26 – 3.16 (m, 2H, H8); 3.04 – 2.88 (m, 2H, $ArCH_2$); 2.58 (s, 3H, 7⁗-CH_3); 2.56 – 2.54 (m, 2H, H4⁗); 2.54 (s, 3H, 5⁗-CH_3); 2.07 (s, 3H, 8⁗-CH_3); 1.85 – 1.78 (m, 2H, H6); 1.72 (t, *J* = 6.9 Hz, 2H, H3⁗); 1.58 – 1.52 (m, 2H, H7); 1.25 (s, 6H, 2 x 2⁗-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.2; C1; 172.0, C4; 157.4, ArC6⁗; 156.8, NCO_2; 156.3, ArC8a⁗; 153.6, CN_3; 143.8, ArC4′; 141.1, ArC8a‴ and ArC9a‴; 141.0, ArC4a‴ and ArC4b‴; 135.4, ArC7⁗; 134.8, ArC5⁗; 133.2, C2″; 130.1, ArCH2′ and ArCH6′; 128.7, ArC8⁗; 128.2, ArCH3‴ and ArCH6‴; 127.6, ArCH2‴ and ArCH7‴; 127.0, ArCH1‴ and ArCH8‴; 125.2, ArCH4‴ and ArCH5‴; 119.8, ArC1′; 117.9, ArC4a⁗; 117.5, C3″; 114.6, ArCH3′ and ArCH5′; 73.6, C2⁗; 68.5, C1″; 67.1, $\underline{C}H_2$-C9‴; 60.4, C9‴; 54.0, C5; 52.2, OCH_3; 46.9, C2; 40.4, C8; 36.5, $ArCH_2$; 32.6, C4⁗; 26.7, 2⁗-CH_3; 25.1, C6;

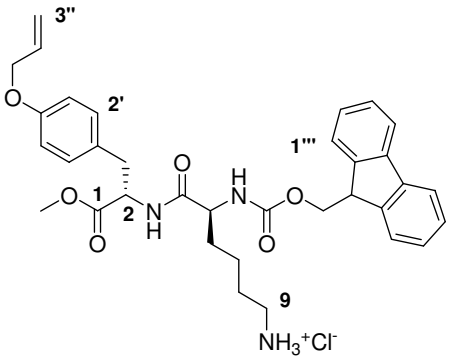
21.3, C3′′′′; 18.5, C7; 17.5, 7′′′′-CH_3; 14.2, 5′′′′-CH_3; 12.0, 8′′′′-CH_3. MS (ESI, +ve) *m/z* 880 (30%), 902 (100%) [MNa^+]. HRMS calcd for $C_{48}H_{58}N_5O_9S$ 880.3955, found 880.3943.

*5.15.4. Methyl (2S,5R)-2-(4-allyloxybenzyl)-9-amino-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxononanoate hydrochloride (**79**)*



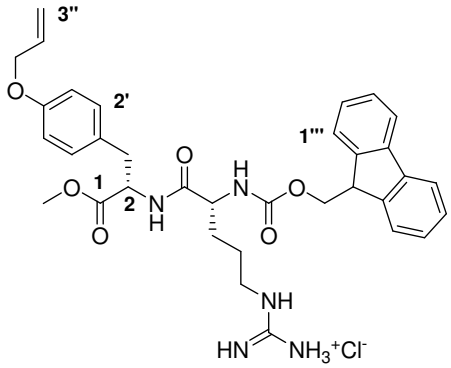
The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **70** (132 mg, 0.19 mmol) to yield **79** (92 mg, 0.15 mmol, 79%) as a white solid. Mp 162-170 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.02 (d, *J* = 8.0 Hz, 1H, NH); 7.79 (d, *J* = 7.6 Hz, 2H, ArH1′′′ and ArH8′′′); 7.64 (t, *J* = 8.4 Hz, 2H, ArH4′′′ and ArH5′′′); 7.38 (t, *J* = 7.2 Hz, 2H, ArH3′′′ and ArH6′′′); 7.41 – 7.26 (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′); 6.00 – 5.87 (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); 4.35 – 4.32 (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); 3.14 – 3.07 (m, 2H, H9); 2.93 – 2.82 (m, 2H, $ArCH_2$); 1.63 – 1.53 (m, 4H, H6 and H7); 1.33 – 1.28 (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, $\underline{C}H_2$-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. MS (ESI, +ve) *m/z* 586.3 (100%) [MH^+]. HRMS calcd for $C_{34}H_{40}N_3O_6$ 586.2917, found 586.2935.

*5.15.5. Methyl (2S,5S)-2-(4-allyloxybenzyl)-9-amino-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxononanoate hydrochloride (**80**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **76** (73 mg, 0.106 mmol) to yield **80** (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′); 6.01 – 5.88 (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, $H3_b$″); 4.67 – 4.59 (m, 1H, H5); 4.40 – 4.30 (m, 4H, H1′ and $O\underline{CH_2}$-H9‴); 4.22 – 4.18 (m, 1H, H9‴); 4.12 – 4.07 (m, 1H, H2); 3.67 (s, 3H, OCH_3); 3.11 – 3.04 (m, 2H, H9); 2.97 – 2.87 (m, 2H, $ArCH_2$); 1.73 – 1.60 (m, 4H, H6 and H7); 1.45 – 1.30 (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. MS (ESI, +ve) *m/z* 586.7 (100%) [MH^+]. HRMS calcd for $C_{34}H_{40}N_3O_6$ 586.2917, found 586.2925.

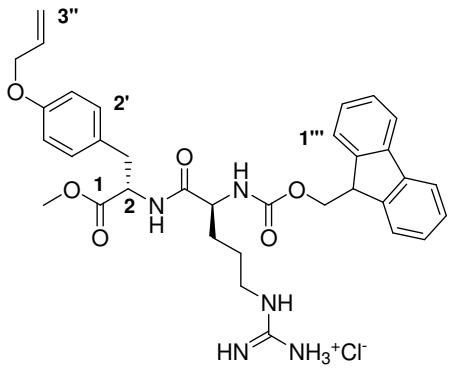
*5.15.6. Methyl (2S,5R)-2-(4-allyloxybenzyl)-3-aza-5-(9H-9-fluorenylmethylcarboxamido)-8-guanidino-4-oxononanoate hydrochloride (**81**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **77** (62 mg, 0.068 mmol) to yield **81** (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‴); 7.40 – 7.26 (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′); 6.00 – 5.86 (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); 4.34 – 4.32 (m, 4H, H1″ and $OC\underline{H}_2$-H9‴); 4.21 – 4.16 (m, 1H, H5); 4.08 – 4.06 (m, 1H, H9‴); 3.69 (s, 3H, OCH_3); 3.12 – 3.07 (m, 2H, H8); 2.94 – 2.86 (m, 2H, $ArCH_2$); 1.69 – 1.59 (m, 2H, H6); 1.57 – 1.43 (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. MS (ESI, +ve) *m/z* 614.6 (100%) [MH^+]. HRMS calcd for $C_{34}H_{40}N_5O_6$ 614.2979, found 614.3007.

*5.15.7. Methyl (2S,5S)-2-(4-allyloxybenzyl)-3-aza-5-(9H-9-fluorenylmethylcarboxamido)-8-guanidino-4-oxononanoate hydrochloride (**82**)*



The title compound was synthesized using the general *N*-Boc deprotection procedure (Procedure A), from **78** (93 mg, 0.10 mmol) to yield **82** (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 – 7.70 (m, 2H, ArH4‴ and ArH5‴); 7.45 – 7.31 (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′); 6.05 – 5.92 (m, 1H, H2″); 5.34 (d, J = 17.1, 1H, $H3_a$″); 5.21 (d, J = 10.8 Hz, 1H, $H3_b$″); 4.47 – 4.42 (m, 2H, H2 and H5); 4.29 – 4.24 (m, 4H, H1″ and $OC\underline{H}_2$-H9‴); 4.09 – 4.07 (m, 1H, H9‴); 3.59 (s, 3H, OCH_3); 3.19 – 3.12 (m, 2H, H8); 3.03 – 2.92 (m, 2H, $ArCH_2$); 1.70 – 1.60 (m,

2H, H6); 1.54 – 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. MS (ESI, +ve) *m/*z 614.8 (100%) [M^+]. HRMS calcd for $C_{34}H_{40}N_5O_6$ 614.2979, found 614.2972.

5.16. Antibacterial Testing

Anti-bacterial testing against *Staphylococcus aureus* ATCC6538P was performed at Avexa Ltd, Melbourne, Australia.

Assay procedure: A standardised inoculate for assays was prepared in 1/10 dilution of seed culture. To a 96 well microtitre plate was added 50 µL of liquid medium [Mueller-Hinton broth medium (MHB) and Mueller-Hinton agar medium (MHA)]. The peptoid compounds were dissolved in a 50% MeOH/H_2O solution for the final concentration of 1 mg/mL. Test solution (50 µL) was added into the top row of the plate. A dilution series was continued until it reached the last row of the plate the excess was discarded. The plates (2 peptoid samples were tested per plate) were incubated at 37 °C and shaken at 100 rpm for 18 h.

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