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Synthesis of carbazole-linked cyclic and acyclic peptoids with antibacterial activity☆

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Abstract—This paper describes the synthesis of several novel cyclic and acyclic peptoids, the former structurally comprising a tripeptide moiety linked through a carbazole scaffold. In a key step, a ring-closing metathesis reaction was used giving efficient access to this new class of cyclic peptoids. The target compounds were tested against *Staphylococcus aureus* (ATCC 6538P) and their minimum inhibitory concentration (MIC) values were determined. These compounds showed moderate to poor activities with MIC values ranging from 15–250 μg/mL.

1. Introduction

The emergence and worldwide spread of drug-resistant bacteria continues to threaten the efficacy of our currently available agents. Of particular concern is the increasing occurrence of resistance to the drugs of last resort, such as the glycopeptide vancomycin, an antibiotic effective against Gram-positive organisms. Resistance to vancomycin in enterococci was first reported in 1988,[1] almost 30 years after its initial use. Vancomycin-resistant enterococci (VRE) strains appear to be emerging at an increasing rate,[2] and now strains of methicillin-resistant *Staphylococcus aureus* (MRSA), that are also resistant to vancomycin, have been reported.[3] Recently, the promising new antibacterial drug linezolid (Zyvox) reportedly failed in the treatment of both MRSA[4] and VRE[5] infections.

There is clearly a pressing need for the development of new antibacterial drugs, preferably with a novel mechanism of action. However, in the case of vancomycin, the mechanism of resistance in enterococci has been well characterized,[6] thereby facilitating the design of compounds that could be effective against VRE. In susceptible bacteria, vancomycin interferes with bacterial cell wall synthesis by inhibiting the formation of the strengthening crosslinks in peptidoglycan. Through binding across the terminal three amino acids, L-lysyl-D-alanyl-D-alanine, of peptidoglycan precursors (Fig. 1), vancomycin blocks the transpeptidase enzyme responsible for crosslinking adjacent polysaccharide chains.[7] As a result, the peptidoglycan layer of the cell wall is substantially weakened and cell lysis occurs. VRE successfully elude vancomycin by synthesizing peptidoglycan precursors that terminate in D-lactate instead of

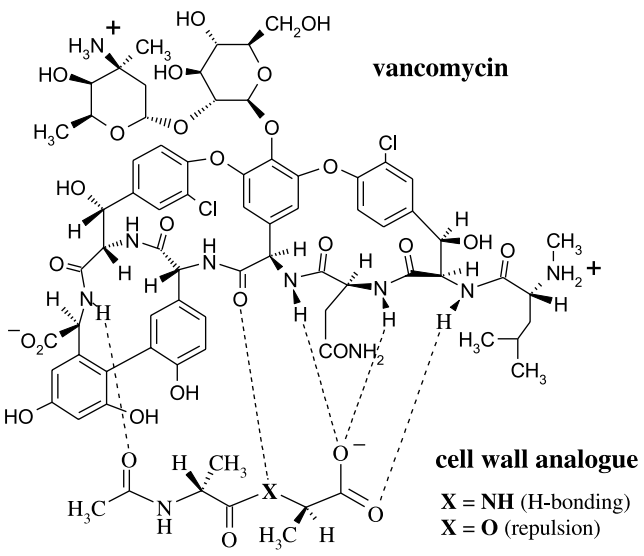

Figure 1. Exploded view of the binding interaction between vancomycin and cell wall analogues, which represent the terminal portion of peptidoglycan precursors known to be involved in this binding event.[7]

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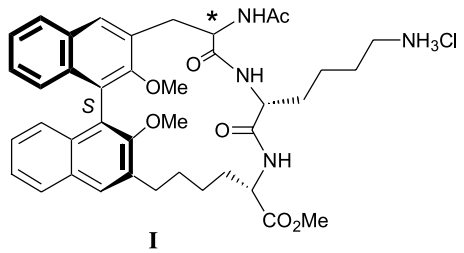
D-alanine.[6] In effect, this substitution converts an NH to an O, which not only replaces one of the hydrogen bonds with a repulsive interaction, but weakens the other existing binding interactions in the complex.[7] The end result is a 1000-fold loss in binding affinity,[7] and consequently, a greatly diminished drug efficacy.

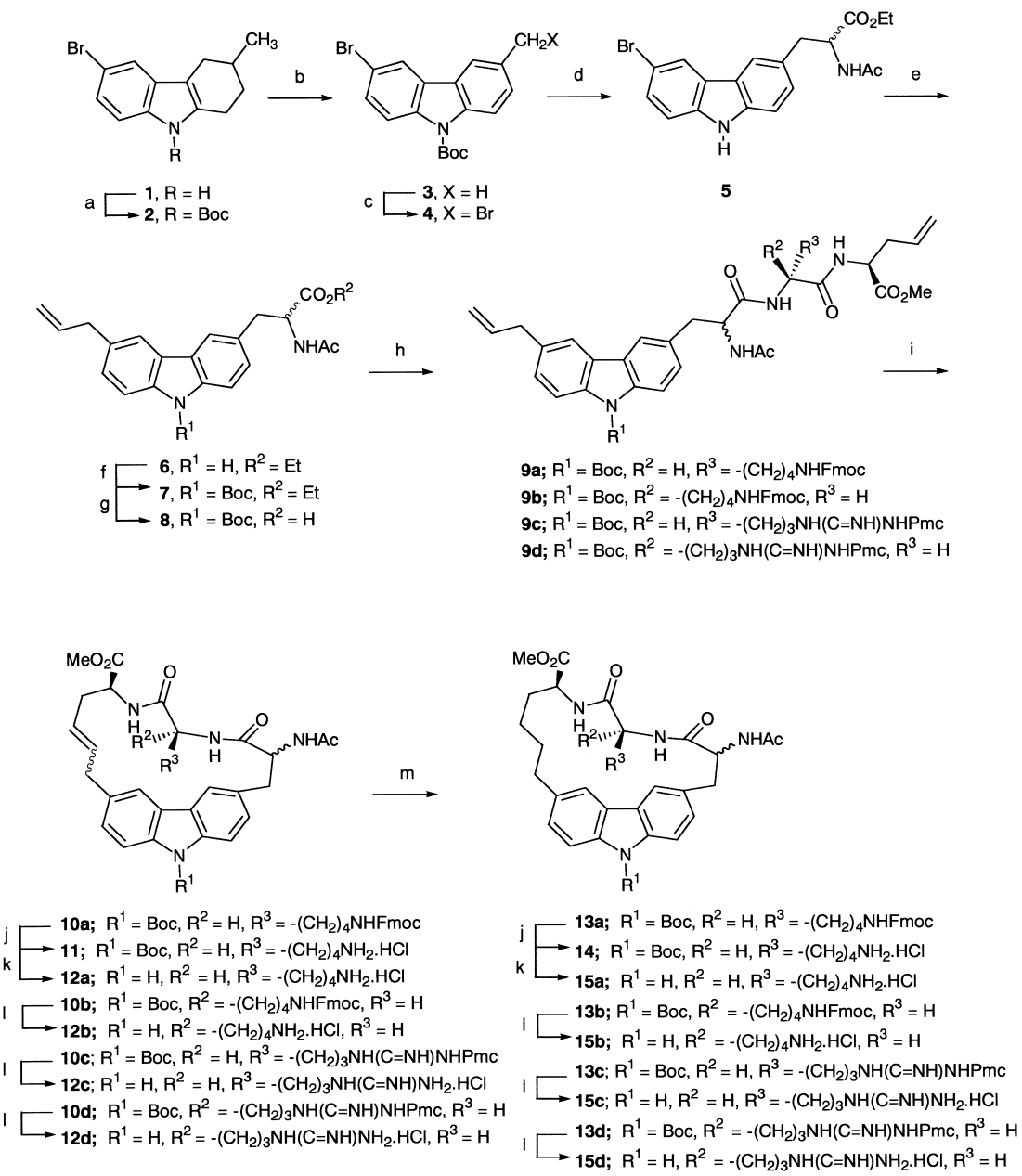
As part of a program aimed at the development of new antibacterial agents, we recently reported the synthesis of a 1,1′-binaphthyl-linked cyclic peptoid **I**[8] and a related carbazole-linked cyclic peptoid.[9] Both compounds showed promising antibacterial activity against *S. aureus*.[8,9] These peptoids, although much simpler than vancomycin, were designed to incorporate the necessary structural features for binding to both the L-lys-D-ala-D-ala and the L-lys-D-ala-D-lac termini. These structural features included: (1) a basic amino acid residue (L-lysine) to facilitate an ionic interaction with the terminal carboxy group of D-ala or D-lac, (2) a tripeptide moiety to provide sites for a number of H-bonding interactions, and (3) a 1,1′-binaphthyl or carbazole system to promote the formation of hydrophobic interactions with the alanine methyl groups of the cell wall terminus. We report here the full details for the synthesis and antibacterial activity of this carbazole-linked cyclic peptoid and several of its analogues that incorporate D-lysine or L- or D-arginine instead of L-lysine as the crucial basic residue.



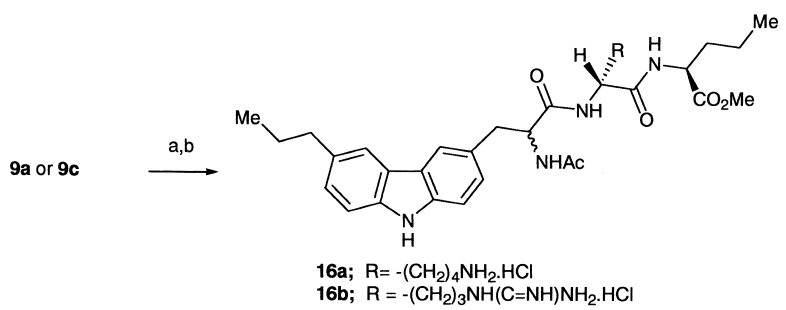
I

2. Synthesis of carbazole-linked peptides

A key step in the synthesis of our target molecules **11**, **12a–d**, **14** and **15a–d** was the ring-closing metathesis reaction between the allyl-glycine residue and the aryl–allyl group in compounds **9a–d** (Scheme 1) that efficiently provided **10a–d**, the protected versions of **11** and **12a–d**. The synthesis of these target cyclic peptoids started with the tetrahydrocarbazole **1**, that was readily prepared in 74% yield via a Fischer indole synthesis[10] from commercially available 4-bromophenylhydrazine and 4-methylcyclohexanone (cyclohexane/glacial acetic acid, reflux 22 h, 77% yield). *N*-Boc protection of **1** followed by aromatization of the product **2** with DDQ[11] in benzene solution at reflux gave the carbazole **3** in 71% overall yield. Benzylic bromination[12] of **3** gave the bromomethyl derivative **4** which was converted into the α-amido-ester **5** in a one-pot reaction involving initial alkylation with the sodium salt of diethyl acetamidomalonate[13] in DMSO at room temperature, followed by addition of water (2 equiv.) and lithium chloride (1 equiv.) and heating the mixture at reflux for 1.75 h.[14] This method resulted in clean mono-ethoxycarbonylation and loss of the *N*-Boc group and gave **5** in 70% overall yield. A Stille-type allylation[15] between the 6′-bromo group in **5** and allyltributylstannane gave the allylated product **6** in 91% yield, which was then *N*-protected to give the *N*-Boc derivative **7**. The ester group in **7** was converted into its carboxylic acid derivative **8** in high yield (92%) upon mild basic hydrolysis (LiOH/THF/H_2O) with subsequent acidification.[16] We chose to work with racemic **8** in this work since our previous work with the tripeptide **I** had shown that the stereochemistry at the α-carbon, marked with an asterisk in this structure, had little influence on the antibacterial activity. Furthermore, we had found it difficult to prepare compounds with this α-position stereochemically pure. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)-mediated coupling of the carboxylic acid group of racemic **8** with the individual dipeptides, *N*-ε-Fmoc-L-lysine-L-allylglycine methyl ester, *N*-ε-Boc-D-lysine-L-allylglycine methyl ester, *N*-ε-Pmc-L-arginine-L-allylglycine methyl ester and *N*-ε-Pmc-D-arginine-L-allylglycine methyl ester gave the key tripeptide derivatives **9a–d** in good yield (58–82%) and as a mixture of diastereomers that could not be separated by column chromatography. A ring-closing metathesis reaction[17,18] of **9a–d** at high dilution in dichloromethane solution at reflux, using commercially available benzylidene bis(tricyclohexylphosphine)dichlororuthenium (Grubbs' catalyst, 10 mol%), provided the fully protected cyclic peptoids **10a–d** in excellent yields (97–100%). The structure of these compounds was clear from low-resolution MS and HRMS analysis (ES, +ve), however, their ^{1}H and ^{13}C NMR spectra were consistent with a mixture of diastereomers, *E*- and *Z*-isomers and amide rotamers. Consequently, the determination of the ratio of (*E*) and (*Z*)-isomers produced could not be calculated with confidence. However, the ^{1}H NMR spectrum of **10a** showed that the major isomer had an olefinic resonance as a doublet of triplets at δ 5.83. The coupling constants for this resonance were 15 and 7 Hz, the larger coupling consistent with the (*E*)-alkene geometry. The ^{1}H NMR spectra of **10b–d** were more difficult to interpret due to peak broadening due to amide rotamers. We assume however, by analogy, that the major product in each of these cases is also the (*E*)-alkene. The ^{13}C NMR spectra of **10a–d** were also consistent with the major product having the (*E*)-geometry. The chemical shifts of the benzylic and allylic carbons of the system Ar*C*H_2–CH=CH–*C*H_2 in the minor isomers were consistently about 5 ppm upfield of those for the major isomers. The upfield shift of these methylene groups in the (*Z*)-alkene would be expected due to the γ-shielding effect.[19] Deprotection of the *N*-Fmoc group in **10a** using piperidine, followed by anion exchange with HCl and recrystallization from methanol gave one of the target molecules **11** as its hydrochloride salt, in 81% overall yield, with the *N*-Boc protecting group on the carbazole nitrogen still intact. Treatment of the *N*-Fmoc protected derivatives **10a** and **10b** first with trifluoroacetic acid TFA and then piperidine, followed by anion exchange with HCl and recrystallization from methanol gave the target molecules **12a** and **12b**, respectively, as their hydrochloride salts. The (*E*)-alkene geometry of the major isomer of **12a** was clear from its ^{1}H NMR spectrum (δ 5.83, dt, J=15, 7 Hz). In the case of the *N*-Pmc protected derivatives **10c** and **10d**, treatment of these compounds with TFA, followed by anion exchange with HCl and recrystallization from methanol gave the target molecules **12c** and **12d**, respectively as their hydrochloride salts.



Scheme 1. *Reagents*: (a) NaH, THF, (*tert*-BuO)$_2$CO, room temperature, 21 h, 86%. (b) DDQ (2 equiv.), 3 Å mol. sieves, benzene, reflux, 20 h, (83%). (c) NBS (1.1 equiv.), CCl_4, reflux with irradiation (150 W halogen lamp), 2.5 h, 69%. (d) (i) NaH, diethyl acetamidomalonate, DMSO, room temperature, 0.5 h; (ii) water (2 equiv.), LiCl (1 equiv.), reflux, 1.75 h, 70%. (e) $PdCl_2$ (5 mol%), Ph_3P (20 mol%), allyltributylstannane (1.2 equiv.), sealed tube, 110°C, 22 h, 91%. (f) Cs_2CO_3 (2 equiv.), (*tert*-BuO)$_2$CO (1.5 equiv.), DMF, room temperature, 20 h, 78%. (g) LiOH (0.15 M), THF/water (2.5:1), 0°C, 3 h, 92%. (h) diprotected dipeptide methyl ester (1 equiv., see discussion for details), EDCI (1 equiv.), DMAP (1 crystal), DCM/DMF/MeCN (5:2:15), room temperature, 16 h, 58–82%. (i) $(Cy_3P)_2(Cl)_2Ru{=}CHPh$ (10 mol%), DCM, reflux, 23 h, 97–100%. (j) (i) piperidine, THF, 50°C, 38 h; (ii) MeOH, 1 M HCl in ether and crystallization. (k) (i) TFA; (ii) piperidine; (iii) MeOH, 1M HCl in ether and crystallization. (l) (i) TFA; (ii) MeOH, 1M HCl in ether and crystallization. (m) Pd/C, H_2 (1 atm); room temperature.



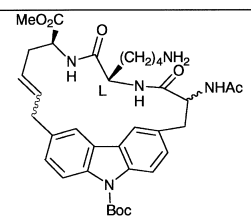
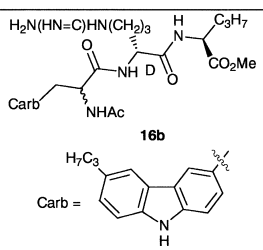
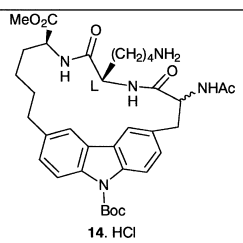
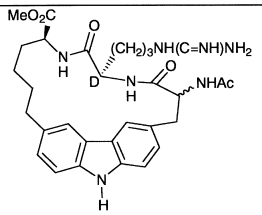
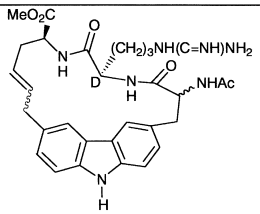
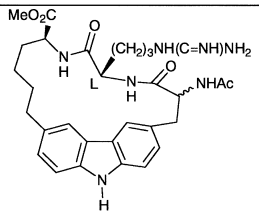
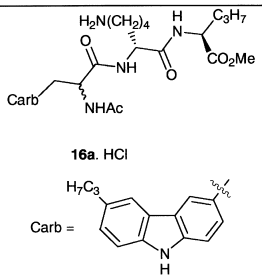
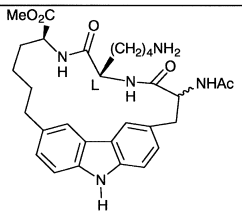
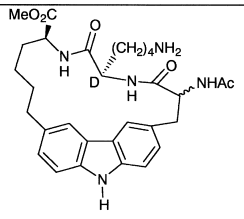
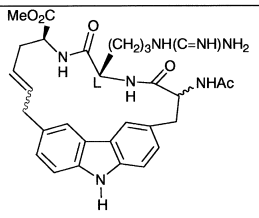
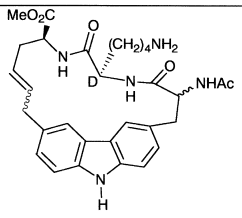
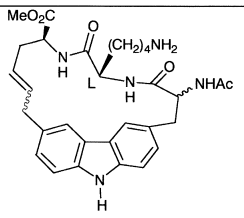
Scheme 2. *Reagents*: (a) Pd/C, EtOAc/MeOH (1:1), H_2, (1 atm), room temperature. (b) (i) TFA/DCM (1:1), room temperature; (ii) MeOH, 1 M HCl in ether and crystallization.

Hydrogenolysis of the alkene moiety of **10a–d** over palladium on carbon gave the dihydro derivatives **13a–d**, respectively. These were then converted to their respective hydrochloride salts **14** and **15a–d**, using the basic and acidic deprotection methods described above. The uncyclized derivatives, **16a** and **16b** were also prepared as their hydrochloride salts for antibacterial testing from **9a** and **9c**, respectively, by catalytic hydrogenation followed by deprotection (Scheme 2).

3. Antibacterial testing

The target compounds were tested against *S. aureus* (ATCC 6538P) (broth dilution assay) and their minimum inhibitory concentration (MIC) values are shown in Table 1. The control was vancomycin which had a MIC value of 1.25 μg/mL under the test conditions. These compounds showed moderate to poor activities ranging from a MIC of 15 μg/mL for the *N*-Boc-L-lysine compound **11** to 250 μg/mL for its *N*-Boc deprotected derivative **12a**. This major difference in activities may suggest that the extra hydrophobicity provided by the *N*-Boc group in **11**, is important for activity. Consistent with this hypothesis is the relatively high activity of the *N*-Boc-L-lysine dihydro derivative **14**. Of the *N*-Boc-carbazole deprotected derivatives **12a–d** and **15a–d**, the D-arginine derivatives **12d** and **15d**, showed the best activities. Interestingly, the uncyclized, D-arginine derivative **16b** was the second most active compound (Table 1). As was expected, the fully protected versions of these compounds showed no antibacterial activities (MICs>250 μg/mL), consistent with our hypothesis that a basic amino residue is required for activity.

Table 1. Minimum inhibitory concentrations (MIC) values for synthesised compounds against *Staphylococcus aureus* (ATCC 6538P)

 **11**. HCl MIC 15 μg/mL	 **16b** MIC 15-31 μg/mL	 **14**. HCl MIC 31 μg/mL
 **15d**. HCl MIC 31 μg/mL	 **12d**. HCl MIC 31-62 μg/mL	 **15c**. HCl MIC 31-62 μg/mL
 **16a**. HCl MIC 62 μg/mL	 **15a**. HCl MIC 62 μg/mL	 **15b**. HCl MIC 62 μg/mL
 **12c**. HCl MIC 125 μg/mL	 **12b**. HCl MIC 125 μg/mL	 **12a**. HCl MIC 250 μg/mL

In summary, we have developed an efficient synthetic route to novel carbazole-linked cyclic peptoids that is sufficiently flexible to allow the introduction of various basic D- and L-amino acids. Some of these compounds show promising antibacterial activities against *S. aureus*. While the range of compounds has been limited, these preliminary biological results perhaps suggest that both a large hydrophobic group and a D-arginine residue are required for maximum antibacterial activity. However, a more extensive range of compounds will need to be studied in order to explore the existence of any structure/activity relationships.

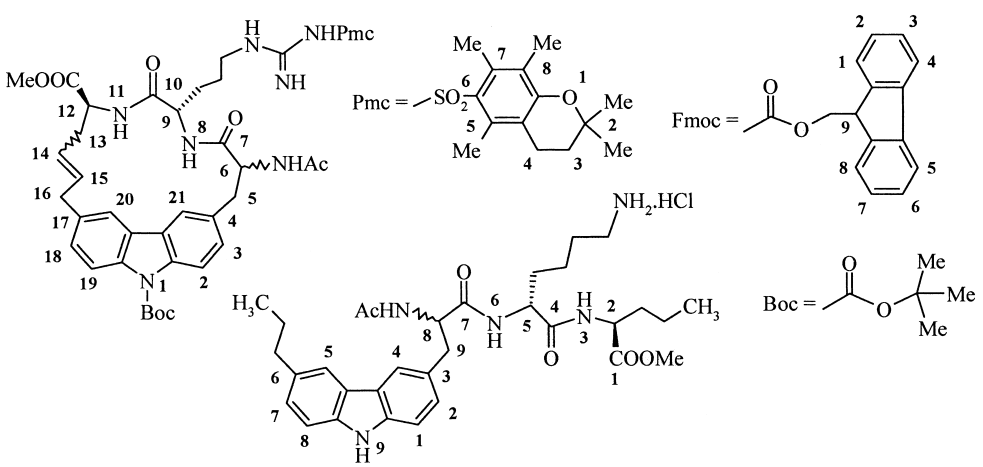
4. Experimental

Full details for the synthesis of compounds **11**, **12a**, **14** and **15a** from **1** according to Scheme 1 and full characterization data for compounds reported in Table 1 are provided here. Full details for the synthesis of the other compounds reported in Schemes 1 and 2, together with the antibacterial testing procedure are available as supplementary material with this article.

4.1. General

Melting point (mp) determinations were carried out on a Gallenkamp melting point apparatus. Chemical ionization (CI) and electron impact (EI) mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer by a direct insertion technique with an electron beam energy of 70 eV. Electrospray (ES) mass spectra were obtained on a VG Quattro spectrometer. High-resolution mass spectra (HRMS) were determined on a VG Autospec spectrometer or 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. Elemental microanalyses were determined by Mr G. Blazak at the University of Queensland. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained as specified on a Varian Unity 300 MHz, Varian Mercury 300 MHz, Varian Unity 400 MHz, Varian Inova 500 MHz or a Bruker DMX600 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. Proton and carbon assignments were determined through the interpretation of several two-dimensional spectra (COSY, TOCSY, ROESY, HSQC, HMBC), which were obtained on the 500 MHz spectrometer. Where samples exhibited several isomers [diastereoisomers, (*E*) or (*Z*) isomers and/or rotamers], the minor form is indicated by an asterisk. In general, the major and minor isomers 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. Reverse phase (RP) TLC was conducted using Merck RP-18 F_{254}s chemically modified, pre-coated aluminium plates. Preparative TLC was done on Merck Silica gel 60 F_{254} pre-coated glass plates (0.2 mm thickness). All column chromatography was performed under 'flash' conditions on Merck Silica gel 60 (230–400 mesh). Chromatography solvent mixtures were measured by volume. Organic solvent extracts were dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure with a Büchi rotary evaporator. All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and TLC analysis. Starting materials and reagents were purchased from Sigma-Aldrich Pty Ltd and were used as received. Petroleum spirit (PS) refers to the 40–60°C bp range material. Ether refers to anhydrous diethyl ether, DCM to dichloromethane. NBS was recrystallized from water and dried over phosphorus pentoxide before use. The Grubbs' ruthenium catalyst used was specifically benzylidene bis(tricyclohexylphosphine)dichlororuthenium. ^{1}H and ^{13}C NMR spectra for all cyclized and uncyclized derivatives were assigned using the numbering systems illustrated below. Structures have been simplified using the following abbreviations for protecting groups.

4.1.1. 6-Bromo-2,3,4,9-tetrahydro-3-methyl-1*H*-carbazole (1). To a solution of 4-methylcyclohexanone (5.47 mL, 44.6 mmol), cyclohexane (70 mL) and glacial acetic acid (50 mL) was added 4-bromophenylhydrazine hydrochloride (10.0 g, 44.6 mmol) and the reaction mixture was heated to reflux for 22 h under a nitrogen atmosphere. The cooled reaction mixture was filtered and the filtrate was evaporated. Ether was added and the mixture was washed with a saturated $NaHCO_3$ solution and then water; the ether solution was dried and evaporated. The crude product was recrystallized from EtOH at ice bath temperature, filtered, washed with cold PS and dried in vacuo to afford **1** (9.07 g,



34.4 mmol, 77%) as an off-white solid, mp 108–110°C. R_f: 0.80 in PS/DCM (1:1). ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.57, d, J=1.5 Hz, 2H, ArH-5 and NH; 7.18, dd, J=8.5, 1.5 Hz, 1H, ArH-7; 7.06, d, J=8.5 Hz, 1H, ArH-8; 2.77, dd, J=15.5, 5.0 Hz, 1H, C*H*H-4; 2.73–2.65, m, 2H, CH_2-1; 2.21, dd, J=15.0, 9.5 Hz, 1H, CH*H*-4; 2.01–1.92, m, 1H, C*H*H-2; 1.97–1.88, m, 1H, CH-3; 1.64–1.50, m, 1H, CH*H*-2; 1.14, d, J=6.5 Hz, 3H, CH_3. ^{13}C NMR [75 MHz, $CDCl_3$] δ 135.3, ArC-9a; 134.6, ArC-8a; 129.6, ArC-4b; 123.6, ArCH-7; 120.4, ArCH-5; 112.3, ArC-6; 111.6, ArCH-8; 110.0, ArC-4a; 31.2, CH_2-2; 29.5, CH-3; 29.1, CH_2-4; 22.8, CH_2-1; 21.5, CH_3. Mass spectrum (CI^+) m/z 264 (^{79}Br, 100%) [MH^+]. HRMS (CI^+) calcd for $C_{13}H_{14}^{79}BrN$+H: 264.0388; found: 264.0371. Anal. calcd for $C_{13}H_{14}BrN$: C, 59.11; H, 5.34; N, 5.30. Found: C, 59.33; H, 5.38; N, 5.26.

4.1.2. 6-Bromo-9-*tert*-butoxycarbonyl-2,3,4,9-tetrahydro-3-methyl-1*H*-carbazole (2). Sodium hydride (1.17 g, 29.2 mmol) was washed twice with PS under a nitrogen atmosphere, a solution of **1** (7.00 g, 26.5 mmol) in dry THF (25 mL) was added and the mixture was stirred for 30 min at room temperature. A solution of di-*tert*-butyldicarbonate (8.67 g, 39.8 mmol) in dry THF (55 mL) was added and the reaction mixture was stirred for a further 20.5 h. The reaction solvent was evaporated, ether was added and the ether mixture was washed with water, dried and evaporated. The crude product was dissolved in EtOH, the solvent evaporated to a minimal volume and the product recrystallized at ice bath temperature. The recrystallized solid was filtered, washed with cold methanol and dried in vacuo to afford **2** (8.33 g, 22.9 mmol, 86%) as an off-white solid, mp 123–125°C. R_f: 0.70 in PS/DCM (2:1). ^{13}C NMR [500 MHz, $CDCl_3$] δ 7.97, d, J=9.0 Hz, 1H, ArH-8; 7.46, d, J=2.0 Hz, 1H, ArH-5; 7.29, dd, J=8.7, 2.0 Hz, 1H, ArH-7; 3.08, br d, 1H, C*H*H-1; 2.95–2.85, m, 1H, CH*H*-1; 2.68, dd, J=15.5, 5.0 Hz, 1H, C*H*H-4; 2.13, dd, J=15.5, 9.5 Hz, 1H, CH*H*-4; 1.98–1.91, m, 1H, C*H*H-2; 1.88, m, 1H, CH-3; 1.64, s, 9H, $C(CH_3)_3$; 1.47, m, 1H, CH*H*-2; 1.10, d, J=7.0 Hz, 3H, $CHCH_3$. ^{13}C NMR [75 MHz, $CDCl_3$] δ 150.4, CO; 136.7, ArC-9a; 134.8, ArC-8a; 131.5, ArC-4b; 125.9, ArCH-7; 120.2, ArCH-5; 116.8, ArCH-8; 115.8, ArC-6; 115.7, ArC-4a; 83.6, $C(CH_3)_3$; 31.6, CH_2-2; 29.1, CH_2-4; 28.3, CH-3; 28.3, $C(CH_3)_3$; 25.5, CH_2-1; 21.4, $CHCH_3$. Mass spectrum (CI^+) m/z 364 (^{79}Br, 15%) [MH^+], 308 (^{79}Br, 100%) [$MH^+-C(CH_3)_3$], 264 (^{79}Br, 86%) [$MH^+-CO_2C(CH_3)_3$]. HRMS (EI^+) calcd for $C_{18}H_{22}^{79}BrNO_2$: 363.0834; found: 363.0832. Anal. calcd for $C_{18}H_{22}BrNO_2$: C, 59.35; H, 6.09; N, 3.85. Found: C, 59.50; H, 6.20; N, 3.79.

4.1.3. Dehydrogenation of carbazole 2. To a mixture of **2** (2.0 g, 5.49 mmol), DDQ (2.62 g, 11.5 mmol) and activated 3 Å molecular sieves was added anhydrous benzene (17 mL) under a nitrogen atmosphere, and the mixture was heated to reflux for 20 h. The cooled reaction mixture was filtered and the filtrate evaporated. The crude product was purified by column chromatography (PS with gradient elution to PS/DCM 3:1) to afford 3-bromo-9-*tert*-butoxycarbonyl-6-methyl-9*H*-carbazole **3** (1.64 g, 4.56 mmol, 83%) as a colourless solid, mp 94–96°C. R_f: 0.66 in PS/DCM (2:1). ^{13}C NMR [300 MHz, $CDCl_3$] δ 8.14, d, J=9.0 Hz, 1H, ArH-1; 8.10, d, J=8.7 Hz, 1H, ArH-8; 7.99, d, J=2.1 Hz, 1H, ArH-4; 7.65, br s, 1H, ArH-5; 7.50, dd, J=8.9, 2.1 Hz, 1H, ArH-2; 7.27, dd, J=8.4, 1.8 Hz, 1H, ArH-7; 2.48, s, 3H, $ArCH_3$; 1.74, s, 9H, $C(CH_3)_3$. ^{13}C NMR [75 MHz, $CDCl_3$] δ 150.7, CO; 137.3, ArC-9a; 136.7, ArC-8a; 132.7, ArC-6; 129.4, ArCH-2; 128.9, ArCH-7; 127.5, ArC-4a; 124.5, ArC-4b; 122.2, ArCH-4; 119.7, ArCH-5; 117.7, ArCH-1; 115.9, ArCH-8 and ArC-3; 84.1, $C(CH_3)_3$; 28.3, $C(CH_3)_3$; 21.2, $ArCH_3$. Mass spectrum (EI^+) m/z 359 (^{79}Br, 4%) [M^+], 304 (^{79}Br, 100%) [$MH^+-C(CH_3)_3$], 260 (^{79}Br, 52%) [$MH^+-CO_2C(CH_3)_3$], 226 (30%) [MH^+−Br, $C(CH_3)_3$], 182 (17%) [MH^+−Br, $CO_2C(CH_3)_3$]. HRMS (CI^+) calcd for $C_{18}H_{18}^{79}BrNO_2$+H: 360.0599; found: 360.0600. Anal. calcd for $C_{18}H_{18}BrNO_2$: C, 60.01; H, 5.04; N, 3.89. Found: C, 59.89; H, 5.05; N, 3.86.

4.1.4. Bromination of carbazole 3. A suspension of **3** (653 mg, 1.81 mmol) and recrystallized NBS (355 mg, 2.00 mmol) in CCl_4 was heated to reflux under nitrogen with irradiation from a 150 W halogen lamp for 2.5 h. The reaction mixture was cooled over an ice bath and filtered, and the filtrate evaporated. The crude product was purified by column chromatography (PS with gradient elution to PS/DCM 1:1) to afford 3-bromo-6-bromomethyl-9-*tert*-butoxycarbonyl-9*H*-carbazole **4** (551 mg, 1.26 mmol, 69%) as a colourless solid, mp ca. 150°C (dec). R_f: 0.56 in PS/DCM (2:1). ^{13}C NMR [400 MHz, $CDCl_3$] δ 8.22, d, J=8.4 Hz, 1H, ArH-8; 8.16, d, J=8.8 Hz, 1H, ArH-1; 8.07, d, J=2.0 Hz, 1H, ArH-4; 7.93, d, J=1.6 Hz, 1H, ArH-5; 7.54, dd, J=8.8, 2.0 Hz, 1H, ArH-2; 7.50, dd, J=8.8, 2.0 Hz, 1H, ArH-7; 4.66, s, 2H, CH_2; 1.73, s, 9H, CH_3. ^{13}C NMR [75 MHz, $CDCl_3$] δ 150.5, CO; 138.5, ArC-9a; 137.7, ArC-8a; 132.9, ArC-6; 130.1, ArCH-2; 128.8, ArCH-7; 127.0, ArC-4a; 124.9, ArC-4b; 122.5, ArCH-4; 120.3, ArCH-5; 117.8, ArCH-1; 116.7, ArCH-8; 116.3, ArC-3; 84.6, $C(CH_3)_3$; 33.7, CH_2; 28.3, CH_3. Mass spectrum (EI^+) m/z 439 ($^{79/81}$Br, 8%) [M^+], 383 ($^{79/81}$Br, 14%) [$M^+-C(CH_3)_3$], 302 (^{79}Br, 54%) [M^+−Br, $C(CH_3)_3$], 258 (^{79}Br, 68%) [M^+-CO_2, Br, $C(CH_3)_3$], 179 (41%) [M^+−2Br, $CO_2C(CH_3)_3$], 57 (100%) [$C(CH_3)_3^+$]. HRMS (EI^+) calcd for $C_{18}H_{17}^{79}Br_2NO_2$: 436.9626; found: 436.9670. Anal. calcd for $C_{18}H_{17}Br_2NO_2$: C, 49.23; H, 3.90; N, 3.19. Found: C, 49.42; H, 3.92; N, 3.04.

4.1.5. Ethyl (2*R*/*S*)-2-acetamido-3-(6-bromo-9*H*-carbazol-3-yl)propanoate (5). Sodium hydride (71 mg, 1.78 mmol) was washed twice with PS under a nitrogen atmosphere, a solution of diethyl acetamidomalonate (368 mg, 1.70 mmol) in anhydrous DMSO (10 mL) was added and the mixture was stirred at room temperature for 30 min. After this period, **4** (820 mg, 1.87 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. Lithium chloride (71 mg, 1.70 mmol) and distilled water (0.06 mL, 3.40 mmol) were added and the reaction mixture was heated to reflux for 1.75 h. The reaction mixture was diluted with ether, the ether mixture was washed with brine and then water, the combined water washings were extracted further with ether, and these extracts were washed with water. The combined ether extracts were dried and evaporated, and the crude product was purified by column chromatography (PS with gradient elution to DCM and finally EtOAc) to afford **5** (481 mg, 1.19 mmol, 70%) as a pale yellow solid. ^{13}C NMR [300 MHz, $CDCl_3$] δ 8.49, s, 1H, ArN*H*; 8.05, d, J=1.8 Hz, 1H, ArH-5; 7.69, s, 1H, ArH-4; 7.43, dd,

J=8.6, 1.8 Hz, 1H, ArH-7; 7.25, d, J=9.0 Hz, 1H, ArH-1; 7.23, d, J=8.4 Hz, 1H, ArH-8; 7.12, dd, J=8.3, 1.5 Hz, 1H, ArH-2; 6.05, d, J=7.5 Hz, 1H, N*H*Ac; 4.90, dt, J=7.8, 6.0 Hz, 1H, NCH; 4.16, q, J=7.2 Hz, 2H, OCH_2; 3.27, dd, J=14.1, 6.3 Hz, 1H, ArC*H*H; 3.20, dd, J=14.0, 5.9 Hz, 1H, ArCH*H*; 1.96, s, 3H, $COCH_3$; 1.22, t, J=7.2 Hz, 3H, OCH_2CH_3. ^{13}C NMR [75 MHz, $CDCl_3$] δ 171.8, *C*OOEt; 169.9, *C*OCH_3; 139.0, ArC-8a; 138.4, ArC-9a; 128.5, ArCH-7; 127.6, ArCH-2; 126.9, ArC-3; 124.6, ArC-4b; 122.8, ArCH-5; 122.4, ArC-4a; 120.9, ArCH-4; 112.1, ArCH-8; 112.0, ArC-6; 110.9, ArCH-1; 61.6, OCH_2; 53.7, NCH; 38.0, $ArCH_2$; 23.2, CO*C*H_3; 14.1, OCH_2CH_3. Mass spectrum (CI$^+$) m/z 403 (^{79}Br, 44%) [MH$^+$], 325 (100%) [MH$^+-$Br]. HRMS (CI$^+$) calcd for $C_{19}H_{19}^{79}BrN_2O_3$+H: 403.0657; found: 403.0664.

4.1.6. Ethyl (2*R*/*S*)-2-acetamido-3-(6-allyl-9*H*-carbazol-3-yl)propanoate (6). To a glass, high-pressure tube containing **5** (1.0 g, 2.48 mmol), palladium chloride (22 mg, 0.12 mmol) and triphenylphosphine (130 mg, 0.50 mmol) was added anhydrous DMF (10 mL) followed by allyltributyltin (0.92 mL, 2.98 mmol). The tube was sealed under nitrogen and the reaction mixture heated in a 110°C oil bath for 22 h. The cooled reaction mixture was diluted with ether, the ether mixture was washed with brine and then water, and the ether layer was dried and evaporated. The crude product was purified by column chromatography (PS with gradient elution to DCM/EtOAc 2:1) to afford **6** (823 mg, 2.26 mmol, 91%) as a pale-yellow solid, mp 100–101°C. R_f: 0.44 in DCM/EtOAc (4:1). ^{13}C NMR [300 MHz, $CDCl_3$] δ 8.13, br s, 1H, ArN*H*; 7.80, s, 1H, ArH-5; 7.76, s, 1H, ArH-4; 7.32, d, J=8.7 Hz, 1H, ArH-8; 7.29, d, J=8.4 Hz, 1H, ArH-1; 7.22, dd, J=8.7, 1.2 Hz, 1H, ArH-7; 7.10, dd, J=8.4, 1.5 Hz, 1H, ArH-2; 6.05, ddt, J=16.8, 10.2, 6.6 Hz, 1H, CH_2CH=CH_2; 5.96, d, J=8.4 Hz, 1H, N*H*Ac; 5.11, dd, J=17.4, 1.8 Hz, 1H, CH_2CH=C*H*H; 5.08, dd, J=9.3, 2.1 Hz, 1H, CH_2-CH=CH*H*; 4.90, dt, J=7.8, 6.3 Hz, 1H, NCH; 4.17, q, J=7.2 Hz, 2H, OCH_2; 3.54, d, J=6.6 Hz, 2H, CH_2-CH=CH_2; 3.26, d, J=5.7 Hz, 2H, $ArCH_2$-3; 1.97, s, 3H, $COCH_3$; 1.23, t, J=7.2 Hz, 3H, OCH_2CH_3. ^{13}C NMR [75 MHz, $CDCl_3$] δ 171.9, *C*OOEt; 169.7, *C*OCH_3; 139.0, ArC-9a; 138.4, ArC-8a; 138.3, CH_2CH=CH_2; 131.1, ArC-6; 126.9, ArCH-2; 126.8, ArCH-7; 126.4, ArC-3; 123.4, ArC-4a; 123.2, ArC-4b; 120.9, ArCH-4; 119.8, ArCH-5; 115.4, CH_2CH=*C*H_2; 110.6, ArCH-1; 110.5, ArCH-8; 61.5, OCH_2; 53.7, CHN; 40.2, *C*H_2CH=CH_2; 38.0, $ArCH_2$-3; 23.2, CO*C*H_3; 14.1, OCH_2CH_3. Mass spectrum (CI$^+$) m/z 365 (100%) [MH$^+$], 220 (15%). HRMS (CI$^+$) calcd for $C_{22}H_{24}N_2O_3$+H: 365.1865; found: 365.1859.

4.1.7. Ethyl (2*R*/*S*)-2-acetamido-3-[6-allyl-9-*tert*-butoxycarbonyl-9*H*-carbazol-3-yl]-propanoate (7). A suspension of **6** (823 mg, 2.26 mmol) and cesium carbonate (1.47 g, 4.52 mmol) in anhydrous DMF (20 mL) was stirred at room temperature under a nitrogen atmosphere for 15 min before a solution of di-*tert*-butyl-dicarbonate (739 mg, 3.39 mmol) in anhydrous DMF (6 mL) was added. The reaction mixture was stirred at room temperature for 20 h. After this period the reaction mixture was diluted with ether, and the ether mixture was washed with brine followed by water, and then dried and evaporated. The crude product was purified by column chromatography (PS with gradient elution to DCM/EtOAc 5:1) to afford **7** (820 mg, 1.77 mmol, 78%) as a pale yellow solid, mp 131–132°C. R_f: 0.58 in DCM/EtOAc (4:1). ^{13}C NMR [300 MHz, $CDCl_3$] δ 8.18, d, J=8.1 Hz, 1H, ArH-8; 8.16, d, J=8.1 Hz, 1H, ArH-1; 7.71, d, J=1.2 Hz, 1H, ArH-4; 7.68, d, J=1.5 Hz, 1H, ArH-5; 7.27, dd, J=8.5, 1.5 Hz, 1H, ArH-2; 7.17, dd, J=8.5, 1.8 Hz, 1H, ArH-7; 6.03, ddt, J=16.5, 9.9, 6.9 Hz, 1H, CH_2CH=CH_2; 5.11, dd, J=17.7, 1.8 Hz, 1H, CH_2-CH=C*H*H; 5.10, dd, J=10.2, 1.8 Hz, 1H, CH_2CH=CH*H*; 4.90, dt, J=7.5, 6.0 Hz, 1H, NCH; 4.17, q, J=7.2 Hz, 2H, OCH_2; 3.52, d, J=6.6 Hz, 2H, CH_2CH=CH_2; 3.28, dd, J=14.0, 5.7 Hz, 1H, ArC*H*H-3; 3.22, dd, J=14.1, 5.7 Hz, 1H, ArCH*H*-3; 1.98, s, 3H, $COCH_3$; 1.72, s, 9H, $C(CH_3)_3$; 1.23, t, J=7.2 Hz, 3H, OCH_2CH_3. ^{13}C NMR [75 MHz, $CDCl_3$] δ 171.7, COOEt; 169.6, *C*OCH_3; 151.0, Boc CO; 137.9, ArC-9a; 137.7, CH_2CH=CH_2; 137.2, ArC-8a; 134.8, ArC-6; 130.4, ArC-3; 128.1, ArCH-2; 128.0, ArCH-7; 125.9, ArC-4a; 125.6, ArC-4b; 120.1, ArCH-4; 119.2, ArCH-5; 116.2, ArCH-1; 116.1, ArCH-8; 115.8, CH_2-CH=*C*H_2; 83.8, *C*$(CH_3)_3$; 61.6, OCH_2; 53.5, NCH; 40.0, *C*H_2CH=CH_2; 37.8, $ArCH_2$-3; 28.3, C(*C*$H_3)_3$; 23.2, CO*C*H_3; 14.2, OCH_2CH_3. Mass spectrum (CI$^+$) m/z 465 (31%) [MH$^+$], 409 (24%) [MH$^+-$C$(CH_3)_3$], 365 (100%) [MH$^+-$$CO_2C(CH_3)_3$], 245 (20%). HRMS (ES$^+$) calcd for $C_{27}H_{32}N_2O_5$+H: 465.2389; found: 465.2408. Anal. calcd for $C_{27}H_{32}N_2O_5$: C, 69.80; H, 6.94; N, 6.03; O, 17.22. Found: C, 69.87; H, 7.14; N, 5.88.

4.1.8. (2*R*/*S*)-2-Acetamido-3-[6-allyl-9-*tert*-butoxycarbonyl-9*H*-carbazol-3-yl]propanoic acid (8). To an ice-cold solution of **7** (900 mg, 1.94 mmol) in THF (25 mL) was added a solution of lithium hydroxide (220 mg, 5.24 mmol) in distilled water (10 mL), for a 0.15 M LiOH final concentration, and the reaction mixture was stirred at 0°C for 3 h. After this period the THF portion of the solvent was evaporated, the aqueous mixture remaining was diluted with distilled water and washed with ether. The aqueous layer was acidified to pH<2 with a 10% HCl solution, and the product was extracted with ether, after saturating the aqueous layer with a sufficient amount of NaCl. Finally, the ether extracts were diluted with DCM to fully solvate the product, and then dried and evaporated to afford **8** (782 mg, 1.79 mmol, 92%) as a colourless solid, mp 178–179°C. R_f: 0.81 in DCM/MeOH (2:1). ^{13}C NMR [300 MHz, $(CD_3)_2CO$] δ 8.21, d, J=8.4 Hz, 1H, ArH-8; 8.20, d, J=8.7 Hz, 1H, ArH-1; 7.96, d, J=1.2 Hz, 1H, ArH-4; 7.89, d, J=0.9 Hz, 1H, ArH-5; 7.39, dd, J=8.4, 1.5 Hz, 2H, ArH-2 and NH (obscured); 7.33, dd, J=8.5, 1.8 Hz, 1H, ArH-7; 6.07, ddt, J=16.9, 9.9, 6.9 Hz, 1H, CH_2CH=CH_2; 5.14, dd, J=17.2, 1.5 Hz, 1H, CH_2CH=C*H*H; 5.07, dd, J=9.9, 1.5 Hz, 1H, CH_2CH=CH*H*; 4.80, m, 1H, NCH; 3.55, d, J=6.9 Hz, 2H, CH_2CH=CH_2; 3.34, dd, J=13.8, 5.4 Hz, 1H, ArC*H*H-3; 3.15, dd, J=13.8, 8.1 Hz, 1H, ArCH*H*-3; 1.89, s, 3H, $COCH_3$; 1.76, s, 9H, $C(CH_3)_3$. ^{13}C NMR [300 MHz, $(CD_3)_2CO$] δ 173.2, COOH; 170.3, *C*OCH_3; 151.6, Boc CO; 138.9, CH_2CH=CH_2; 138.3, ArC-9a; 138.0, ArC-8a; 135.8, ArC-6; 133.1, ArC-3; 129.2, ArCH-2; 128.6, ArCH-7; 126.5, ArC-4a; 126.5, ArC-4b; 121.2, ArCH-4; 120.2, ArCH-5; 116.9, ArCH-1; 116.7, ArCH-8; 115.9, CH_2CH=*C*H_2; 84.5, *C*$(CH_3)_3$; 54.6 and 54.6, NCH; 40.5, *C*H_2CH=CH_2; 38.0, $ArCH_2$-3; 28.4, C(*C*$H_3)_3$; 22.6 and 22.6, CO*C*H_3. Mass spectrum (ES$^+$) m/z

437 (19%) [MH^+], 381 (100%) [$MH^+-C(CH_3)_3$]; (ES^-) *m/z* 435 (100%) [$M-H^-$]. HRMS (ES^+) calcd for $C_{25}H_{28}N_2O_5$+H: 437.2076; found: 437.2072. Anal. calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42; O, 18.33. Found: C, 68.90; H, 6.69; N, 6.34.

4.1.9. Methyl (2*S*,5*S*,8*R*/*S*)-8-acetamido-2-allyl-9-[6-allyl-9-*tert*-butoxycarbonyl-9*H*-carbazol-3-yl]-3,6-diaza-5-{4-[(fluorenylmethoxycarbonyl)amino]butyl}-4,7-dioxononanoate (9b). To a mixture of **8** (467 mg, 1.07 mmol), the dipeptide (513 mg, 1.07 mmol) and DMAP (1 crystal) was added dry DCM (3 mL), anhydrous CH_3CN (18 mL) and anhydrous DMF (3 mL). The mixture was warmed and stirred vigorously under nitrogen to give a translucent solution before EDCI (206 mg, 1.07 mmol) was added. The reaction mixture was stirred and warmed in a 30°C oil bath, under a nitrogen atmosphere, for 18 h. After this period, the reaction solvent was evaporated, DCM was added and the mixture was washed with brine followed by water. The DCM layer was diluted with MeOH (2 mL), dried and evaporated, and the crude product was purified by column chromatography (PS with gradient elution to DCM/MeOH 20:1). The purified product was triturated with DCM/ether to **9b** (735 mg, 0.82 mmol, 77%) as a cream solid, mp 159–161°C. R_f: 0.43 in 10% MeOH in DCM. ^{13}C NMR [500 MHz, $CDCl_3$, isomer ratio 67:33] δ 8.16, d, *J*=7.5 Hz, 0.7H, ArH-1; 8.14*, d, *J*=7.5 Hz, 0.3H, ArH-1; 8.10, d, *J*=8.0 Hz, 0.7H, ArH-8; 8.08*, d, *J*=8.0 Hz, 0.3H, ArH-8; 7.74, s, 1H, ArH-4; 7.70, d, *J*=7.5 Hz, 1.3H, Fmoc ArH-4 and Fmoc ArH-5; 7.69*, d, *J*=7.5 Hz, 0.7H, Fmoc ArH-4 and Fmoc ArH-5; 7.64*, s, 0.3H, ArH-5; 7.60, s, 0.7H, ArH-5; 7.54, d, *J*=7.5 Hz, 1.3H, Fmoc ArH-1 and Fmoc ArH-8; 7.51*, d, *J*=7.5 Hz, 0.7H, Fmoc ArH-1 and Fmoc ArH-8; 7.40–7.35*, m, 0.3H, NH-6; 7.34, t, *J*=7.5 Hz, 2H, Fmoc ArH-3 and Fmoc ArH-6; 7.29–7.18, m, 4H, Fmoc ArH-2, Fmoc ArH-7, ArH-2 and ArH-7; 7.15*, d, *J*=7.0 Hz, 0.3H, NH-3; 7.11, d, *J*=7.5 Hz, 0.7H, NH-3; 7.05, d, *J*=7.5 Hz, 0.7H, NH-6; 6.89*, d, *J*=7.5 Hz, 0.3H, N*H*Ac; 6.81, d, *J*=7.5 Hz, 0.7H, N*H*Ac; 5.98, m, 1H, $ArCH_2CH$=CH_2; 5.61, m, 1H, CH_2CH=CH_2; 5.41*, br s, 1H, N*H*Fmoc; 5.12–4.98, m, 5H, N*H*Fmoc, $ArCH_2$-CH=CH_2 and CH_2CH=CH_2; 4.93*, br d, *J*=7.0 Hz, 0.3H, NCH-8; 4.86, dt, *J*=7.5, 7.0 Hz, 0.7H, NCH-8; 4.59*, br d, *J*=6.5 Hz, 0.3H, NCH-5; 4.52, br d, *J*=6.0 Hz, 0.7H, NCH-2; 4.51–4.41, m, 1H, NCH-5 and NCH-2*; 4.32, d, *J*=7.0 Hz, 2H, OCH_2; 4.13, t, *J*=6.5 Hz, 1H, Fmoc CH; 3.64*, s, 1H, OCH_3; 3.62, s, 2H, OCH_3; 3.45*, d, *J*=5.5 Hz, 0.7H, $ArCH_2CH$=CH_2; 3.44, d, *J*=6.5 Hz, 1.3H, $ArCH_2CH$=CH_2; 3.24–3.12, m, 2H, $ArCH_2$-9; 3.08*, br d, *J*=6.0 Hz, 0.7H, $NCH_2(CH_2)_3$; 2.94–2.77, m, 1.3H, $NCH_2(CH_2)_3$; 2.53–2.31, m, 2H, CH_2CH=CH_2; 1.93, s, 2H, $COCH_3$; 1.92*, s, 1H, $COCH_3$; 1.84–1.55*, m, 0.7H, $N(CH_2)_3CH_2$; 1.68, s, 9H, $C(CH_3)_3$; 1.60–1.49, m, 0.65H, $N(CH_2)_3CH_2$; 1.46–1.26, m, 2.05H, $N(CH_2)_3CH_2$, $N(CH_2)_2CH_2CH_2$* and $NCH_2CH_2(CH_2)_2$*; 1.22–1.06, m, 1.3H, $NCH_2CH_2(CH_2)_2$; 1.04–0.89, m, 1.3H, $N(CH_2)_2$-CH_2CH_2. ^{13}C NMR [75 MHz, $CDCl_3$] δ 171.9, *C*OOMe; 171.3*, CO-7; 171.0, CO-7; 170.9*, CO-4; 170.8, CO-4; 170.5*, NH*C*OCH$_3$; 170.3, NH*C*OCH$_3$; 156.7*, Fmoc CO; 156.5, Fmoc CO; 150.9, Boc CO; 143.9, Fmoc ArC-8a and Fmoc ArC-9a; 143.9*, Fmoc ArC-8a and Fmoc ArC-9a; 141.2, Fmoc ArC-4a and Fmoc ArC-4b; 137.8*, ArC-9a; 137.7, ArC-9a; 137.7, $ArCH_2CH$=CH_2; 137.6*, $ArCH_2$-*C*H=CH_2; 137.2*, ArC-8a; 137.1, ArC-8a; 134.9, ArC-6; 134.8*, ArC-6; 132.1, $CHCH_2CH$=CH_2; 131.9*, $CHCH_2$-*C*H=CH_2; 130.9, ArC-3; 130.9*, ArC-3; 128.0, ArCH-2; 127.9, ArCH-7; 127.6, Fmoc ArCH-3 and Fmoc ArCH-6; 127.0, Fmoc ArCH-2 and Fmoc ArCH-7; 126.0, ArC-4a; 125.6*, ArC-4b; 125.5, ArC-4b; 125.0, Fmoc ArCH-1 and Fmoc ArCH-8; 120.1, ArCH-4; 120.0, Fmoc ArCH-4 and Fmoc ArCH-5; 119.3, ArCH-5; 119.3*, $CHCH_2CH$=*C*H_2; 119.1, $CHCH_2CH$=*C*H_2; 116.4, ArCH-1; 116.3*, ArCH-1; 116.1, ArCH-8; 115.9, $ArCH_2CH$=*C*H_2; 115.8*, $ArCH_2$-CH=*C*H_2; 84.0, *C*$(CH_3)_3$; 83.8*, *C*$(CH_3)_3$; 66.4, OCH_2; 65.8*, OCH_2; 55.4*, NCH-8; 54.8, NCH-8; 52.8, NCH-5; 52.3, OCH_3; 51.7, NCH-2; 47.2*, Fmoc CH; 47.2, Fmoc CH; 40.2*, N*C*$H_2(CH_2)_3$; 39.9, N*C*$H_2(CH_2)_3$; 39.9, Ar*C*H_2-CH=CH_2; 38.5, $ArCH_2$-9; 37.9*, $ArCH_2$-9; 36.0, CH*C*H_2-CH=CH_2; 35.9*, CH*C*H_2CH=CH_2; 31.7*, $N(CH_2)_3CH_2$; 31.3, $N(CH_2)_3CH_2$; 29.1, $NCH_2CH_2(CH_2)_2$; 28.3, C(*C*$H_3)_3$; 23.1, CO*C*H_3; 21.9*, $N(CH_2)CH_2CH_2$; 21.7, $N(CH_2)CH_2$-CH_2. Mass spectrum (ES^+) *m/z* 898 (81%) [MH^+]. HRMS (ES^+) calcd for $C_{52}H_{59}N_5O_9$+H: 898.4391; found: 898.4359. Anal. calcd for $C_{52}H_{59}N_5O_9$: C, 69.55; H, 6.62; N, 7.80. Found: C, 69.71; H, 6.78; N, 7.67.

4.1.10. (6*R*/*S*,9*S*,12*S*,14*E*/*Z*)-6-Acetamido-8,11-diaza-1-*tert*-butoxycarbonyl-9-{4-[(fluorenylmethoxycarbonyl)-amino]butyl}-12-methoxycarbonyl-7,10-dioxo-[12]-(4,17)carbazolo-14-phene (10a). To a solution of **9b** (200 mg, 0.22 mmol) in dry DCM (56 mL) was added Grubbs' ruthenium catalyst (18 mg, 0.022 mmol) and the reaction mixture was heated to reflux under a nitrogen atmosphere for 23 h. After this period, the reaction solvent was evaporated, and the crude product was purified by column chromatography (PS with gradient elution to DCM/MeOH 10:1) and then triturated with DCM/ether/PS to give **10a** (192 mg, 0.22 mmol, 99%) as a cream solid, mp 192–193°C. R_f: 0.37 in 10% MeOH in DCM. ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 8.70*, br d, *J*=6.5 Hz, NH-11 (*Z* isomer); 8.55, br d, *J*=7.5 Hz, NH-11 (*E* isomer); 8.52, br d, *J*=7.0 Hz, NH-11 (*E* isomer); 8.50, br d, *J*=7.5 Hz, NH-8; 8.41, br d, *J*=8.5 Hz, NH-8; 8.33, br d, *J*=8.0 Hz, N*H*Ac; 8.15–8.05, m, 2H, ArH-2 and ArH-19; 7.91*, br d, *J*=8.5 Hz, N*H*Ac; 7.84, d, *J*=7.0 Hz, Fmoc ArH-4 and Fmoc ArH-5; 7.81*, d, *J*=8.0 Hz, Fmoc ArH-4 and Fmoc ArH-5; 7.72–7.64, m, NH-8; 7.66, d, *J*=6.5 Hz, Fmoc ArH-1 and Fmoc ArH-8; 7.59*, d, *J*=6.0 Hz, Fmoc ArH-1 and Fmoc ArH-8; 7.58, s, ArH-20; 7.55, s, ArH-20; 7.43, br s, ArH-20 and N*H*Ac*; 7.37, dd, *J*=7.2, 7.5 Hz, 2H, Fmoc ArH-3 and Fmoc ArH-6; 7.35–7.25, m, ArH-3 and ArH-18; 7.30, dd, *J*=8.0, 8.0 Hz, 2H, Fmoc ArH-2 and Fmoc ArH-7; 7.30–7.28, m, 1H, N*H*Fmoc; 7.18*, br d, *J*=6.0 Hz, N*H*Ac; 7.11*, d, *J*=8.5 Hz, ArH-3; 5.83, dt, *J*=14.5, 7.0 Hz, $ArCH_2CH$=CH (*E* isomer); 5.76, m, $ArCH_2CH$=CH* (*Z* isomer) and $CHCH_2CH$=CH (*E* isomer); 5.65, m, $CHCH_2$-*C*H=CH (both isomers); 4.88*, br s, NCH-6; 4.67*, br d, *J*=6.5 Hz, NCH-6; 4.62, dt, *J*=4.0, 8.0 Hz, NCH-9; 4.47, dt, *J*=7.5, 8.5 Hz, NCH-12 (*E* isomer) and NCH-9*; 4.44–4.38*, m, NCH-6; 4.40–4.30*, m, NCH-12 (*Z* isomer); 4.33–4.25, m, NCH-6; 4.26, d, 2H, *J*=7.0 Hz, OCH_2; 4.24–4.16, m, 1H, Fmoc CH; 3.64, s, OCH_3; 3.64–3.40*, m, $ArCH_2CH$=CH (*Z* isomer); 3.59*, s, OCH_3; 3.56*, s, OCH_3; 3.53–3.40, m, $ArCH_2CH$=CH (*E* isomer); 3.24–3.06, m, $ArCH_2$-5; 3.04–2.92, m, $ArCH_2$-5; 3.00–2.85, m, $NCH_2(CH_2)_3$; 2.78*, m, $NCH_2(CH_2)_3$; 2.73–2.64*, m,

CHCH_2CH=CH (*Z* isomer); 2.59, br dd, *J*=6.2, 6.5 Hz, CHCH_2CH=CH (*E* isomer); 2.56–2.46*, m, CHCH_2-CH=CH (*Z* isomer); 2.32, m, CHCH_2CH=CH (*E* isomer); 1.90, s, $COCH_3$; 1.89, s, $COCH_3$; 1.86*, $COCH_3$; 1.82–1.48, m, 2H, N$(CH_2)_3$CH_2; 1.68, s, C$(CH_3)_3$; 1.65*, s, C$(CH_3)_3$; 1.46–1.28, m, NCH_2C$H_2(CH_2)_2$; 1.35–1.24*, m, N$(CH_2)_2$CH_2CH_2; 1.24–1.13, m, N$(CH_2)_2$CH_2CH_2; 1.24–1.10*, m, NCH_2C$H_2(CH_2)_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.7, CO-10; 172.4, *C*OOCH_3; 172.3, CO-10; 172.2*, *C*OOCH_3; 171.7*, *C*OOCH_3; 170.1*, CO-7; 169.7, CO-7; 169.4*, *C*OCH_3; 169.2, CO-7; 169.1, *C*OCH_3; 168.9, *C*OCH_3; 156.1, Fmoc CO; 155.9*, Fmoc CO; 150.3, Boc CO; 143.9, Fmoc ArC-8a and Fmoc ArC-9a; 140.7, Fmoc ArC-4a and Fmoc ArC-4b; 136.8, ArC-1a; 136.5*, ArC-19a; 136.4, ArC-19a; 134.6, ArC-17; 131.7, ArCH_2*C*H=CH (*Z* isomer); 131.6, ArC-4; 131.2, ArCH_2*C*H=CH (*E* isomer); 129.4, ArCH-3; 128.8, CHCH_2*C*H=CH; 128.6, CHCH_2*C*H=CH; 128.1, ArCH-18; 128.0, ArCH-18; 127.6, Fmoc ArCH-3 and Fmoc ArCH-6; 127.0, Fmoc ArCH-2 and Fmoc ArCH-7; 125.1, Fmoc ArCH-1 and Fmoc ArCH-8; 124.8, ArC-20a and ArC-20b; 120.1, Fmoc ArCH-4 and Fmoc ArCH-5; 119.5, ArCH-21; 119.4, ArCH-21; 118.3, ArCH-20; 117.9, ArCH-20; 115.7, ArCH-2; 115.5, ArCH-2* and ArCH-19; 115.2*, ArCH-19; 83.8, *C*$(CH_3)_3$; 65.2, OCH_2; 57.1, NCH-6; 55.9*, NCH-6; 54.6*, NCH-6; 53.9, NCH-12 (*E* isomer); 53.3, NCH-12 (*E* isomer); 53.1*, NCH-12 (*Z* isomer); 52.9*, NCH-6; 52.3*, NCH-12 (*Z* isomer); 52.0, OCH_3; 51.9*, OCH_3; 51.8*, OCH_3; 51.3, NCH-9; 51.0*, NCH-9; 46.8, Fmoc CH; 40.3, N*C*$H_2(CH_2)_3$; 40.3, N*C*$H_2(CH_2)_3$; 39.9*, N*C*$H_2(CH_2)_3$; 39.8*, N*C*$H_2(CH_2)_3$; 38.0, ArCH_2-5; 37.6, ArCH_2-5; 37.5, ArCH_2-5; 37.1, Ar*C*H_2CH=CH (*E* isomer); 37.0, Ar*C*H_2CH=CH (*E* isomer); 33.4, N$(CH_2)_3$*C*H_2; 33.3, N$(CH_2)_3$*C*H_2; 33.1, CH*C*H_2CH=CH (*E* isomer); 32.9, CH*C*H_2CH=CH (*E* isomer); 32.8*, Ar*C*H_2CH=CH (*Z* isomer); 32.4*, Ar*C*H_2CH=CH (*Z* isomer); 29.4, NCH$_2$-*C*$H_2(CH_2)_2$; 29.3, NCH_2*C*$H_2(CH_2)_2$; 29.0*, NCH_2*C*H$_2$-$(CH_2)_2$; 27.8, C(*C*$H_3)_3$ and CH*C*H_2CH=CH* (*Z* isomer); 22.6, CO*C*H_3; 22.4*, CO*C*H_3; 22.1*, N$(CH_2)_2$*C*H_2CH$_2$; 22.0, N$(CH_2)_2$CH_2*C*H$_2$. Mass spectrum (ES$^+$) *m/z* 870 (6%) [MH$^+$]. HRMS (ES$^+$) calcd for $C_{50}H_{55}N_5O_9$+H: 870.4078; found: 870.4099.

4.1.11. (6*R*/*S*,9*S*,12*S*)-6-Acetamido-8,11-diaza-1-*tert*-butoxycarbonyl-9-{4-[(fluorenyl-methoxycarbonyl)amino]butyl}-12-methoxycarbonyl-7,10-dioxo-[12](4,17)-carbazolophane (13a). To a solution of **10a** (350 mg, 0.40 mmol) in THF/MeOH (110 mL, 8:3) was added 10% Pd/C (85 mg, 0.040 mmol) and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 22.5 h. The reaction mixture was diluted with THF/MeOH and filtered through celite, and the filtrate was evaporated. The residue was retreated as described above, with a stirring period of 19.5 h. By MS (ES$^+$) the reduction was shown to be incomplete with the alkene present in a ratio of 1:2 (alkene/reduced). The partially reduced compound was retreated twice (Pd/C, H_2), with stirring periods of 20 and 26 h, to give **13a** (339 mg, 0.39 mmol, 97%) as a cream solid, mp 136–138°C. R_f: 0.39 in 10% MeOH in DCM. ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 8.37, br d, *J*=8.5 Hz, NH-8* and NH-11; 8.35, br d, *J*=8.5 Hz, NH-8* and NH-11; 8.27, br d, *J*=8.0 Hz, NH-8; 8.14–8.04, m, 2H, ArH-2 and ArH-19; 7.86, d *J*=7.5 Hz, Fmoc ArH-4 and Fmoc ArH-5; 7.83*, d, *J*=7.5 Hz, Fmoc ArH-4 and Fmoc ArH-5; 7.73–7.64, m, 2H, Fmoc ArH-1 and Fmoc ArH-8; 7.67, s, ArH-21; 7.66, br d, *J*=7.0 Hz, N*H*Ac; 7.62, s, ArH-20 and ArH-21*; 7.56*, br d, *J*=7.0 Hz, N*H*Ac; 7.44–7.36, m, 2H, Fmoc ArH-3 and Fmoc ArH-6; 7.42–7.30, m, ArH-3; 7.30, dd, *J*=7.5, 7.5 Hz, 2H, Fmoc ArH-2 and Fmoc ArH-7; 7.27, d, *J*=8.0 Hz, ArH-18; 7.21–7.15, m, ArH-3 and N*H*Fmoc; 4.85*, br s, NCH-6; 4.56, br d, *J*=8.5 Hz, NCH-12; 4.53, br d, *J*=8.5 Hz, NCH-12; 4.45*, br d, *J*=5.0 Hz, NCH-9; 4.35, m, NCH-6 and NCH-9; 4.27*, d, *J*=7.0 Hz, OCH_2; 4.25, d, *J*=7.0 Hz, OCH_2; 4.19, t, *J*=6.0 Hz, 1H, Fmoc CH; 3.64*, s, OCH_3; 3.63, s, OCH_3; 3.25–3.15, m, ArCH_2-5; 3.12*, br d, *J*=12.0 Hz, ArCH_2-5; 3.00–2.92, m, ArCH_2-5; 2.98–2.84, m, NC$H_2(CH_2)_3$ and ArC$H_2(CH_2)_3$; 2.80–2.68, m, ArC$H_2(CH_2)_3$; 2.02–1.88, m, 2H, ArCH_2C$H_2(CH_2)_2$; 1.94*, s, $COCH_3$; 1.89, s, $COCH_3$; 1.80–1.59, m, 2H, Ar$(CH_2)_3$CH_2; 1.75–1.41, m, 2H, N$(CH_2)_3$CH_2; 1.68, s, 9H, C$(CH_3)_3$; 1.43–1.23, m, 2H, NCH_2C$H_2(CH_2)_2$; 1.38–1.24, m, 2H, Ar$(CH_2)_2$CH_2CH_2; 1.22–1.07, m, 2H, N$(CH_2)_2$CH_2CH_2. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.8, *C*OOCH_3; 172.7, *C*OOCH_3; 172.3, CO-10; 172.2, CO-10; 169.5, CO-7; 169.0*, *C*OCH_3; 168.9, *C*OCH_3; 156.0, Fmoc CO; 150.3, Boc CO; 143.9, Fmoc ArC-8a and Fmoc ArC-9a; 140.7, Fmoc ArC-4a and Fmoc ArC-4b; 136.7, ArC-1a; 136.6*, ArC-1a; 136.1, ArC-19a; 136.0*, ArC-19a; 135.7, ArC-17; 131.7, ArC-4; 128.9*, ArCH-3; 128.7, ArCH-3; 128.6, ArCH-18; 127.6, Fmoc ArCH-3 and Fmoc ArCH-6; 127.0, Fmoc ArCH-2 and Fmoc ArCH-7; 125.1, Fmoc ArCH-1 and Fmoc ArCH-8; 124.9, ArC-20a and ArC-20b; 120.1, Fmoc ArCH-4 and Fmoc ArCH-5; 119.8, ArCH-21; 119.6, ArCH-21; 117.7, ArCH-20; 117.5, ArCH-20; 115.8, ArCH-2 and ArCH-19; 115.3*, ArCH-2; 83.8, *C*$(CH_3)_3$; 65.2, OCH_2; 56.8, NCH-6; 52.7*, NCH-6; 52.0, OCH_3; 51.7*, OCH_3; 51.5*, NCH-9; 51.3, NCH-12; 51.1, NCH-12; 51.1, NCH-9; 40.3*, N*C*$H_2(CH_2)_3$; 40.2, N*C*$H_2(CH_2)_3$; 38.0, ArCH_2-5; 37.3, ArCH_2-5; 33.5, N$(CH_2)_3$*C*H_2; 33.4, N$(CH_2)_3$*C*H_2; 32.9, Ar*C*$H_2(CH_2)_3$; 30.7, Ar$(CH_2)_3$*C*H_2; 30.6, Ar$(CH_2)_3$*C*H_2; 29.1, NCH_2*C*H$_2$-$(CH_2)_2$; 27.8, C(*C*$H_3)_3$; 27.1, ArCH_2*C*$H_2(CH_2)_2$; 27.0, ArCH_2*C*$H_2(CH_2)_2$; 23.2, Ar$(CH_2)_2$*C*H_2CH$_2$; 23.1, Ar$(CH_2)_2$*C*H_2CH$_2$; 22.7, CO*C*H_3; 22.1, N$(CH_2)_2$*C*H_2CH$_2$; 21.7, N$(CH_2)_2$CH_2*C*H$_2$. Mass spectrum (ES$^+$) *m/z* 872 (6%) [MH$^+$]. HRMS (ES$^+$) calcd for $C_{50}H_{57}N_5O_9$+H: 872.4235; found: 872.4270.

4.1.12. (6*R*/*S*,9*S*,12*S*,14*E*/*Z*)-6-Acetamido-9-(4-aminobutyl)-8,11-diaza-1-*tert*-butoxycarbonyl-12-methoxycarbonyl-7,10-dioxo-[12](4,17)carbazolo-14-phene hydrochloride (11). To a solution of **10a** (100 mg, 0.11 mmol) in dry THF (25 mL) was added a solution of piperidine (0.006 mL, 0.057 mmol) in dry THF under a nitrogen atmosphere and the reaction mixture was stirred and heated in a 50°C oil bath for 21.5 h. As incomplete deprotection was detected by TLC, more piperidine (0.004 mL, 0.042 mmol) was added in dry THF and the reaction mixture was heated for a further 16.5 h. The reaction solvent was evaporated, and PS was added and decanted to remove the Fmoc by-products. The crude product was dissolved in MeOH (10 mL) and 1 M HCl-in-ether (0.23 mL, 0.023 mmol) was added under a nitrogen atmosphere. After stirring for 20 min, the reaction solvent was evaporated and the product was recrystallized at ice bath temperature from MeOH/ether/PS to give **11** (64 mg,

0.094 mmol, 81%) as a cream solid, mp ca. 230°C (dec). R_f: 0.57 in MeOH/NEt_3 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 8.84*, br d, J=7.5 Hz, NH-11; 8.82*, br d, J=8.0 Hz, NH-11; 8.70, br d, J=7.5 Hz, NH-11; 8.63, br d, J=7.5 Hz, NH-11; 8.49*, br d, J=10.0 Hz, NH-8; 8.47, br d, J=9.5 Hz, N*H*Ac; 8.41*, br d, J=8.5 Hz, NH-8; 8.38–8.28, m, N*H*Ac; 8.24–8.16*, m, NH-11; 8.14–7.93, m, 2H, ArH-2 and ArH-19; 8.04, br s, NH_2; 7.97*, br s, NH_2; 7.83–7.77*, m, NH-8; 7.69, br d, J=8.0 Hz, NH-8; 7.57*, s, ArH-21; 7.55, s, ArH-20; 7.53, s, ArH-20; 7.50*, s, ArH-20; 7.49*, br d, J=8.5 Hz, N*H*Ac; 7.41, s, ArH-21; 7.38–7.30*, m, ArH-3; 7.30, br d, J=8.0 Hz, ArH-18; 7.22, br d, J=6.5 Hz, N*H*Ac; 7.16*, br d, J=8.0 Hz, ArH-3; 7.10, br d, J=8.0 Hz, ArH-3; 5.89–5.79, m, $ArCH_2CH$=CH (E isomer); 5.81–5.70, m, $ArCH_2CH$=CH* (Z isomer) and $CHCH_2CH$=CH; 5.72–5.62, m, $CHCH_2CH$=CH; 5.65–5.42, m, $CHCH_2CH$=CH; 4.84*, br s, NCH-6; 4.62*, br d, J=3.5 Hz, NCH-6 and NCH-9; 4.46, br d, J=3.5 Hz, NCH-9 and NCH-12; 4.31*, br d, J=8.0 Hz, NCH-12; 4.28*, br d, J=7.5 Hz, NCH-12; 4.18, br s, NCH-6; 3.72–3.36, m, $ArCH_2CH$=CH; 3.65, s, OCH_3; 3.60*, s, OCH_3; 3.57*, s, OCH_3; 3.22, −2.84, m, 2H, $ArCH_2$-5; 2.78–2.50, m, 2H, $NCH_2(CH_2)_3$; 2.59, br d, J=11.0 Hz, $CHCH_2CH$=CH; 2.42–2.28, m, $CHCH_2CH$=CH; 2.33, br d, J=11.0 Hz, $CHCH_2CH$=CH; 1.90, s, $COCH_3$; 1.87, s, $COCH_3$; 1.84–1.45, m, 2H, $N(CH_2)_3CH_2$; 1.77*, s, $COCH_3$; 1.73*, s, $COCH_3$; 1.67, s, 9H, $C(CH_3)_3$; 1.62–1.40, m, 2H, $NCH_2CH_2(CH_2)_2$; 1.32, m, $N(CH_2)_2CH_2CH_2$; 1.21, m, $N(CH_2)_2CH_2CH_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.6, CO-10; 172.4, CO-10 and $COOCH_3$; 172.3, CO-10 and $COOCH_3$; 171.7, CO-7 and $COOCH_3$; 171.4*, CO-7; 170.3*, CO-7; 169.8, CO-7; 169.3, $COCH_3$; 169.2, $COCH_3$; 168.9, $COCH_3$; 150.3, Boc CO; 136.7, ArC-1a; 136.6*, ArC-1a; 136.4*, ArC-19a; 136.3, ArC-19a and ArC-17*; 134.6, ArC-17; 132.7*, ArC-4; 131.9*, $ArCH_2CH$=CH (Z isomer); 131.6, $ArCH_2CH$=CH (E isomer); 131.5, ArC-4; 131.1, $ArCH_2CH$=CH (E isomer); 130.5*, $ArCH_2CH$=CH (Z isomer); 129.4, ArCH-3 and $CHCH_2CH$=CH*; 128.8*, ArCH-3; 128.7, $CHCH_2CH$=CH; 128.3*, $CHCH_2CH$=CH; 128.2, $CHCH_2CH$=CH; 128.0, ArCH-18; 125.3*, ArC-20a; 125.0, ArC-20a; 125.0*, ArC-20b; 124.7, ArC-20b; 120.4*, ArCH-21; 120.0*, ArCH-21; 119.5, ArCH-21; 119.4, ArCH-21; 118.7*, ArCH-20; 118.2, ArCH-20; 117.8, ArCH-20; 115.7, ArCH-19; 115.5*, ArCH-2 and ArCH-19; 115.2, ArCH-2; 83.9, $C(CH_3)_3$; 83.9*, $C(CH_3)_3$; 57.3, NCH-6; 56.2*, NCH-6; 54.7*, NCH-6; 53.9, NCH-12; 53.4, NCH-12; 53.2*, NCH-2; 52.8*, NCH-6; 52.3*, NCH-12; 52.1, OCH_3; 52.0*, NCH-12; 51.8*, OCH_3; 51.1*, NCH-9; 50.8*, NCH-9; 50.7, NCH-9; 38.5, $NCH_2(CH_2)_3$; 38.3*, $NCH_2(CH_2)_3$; 38.2, $ArCH_2CH$=CH (E isomer); 37.9, $ArCH_2$-5; 37.5, ArCH-5; 37.1, $ArCH_2$-CH=CH (E isomer); 36.9, $ArCH_2CH$=CH (E isomer); 33.9, $CHCH_2CH$=CH (E isomer); 32.9, $CHCH_2CH$=CH (E isomer) and $N(CH_2)_3CH_2$; 32.8, $N(CH_2)_3CH_2$; 32.7*, $ArCH_2CH$=CH (Z isomer); 27.8, $C(CH_3)_3$ and $CHCH_2$-CH=CH* (Z isomer); 26.4*, $NCH_2CH_2(CH_2)_2$; 26.2, $NCH_2CH_2(CH_2)_2$; 22.7, $COCH_3$; 22.6, $COCH_3$; 22.4*, $COCH_3$; 22.0, $N(CH_2)_2CH_2CH_2$; 21.6, $N(CH_2)_2CH_2CH_2$; 21.2, $N(CH_2)_2CH_2CH_2$. Mass spectrum (ES^+) m/z 648 (100%) [MH^+]. HRMS (ES^+) calcd for $C_{35}H_{45}N_5O_7$+H: 648.3397; found: 648.3391.

4.1.13. (6*R*/*S*,9*S*,12*S*)-6-Acetamido-9-(4-aminobutyl)-8,11-diaza-1-*tert*-butoxycarbonyl-12-methoxycarbonyl-7,10-dioxo-[12](4,17)carbazolophane hydrochloride (14). To a solution of **13a** (100 mg, 0.11 mmol) in anhydrous CH_3CN (40 mL) was added a solution of piperidine (0.006 mL, 0.057 mmol) in anhydrous CH_3CN under a nitrogen atmosphere and the reaction mixture was stirred and heated in a 65°C oil bath for 25 h. The reaction solvent was evaporated, and PS was added and decanted to remove the Fmoc by-products. The crude product was dissolved in MeOH (10 mL) and 1 M HCl-in-ether (0.23 mL, 0.23 mmol) was added under a nitrogen atmosphere. After stirring for 15 min, the reaction solvent was evaporated and the product was recrystallized at ice bath temperature from MeOH/ether/PS to give **14** (55 mg, 0.080 mmol, 70%) as a pale yellow solid, mp ca. 190°C (dec). R_f: 0.57 in MeOH/NEt_3 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 8.47–8.28, m, NH-11; 8.40–8.28, m, N*H*Ac; 8.40–8.22*, m, NH-8; 8.08–7.94, m, 2H, ArH-2 and ArH-19; 8.05–7.90, m, NH_2; 7.75–7.57, m, NH-8; 7.64–7.50, m, 1H, ArH-21; 7.61–7.52, m, 1H, ArH-20; 7.58–7.48*, m, N*H*Ac; 7.36–7.27, m, ArH-3; 7.27–7.18, m, 1H, ArH-18; 7.18–7.10*, m, ArH-3; 4.82–4.73*, m, NCH-6; 4.57–4.45, m, NCH-12; 4.45–4.37*, m, NCH-9; 4.35–4.28, m, NCH-9; 4.28–4.21, m, NCH-6; 3.61, s, OCH_3; 3.55*, s, OCH_3; 3.20–3.00, m, $ArCH_2$-5; 2.97–2.83, m, $ArCH_2$-5; 2.94–2.83, m, $ArCH_2(CH_2)_3$; 2.78–2.66, m, $ArCH_2(CH_2)_3$; 2.70–2.52, 2H, $NCH_2(CH_2)_3$; 2.00–1.83, m, 2H, $ArCH_2CH_2(CH_2)_2$; 1.90*, s, $COCH_3$; 1.87, s, $COCH_3$; 1.78–1.60, m, 2H, $Ar(CH_2)_3CH_2$; 1.70–1.34, m, $N(CH_2)_3CH_2$; 1.64, s, 9H, $C(CH_3)_3$; 1.55–1.38, m, 2H, $NCH_2CH_2(CH_2)_2$; 1.38–1.18, m, 2H, $Ar(CH_2)_2CH_2CH_2$; 1.26–1.07, m, 2H, $N(CH_2)_2CH_2CH_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.8, $COOCH_3$; 172.3, CO-10; 172.2, CO-10; 169.6, CO-7; 169.2, CO-7; 169.0, $COCH_3$; 150.3, Boc CO; 136.6, ArC-1a; 136.5*, ArC-1a; 136.2*, ArC-17; 136.0, ArC-19a; 135.7, ArC-17; 131.8*, ArC-4; 131.7; ArC-4; 129.0*, ArCH-3; 128.7, ArCH-3 and ArCH-18; 124.9, ArC-20a and ArC-20b; 119.8, ArCH-21; 119.6*, ArCH-21; 117.5, ArCH-20; 117.4*, ArCH-20; 115.8, ArCH-2 and ArCH-19; 115.3*, ArCH-2; 83.9, $C(CH_3)_3$; 83.8*, $C(CH_3)_3$; 57.1, NCH-6; 52.8*, NCH-6; 52.2, OCH_3; 51.9*, OCH_3; 51.2*, NCH-9; 51.1, NCH-12; 50.6, NCH-9; 38.5, $NCH_2(CH_2)_3$; 38.0, $ArCH_2$-5; 37.2, $ArCH_2$-5; 32.9, $ArCH_2(CH_2)_3$ and $N(CH_2)_3CH_2$; 30.6, $Ar(CH_2)_3CH_2$; 27.9, $C(CH_3)_3$; 27.0, $ArCH_2CH_2(CH_2)_2$; 26.6*, NCH_2CH_2-$(CH_2)_2$; 26.3, $NCH_2CH_2(CH_2)_2$; 23.2, $Ar(CH_2)_2CH_2CH_2$; 23.1, $Ar(CH_2)_2CH_2CH_2$; 22.8, $COCH_3$; 22.7, $COCH_3$; 21.7*, $N(CH_2)_2CH_2CH_2$; 21.4, $N(CH_2)_2CH_2CH_2$. Mass spectrum (ES^+) m/z 650 (31%) [MH^+]. HRMS (ES^+) calcd for $C_{35}H_{47}N_5O_7$+H: 650.3554; found: 650.3539.

4.1.14. (6*R*/*S*,9*S*,12*S*,14*E*/*Z*)-6-Acetamido-9-(4-aminobutyl)-8,11-diaza-12-methoxycarbonyl-7,10-dioxo-[12](4,17)carbazolo-14-phene hydrochloride (12a). A solution of **10a** (40 mg, 0.046 mmol) in TFA (2 mL) was stirred under a nitrogen atmosphere at room temperature for 1.5 h. The reaction mixture was diluted with DCM and evaporated several times to remove TFA by co-evaporation. The crude product was dissolved in anhydrous CH_3CN (4 mL) and a solution of piperidine (0.002 mL, 0.023 mmol) in anhydrous CH_3CN was added under a nitrogen atmosphere. The reaction mixture was stirred and heated

in a 65°C oil bath for 18 h. The reaction solvent was evaporated and PS was added and decanted to remove the Fmoc by-products. The crude product was dissolved in MeOH (5 mL) and 1 M HCl-in-ether (0.09 mL, 0.092 mmol) was added under a nitrogen atmosphere. After stirring for 20 min, the solvent was evaporated and the product recrystallized from MeOH/ether at ice bath temperature to give **12a** (27 mg, 0.046 mmol, 100%) as a cream solid, mp ca. 160°C (dec). R_f: 0.77 in MeOH/NEt_3 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 11.17*, br s, ArN*H*; 11.15*, br s, ArN*H*; 11.06, br s, ArN*H*; 11.03, br s, ArN*H*; 8.85, br d, *J*=6.5 Hz, NH-11; 8.71, br d, *J*=8.0 Hz, NH-11; 8.67, *J*=7.5 Hz, NH-11; 8.42, br d, *J*=8.0 Hz, N*H*Ac and NH-8*; 8.30*, br d, *J*=9.5 Hz, NH-8; 8.01, br d, *J*=7.5 Hz, N*H*Ac; 8.00, br s, NH_2; 7.68, br d, *J*=8.5 Hz, NH-8; 7.57, s, ArH-20; 7.56, s, ArH-20; 7.54*, s, ArH-21; 7.52*, s, ArH-20; 7.50*, br d, *J*=8.5 Hz, N*H*Ac; 7.43, s, ArH-21; 7.40–7.22, m, ArH-2 and ArH-19; 7.24–7.08, m, ArH-3 and ArH-18; 7.19*, br d, *J*=7.0 Hz, N*H*Ac; 6.94*, br d, *J*=8.5 Hz, ArH-3; 5.84, dt, *J*=14.5, 7.0 Hz, $ArCH_2$-C*H*=CH (*E* isomer); 5.80–5.70, m, $ArCH_2CH$=C*H*; 5.68, dt, *J*=14.5, 7.0 Hz, $CHCH_2CH$=CH (*E* isomer); 5.45–5.40, m, $CHCH_2CH$=CH; 4.78*, br s, NCH-6; 4.69*, m, NCH-9; 4.62*, br d, *J*=3.0 Hz, NCH-9; 4.55*, br s, NCH-6; 4.44, br d, *J*=9.5 Hz, NCH-9; 4.43, br d, *J*=9.0 Hz, NCH-12; 4.31, dt, *J*=5.0, 7.5 Hz, NCH-6 and NCH-12*; 4.25–4.14, m, NCH-12; 4.20–4.08, m, NCH-6; 3.64, s, OCH_3; 3.59*, s, OCH_3; 3.57*, s, OCH_3; 3.54*, s, OCH_3; 3.50–3.35, m, 2H, $ArCH_2$CH=CH; 3.20–2.98, m, 2H, $ArCH_2$-5; 2.78–2.60, m, 2H, $NCH_2(CH_2)_3$; 2.62–2.51, m, $CHCH_2$-CH=CH; 2.40–2.27, m, $CHCH_2CH$=CH; 1.88, s, $COCH_3$; 1.87, s, $COCH_3$; 1.86–1.47, m, 2H, $N(CH_2)_3CH_2$; 1.73*, s, $COCH_3$; 1.67–1.40, m, $NCH_2CH_2(CH_2)_2$; 1.40–1.14, m, 2H, $N(CH_2)_2CH_2CH_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.7, CO-10; 172.6, CO-10; 172.5, $COOCH_3$; 172.5, $COOCH_3$; 171.7*, $COOCH_3$ and CO-10; 170.4*, CO-7; 170.0, CO-7; 169.3*, $COCH_3$; 169.2, $COCH_3$; 168.8, $COCH_3$; 139.0, ArC-1a; 138.9*, ArC-1a; 138.6, ArC-19a; 138.6*, ArC-19a; 132.1, $ArCH_2CH$=CH; 131.7, $ArCH_2$-CH=CH; 130.7*, ArC-17; 129.2, ArC-17; 129.1, $CHCH_2$-CH=CH; 128.5, $CHCH_2CH$=CH; 127.6*, ArCH-3; 127.3*, ArC-4; 127.0, ArCH-3; 126.5*, ArCH-18; 126.4, ArCH-18; 126.2, ArC-4; 122.5, ArC-20a; 122.4*, ArC-20a; 122.3*, ArC-20b; 122.2, ArC-20b; 120.2*, ArCH-21; 119.6, ArCH-21; 119.5, ArCH-21; 118.8*, ArCH-20; 118.4, ArCH-20; 118.0, ArCH-20; 110.8*, ArCH-19; 110.6, ArCH-19; 110.5, ArCH-2; 110.2*, ArCH-2; 57.6, NCH-6; 56.3, NCH-6; 55.4*, NCH-6; 54.3, NCH-12; 53.9, NCH-12; 53.3*, NCH-6; 52.3*, NCH-12; 52.1, OCH_3; 52.0*, NCH-12; 51.8*, OCH_3; 51.1*, NCH-9; 50.7, NCH-9; 38.6, $NCH_2(CH_2)_3$; 38.3, $ArCH_2$-5; 37.7, $ArCH_2$-5; 37.1, $ArCH_2$-CH=CH; 37.0, $ArCH_2CH$=CH; 33.9*, $CHCH_2CH$=CH; 33.2*, $N(CH_2)_3CH_2$; 33.0, $N(CH_2)_3CH_2$; 32.7, $CHCH_2$-CH=CH; 32.4, $CHCH_2CH$=CH; 26.7, $NCH_2CH_2(CH_2)_2$; 26.5, $NCH_2CH_2(CH_2)_2$; 22.7, $COCH_3$; 22.4*, $COCH_3$; 21.7, $N(CH_2)_2CH_2CH_2$; 21.1, $N(CH_2)_2CH_2CH_2$. Mass spectrum (ES^+) *m/z* 548 (100%) [MH^+]. HRMS (ES^+) calcd for $C_{30}H_{37}N_5O_5$+H: 548.2873; found: 548.2886.

4.1.15. (6*R*/*S*,9*S*,12*S*)-6-Acetamido-9-(4-aminobutyl)-8,11-diaza-12-methoxycarbonyl-7,10-dioxo-[12](4,17)-carbazolophane hydrochloride (15a). To a stirred suspension of **13a** (105 mg, 0.12 mmol) in dry DCM (3 mL) was added TFA (3 mL) under a nitrogen atmosphere, and the translucent reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with DCM and evaporated several times to remove TFA by co-evaporation. The crude product was dissolved in anhydrous CH_3CN (30 mL) and a solution of piperidine (0.006 mL, 0.060 mmol) in anhydrous CH_3CN was added under a nitrogen atmosphere. The reaction mixture was stirred and heated in a 65°C oil bath for 14.5 h. The reaction solvent was evaporated and PS was added and decanted to remove the Fmoc by-products. The crude product was dissolved in MeOH (10 mL) and 1 M HCl-in-ether (0.24 mL, 0.24 mmol) was added under a nitrogen atmosphere. After stirring for 15 min, the solvent was evaporated and the product recrystallized at ice bath temperature from MeOH/ether to give **15a** (43 mg, 0.073 mmol, 61%) as a pale yellow solid, mp ca. 155°C (dec). R_f: 0.63 in MeOH/NEt_3 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 11.04, br s, ArN*H*; 11.00*, br s, ArN*H*; 8.46, br s, NH-11; 8.43, br d, *J*=7.5 Hz, NH-11; 8.38, br d, *J*=6.0 Hz, N*H*Ac; 8.31*, br d, *J*=8.0 Hz, NH-8; 8.00, br s, 2H, NH_2; 7.70, br d, *J*=5.0 Hz, NH-8; 7.62, s, ArH-21; 7.59, s, ArH-20; 7.57, s, ArH-20; 7.41*, br s, N*H*Ac; 7.38–7.25, m, 2H, ArH-2 and ArH-19; 7.18–7.05, m, ArH-3* and ArH-18; 7.05–6.96, m, ArH-3; 4.76*, br s, NCH-6; 4.55, br s, NCH-12; 4.48*, br s, NCH-9; 4.35, br s, NCH-9; 4.29, br s, NCH-6; 3.63, s, OCH_3; 3.20–2.90, m, 2H, $ArCH_2$-5; 3.00–2.85, m, $ArCH_2(CH_2)_3$; 2.78–2.63, m, $ArCH_2(CH_2)_3$; 2.75–2.55, m, 2H, $NCH_2(CH_2)_3$; 2.05–1.95, m, 2H, $ArCH_2CH_2(CH_2)_2$; 1.91*, s, $COCH_3$; 1.88, s, $COCH_3$; 1.85–1.63, m, 2H, $Ar(CH_2)_3CH_2$; 1.80–1.42, m, 2H, $N(CH_2)_3CH_2$; 1.66–1.40, m, 2H, $NCH_2CH_2(CH_2)_2$; 1.50–1.26, m, 2H, $Ar(CH_2)_2$-CH_2CH_2; 1.30–1.10, m, 2H, $N(CH_2)_2CH_2CH_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.8, CO-10; 172.3, $COOCH_3$; 169.7, CO-7; 169.0, $COCH_3$ and CO-7*; 168.7, $COCH_3$; 138.7, ArC-1a; 138.1, ArC-19a; 130.0, ArC-17; 128.5*, ArC-17; 126.9, ArCH-3 and ArCH-18; 126.3*, ArC-4; 126.1, ArC-4; 122.2, ArC-20a and ArC-20b; 119.9, ArCH-21; 119.6, ArCH-21; 117.2, ArCH-20; 117.0, ArCH-20; 110.7, ArCH-19; 110.2, ArCH-2; 57.2, NCH-6; 53.0*, NCH-6; 52.0, OCH_3; 51.1, NCH-12 and NCH-9*; 50.6, NCH-9; 38.4, $NCH_2(CH_2)_3$ and $ArCH_2$-5, 37.4, $ArCH_2$-5; 33.0, $N(CH_2)_3CH_2$; 32.7, $ArCH_2(CH_2)_3$; 30.5, $Ar(CH_2)_3$-CH_2; 26.6, $ArCH_2CH_2(CH_2)_2$; 26.5, $NCH_2CH_2(CH_2)_2$; 26.2, $NCH_2CH_2(CH_2)_2$; 23.2, $Ar(CH_2)_2CH_2CH_2$; 22.9, $Ar(CH_2)_2CH_2CH_2$; 22.6, $COCH_3$; 21.6, $N(CH_2)_2CH_2CH_2$; 21.3, $N(CH_2)_2CH_2CH_2$. Mass spectrum (ES^+) *m/z* 550 (70%) [MH^+]. HRMS (ES^+) calcd for $C_{30}H_{39}N_5O_5$+H: 550.3029; found: 550.3019.

4.2. Characterization data for compounds in Table 1, not reported above

4.2.1. (6*R*/*S*,9*R*,12*S*,14*E*/*Z*)-6-Acetamido-9-(4-aminobutyl)-8,11-diaza-12-methoxycarbonyl-7,10-dioxo-[12](4,17)carbazolo-14-phene hydrochloride (12b). A cream solid, mp ca. 198°C (dec). R_f: 0.64 in MeOH/NEt_3 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 11.19*, br s, ArN*H*; 11.17*, br s, ArN*H*; 11.00, br s, ArN*H*; 10.97, br s, ArN*H*; 8.84*, br d, *J*=5.5 Hz, N*H*Ac; 8.78*, br d, *J*=5.0 Hz, N*H*Ac; 8.71, br d, *J*=3.5 Hz, NH-11; 8.63, br d, *J*=4.0 Hz, NH-11; 8.43, br d, *J*=8.5 Hz, NH-8; 8.40, br d, *J*=8.5 Hz, N*H*Ac; 8.38–8.25, m, N*H*Ac; 8.16*, br s, N*H*Ac; 8.12*, br d,

J=8.0 Hz, N*H*Ac; 8.03, s, ArH-20; 8.02, s, ArH-20; 7.98, br s, NH_2 and ArH-21*; 7.94*, br s, NH_2 and ArH-21; 7.89, br d, J=6.5 Hz, NH-8; 7.88*, s, ArH-20; 7.88–7.82, m, N*H*Ac; 7.86*, s, ArH-21; 7.84*, s, ArH-20; 7.79*, s, ArH-20; 7.75, s, ArH-21; 7.72, s, ArH-21; 7.57, br d, J=8.5 Hz, NH-8; 7.43–7.31, m, ArH-2; 7.31–7.21, m, ArH-3* and ArH-19; 7.20–7.10, m, ArH-18; 7.14, br d, J=8.5 Hz, N*H*Ac; 7.02*, d, J=8.0 Hz, ArH-18; 6.96, d, J=8.0 Hz, ArH-3; 5.88–5.74, m, $ArCH_2CH$═CH; 5.74–5.57, m, $ArCH_2CH$═CH* and $CHCH_2CH$═CH; 5.57–5.35*, m, $CHCH_2CH$═CH; 4.79, br s, NCH-6; 4.65, dt, J=8.0, 6.0 Hz, NCH-9; 4.55, br s, NCH-6; 4.47, dt, J=7.5, 7.0 Hz, NCH-9; 4.47–4.40*, m, NCH-9; 4.40–4.25, m, NCH-6* and NCH-12; 4.20, m, NCH-6 and NCH-12*; 4.15–4.01*, m, NCH-6 and NCH-12; 3.59, s, OCH_3; 3.57, s, OCH_3; 3.47*, OCH_3; 3.55–3.34, m, $ArCH_2CH$═CH; 3.28–2.83, m, $ArCH_2$-5; 3.26–3.13*, m, $ArCH_2CH$═CH; 2.80–2.52, m, $NCH_2(CH_2)_3$; 2.72–2.60, m, $CHCH_2CH$═CH; 2.55–2.45, m, $CHCH_2CH$═CH; 2.44–2.29*, m, $CHCH_2CH$═CH; 1.90, s, $COCH_3$; 1.88, s, $COCH_3$; 1.78*, s, $COCH_3$; 1.77*, s, $COCH_3$; 1.64–1.28, m, $N(CH_2)_3CH_2$; 1.60–1.28, m, $N(CH_2)_3CH_2$; 1.60–1.20, m, $NCH_2CH_2(CH_2)_2$; 1.38–1.06, m, $N(CH_2)_2CH_2CH_2$; 0.90*, m, $N(CH_2)_2CH_2CH_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.0, CO-10; 171.8, CO-7; 171.8, CO-10; 171.7, $COOCH_3$; 171.6, CO-10; 171.2, $COOCH_3$; 171.0*, $COOCH_3$; 170.4*, $COOCH_3$; 170.1*, $COOCH_3$; 169.8*, CO-7; 169.7*, CO-7; 169.5, CO-7; 169.2*, $COCH_3$; 168.9*, CO-7; 168–7, $COCH_3$; 139.0, ArC-1a; 139.0*, ArC-1a; 138.9, ArC-1a; 138.6, ArC-19a; 138.5*, ArC-19a; 138.4, ArC-19a; 132.2*, $ArCH_2CH$═CH; 132.0, $ArCH_2CH$═CH; 128.9, ArC-17; 128.8, ArC-17; 128.1*, $CHCH_2CH$═CH; 127.8, $CHCH_2CH$═CH; 127.4, ArCH-3; 127.3, ArCH-3; 127.2*, ArCH-3; 127.0*, ArCH-18; 126.8, ArC-4; 126.7*, ArCH-18; 126.3, ArC-4 and ArCH-18; 126.1, ArCH-18; 123.1*, ArC-20a; 122.8, ArC-20a; 122.7*, ArC-20a; 122.7, ArC-20b; 122.5*, ArC-20b; 122.3*, ArC-20b; 120.4*, ArCH-21; 120.3, ArCH-21; 120.1*, ArCH-21; 119.9*, ArCH-21; 119.6, ArCH-20; 119.4*, ArCH-20; 119.3*, ArCH-20; 119.2*, ArCH-20; 119.1*, ArCH-20; 110.8*, ArCH-2; 110.6*, ArCH-2; 110.4, ArCH-2; 110.2, ArCH-19; 110.1, ArCH-19; 57.6, NCH-6; 56.3*, NCH-6; 55.6, NCH-6; 53.7, NCH-12; 53.6, NCH-12; 53.4*, NCH-6; 53.1, NCH-6; 52.8*, NCH-9; 52.4*, NCH-12; 52.3, NCH-12; 52.1*, NCH-9; 51.9, OCH_3; 51.8, OCH_3; 51.6, NCH-9; 51.5*, OCH_3; 51.4*, OCH_3; 51.2, NCH-9; 39.0, $ArCH_2$-5; 38.6, $NCH_2(CH_2)_3$; 38.5, $NCH_2(CH_2)_3$ and $ArCH_2$-CH═CH; 38.3, $ArCH_2$-5; 38.0, $ArCH_2$-5; 36.8, $ArCH_2$-CH═CH; 36.8, $ArCH_2CH$═CH; 34.1, $CHCH_2CH$═CH; 33.5, $N(CH_2)_3CH_2$; 33.1, $N(CH_2)_3CH_2$; 32.0, $CHCH_2$-CH═CH; 31.8, $CHCH_2CH$═CH; 31.1, $N(CH_2)_3CH_2$; 26.9, $NCH_2CH_2(CH_2)_2$; 26.6*, $NCH_2CH_2(CH_2)_2$; 26.5*, $NCH_2CH_2(CH_2)_2$; 26.3, $NCH_2CH_2(CH_2)_2$; 22.8*, $COCH_3$; 22.7, $COCH_3$; 22.5*, $COCH_3$; 22.4, $COCH_3$; 22.0*, $N(CH_2)_2CH_2CH_2$; 21.9, $N(CH_2)_2CH_2CH_2$; 21.6, $N(CH_2)_2$-CH_2CH_2; 21.5*, $N(CH_2)_2CH_2CH_2$. Mass spectrum (ES^+) m/z 548 (100%) [MH^+]. HRMS (ES^+) calcd for $C_{30}H_{37}N_5O_5$+H: 548.2873; found: 548.2880.

4.2.2. (6*R*/*S*,9*S*,12*S*,14*E*/*Z*)-6-Acetamido-8,11-diaza-9-[3-(guanidino)propyl]-12-methoxycarbonyl-7,10-dioxo-[12](4,17)carbazolo-14-phene hydrochloride (12c). Pale brown solid, mp 222–224°C. ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 11.02, br s, ArN*H*; 10.99*, br s, ArN*H*; 8.88, br s, NH-11; 8.71, br d, J=6.5 Hz, NH-11; 8.51*, br d, J=8.5 Hz, NH-8; 8.38, br s, N*H*Ac; 8.25, br s, NH-11; 7.94, br s, N*H*Ac; 7.80–7.60, m, $NHCH_2$; 7.72, br s, NH-8; 7.72–7.63*, m, NH-8; 7.59, s, ArH-20; 7.53*, s, ArH-20 and ArH-21; 7.43, s, ArH-21; 7.40–7.25, m, 2H, ArH-2 and ArH-19; 7.30–7.18*, m, N*H*Ac; 7.27–7.10, m, ArH-3 and ArH-18; 7.00–6.80, m, NH(C═N*H*)NH_2; 6.97, d, J=6.5 Hz, ArH-3; 5.92–5.70, m, 1H, $ArCH_2CH$═CH; 5.80–5.61, m, $CHCH_2$-CH═CH; 5.56–5.42, m, $CHCH_2CH$═CH; 4.82*, br s, NCH-6; 4.67*, br s, NCH-9; 4.58*, br s, NCH-6; 4.52, br s, NCH-9; 4.43, br s, NCH-12; 4.35*, br s, NCH-6; 4.20, br s, NCH-6 and NCH-12; 3.65*, s, OCH_3; 3.56, s, OCH_3; 3.52–3.35, m, 2H, $ArCH_2CH$═CH; 3.22–2.84, m, $ArCH_2$-5; 3.15–2.85, m, 2H, $NCH_2(CH_2)_2$; 2.64–2.55, m, $CHCH_2$-CH═CH; 2.44–2.28, m, $CHCH_2CH$═CH; 1.89*, s, $COCH_3$; 1.87–1.50, m, 2H, $N(CH_2)_2CH_2$; 1.73, s, $COCH_3$; 1.53–1.20, m, 2H, $NCH_2CH_2CH_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.5, CO-10; 172.5*, 132.2, $ArCH_2CH$═CH; 131.8, $ArCH_2CH$═CH; 130.4*, ArC-17; 129.6, $ArCH_2CH$═CH and ArC-17; 128.5, $CHCH_2$-CH═CH; 128.3, $CHCH_2CH$═CH; 127.6*, ArCH-3; 127.5*, ArC-4; 127.1, ArCH-3; 126.4*, ArCH-18; 126.2, ArCH-18 and ArC-4; 122.7*, ArC-20a; 122.5, ArC-20a; 122.4*, ArC-20b; 122.3, ArC-20b; 120.0*, ArCH-21; 119.5, ArCH-21; 119.4, ArCH-21; 118.6*, ArCH-20; 118.4, ArCH-20; 110.8*, ArCH-19; 110.7, ArCH-2; 110.5, ArCH-19; 110.3*, ArCH-2; 57.6, NCH-6; 56.1, NCH-6; 55.3*, NCH-6; 54.4, NCH-12; 54.0, NCH-12; 53.3*, NCH-6; 52.4, NCH-12; 52.1, OCH_3; 52.0, NCH-6; 51.9*, OCH_3; 50.8*, NCH-9; 50.4, NCH-9; 40.4*, $NCH_2(CH)_2$; 40.3, $NCH_2(CH_2)_2$; 38.4, $ArCH_2$-CH═CH; 37.9, $ArCH_2$-5; 37.7, $ArCH_2$-5; 37.2, $ArCH_2$-CH═CH; 37.0, $ArCH_2CH$═CH; 34.0, $CHCH_2CH$═CH; 32.9, $CHCH_2CH$═CH; 32.1, $N(CH_2)_2CH_2$; 30.9, $N(CH_2)_2CH_2$; 24.8, $NCH_2CH_2CH_2$; 24.1, $NCH_2CH_2CH_2$; 22.7, $COCH_3$; 22.7*, $COCH_3$; 22.5, $COCH_3$. Mass spectrum (ES^+) m/z 576 (100%) [MH^+]. HRMS (ES^+) calcd for $C_{30}H_{37}N_7O_5$+H: 576.2934; found: 576.2902.

4.2.3. (6*R*/*S*,9*R*,12*S*,14*E*/*Z*)-6-Acetamido-8,11-diaza-9-(3-guanidinopropyl)-12-methoxycarbonyl-7,10-dioxo-[12](4,17)carbazolo-14-phene hydrochloride (12d). A cream solid, mp ca. 215°C (dec). ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 11.02, br s, ArN*H*; 10.95*, br s, ArN*H*; 10.93*, br s, ArN*H*; 8.81, br s, N*H*Ac; 8.71, br s, NH-11; 8.64, br s, NH-11; 8.54*, br d, J=8.5 Hz, NH-8; 8.48–8.32, m, N*H*Ac; 8.41, br d, J=7.5 Hz, NH-8; 8.40–8.10, m, N*H*Ac; 8.10–8.00*, m, N*H*Ac; 8.02*, s, ArH-20; 7.96, s, ArH-21; 7.93, s, ArH-21; 7.90*, s, ArH-20; 7.89–7.80, m, NH-8; 7.88*, s, ArH-20; 7.87–7.80*, m, N*H*Ac; 7.82*, s, ArH-21; 7.76, s, ArH-20; 7.70*, s, ArH-21; 7.68–7.40, m, $NHCH_2$; 7.61, br d, J=7.5 Hz, NH-8; 7.41–7.25, m, 2H, ArH-2 and ArH-19; 7.30–7.19, m, ArH-3; 7.22–7.10, m, ArH-18; 7.18–7.07*, m, N*H*Ac; 7.03*, br d, J=7.0 Hz, ArH-3; 6.96*, br d, J=7.0 Hz, ArH-3; 6.91, v br s, NH(C═N*H*)NH_2; 5.89–5.65, m, $ArCH_2CH$═CH; 5.70–5.32, m, $CHCH_2CH$═CH; 4.82*, br s, NCH-6; 4.71*, br d, J=7.0 Hz, NCH-9; 4.65–4.48, m, NCH-6; 4.57–4.43, m, NCH-9; 4.43–4.32*, m, NCH-6; 4.36–4.17, m, NCH-12; 4.22, br s, NCH-6; 4.07*, br s, NCH-6; 3.77, s, OCH_3; 3.75–3.67, m, $ArCH_2CH$═CH; 3.58*, s, OCH_3; 3.55–3.42*, m, $ArCH_2CH$═CH; 3.54–3.35, m, $ArCH_2CH$═CH; 3.20–2.79, m, 2H, $ArCH_2$-5; 3.15–2.78, m, 2H, $NCH_2(CH_2)_2$; 2.75–2.64*, m, $CHCH_2$-CH═CH; 2.53–2.44*, m, $CHCH_2CH$═CH; 2.48–2.26, m,

CHCH_2CH=CH; 1.91*, s, $COCH_3$; 1.88*, s, $COCH_3$; 1.80–1.36, m, 2H, $N(CH_2)_2CH_2$; 1.74, s, $COCH_3$; 1.53–1.10, m, 2H, $NCH_2CH_2CH_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 171.9, CO-10; 171.8, *C*OOCH$_3$; 171.7, *C*OOCH$_3$; 171.5, CO-10; 171.1*, *C*OOCH$_3$; 170.3*, CO-7; 169.8, *C*OCH$_3$; 169.6, CO-7; 168.8, *C*OCH$_3$; 156.7, C=N; 138.9, ArC-1a; 138.6, ArC-19a; 133.5, ArCH$_2$*C*H=CH; 132.3, ArCH$_2$-*C*H=CH, 132.1, ArCH$_2$*C*H=CH; 130.7, ArCH$_2$*C*H=CH; 130.4*, ArC-4; 130.0, ArC-4; 128.8, ArC-17; 128.1, CHCH$_2$*C*H=CH; 127.8*, ArCH-3; 127.3*, ArCH-3; 126.9, ArCH-3 and CHCH$_2$*C*H=CH; 126.2, ArCH-18; 125.3, CHCH$_2$*C*H=CH; 124.3, CHCH$_2$*C*H=CH; 122.5*, ArC-20a and ArC-20b; 122.2, ArC-20a and ArC-20b; 121.0*, ArCH-21; 120.3, ArCH-21; 119.8*, ArCH-20; 119.5*, ArCH-20; 119.2, ArCH-20; 110.8*, ArCH-2; 110.7, ArCH-2; 110.5, ArCH-19; 110.3*, ArCH-19; 55.5, NCH-6; 53.7*, NCH-6; 53.1, NCH-6; 52.3, NCH-12; 52.0, NCH-12 and OCH_3; 51.8, NCH-6; 51.6*, OCH_3; 51.4*, OCH_3; 51.3*, NCH-9; 50.9, NCH-9; 40.3, N*C*H$_2$(CH$_2$)$_2$; 40.2, N*C*H$_2$(CH$_2$)$_2$; 39.2, ArCH$_2$-5; 38.5, Ar*C*H$_2$CH=CH; 38.1, ArCH$_2$-5; 37.5, ArCH$_2$-5; 36.7, Ar*C*H$_2$CH=CH; 34.1, CH*C*H$_2$CH=CH; 33.0*, Ar*C*H$_2$CH=CH; 31.7*, CH*C*H$_2$-CH=CH; 31.1, N(CH$_2$)$_2$*C*H$_2$; 30.9, N(CH$_2$)$_2$*C*H$_2$; 29.4, N(CH$_2$)$_2$*C*H$_2$; 28.9, N(CH$_2$)$_2$*C*H$_2$; 24.9, NCH$_2$*C*H$_2$CH$_2$; 24.8, NCH$_2$*C*H$_2$CH$_2$; 22.8*, $COCH_3$; 22.7*, CO*C*H$_3$; 22.4, CO*C*H$_3$. Mass spectrum (ES$^+$) *m*/*z* 576 (63%) [MH$^+$]. HRMS (ES$^+$) calcd for $C_{30}H_{37}N_7O_5$+H: 576.2934; found: 576.2906.

4.2.4. (6*R*/*S*,9*R*,12*S*)-6-Acetamido-9-(4-aminobutyl)-8,11-diaza-12-methoxycarbonyl-7,10-dioxo-[12](4,17)-carbazolophane hydrochloride (15b). A pale orange solid, mp ca. 220°C (dec). R_f: 0.59 in MeOH/NEt$_3$ 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 11.14*, br s, ArN*H*; 11.10*, br s, ArN*H*; 10.99, br s, ArN*H*; 10.96, br s, ArN*H*; 8.56, br d, *J*=3.5 Hz, NH-11; 8.47, br s, NH-11; 8.32*, br d, *J*=8.0 Hz, NH-8; 8.27, br s, N*H*Ac; 8.21*, br d, *J*=9.0 Hz, N*H*Ac; 8.10–8.00, m, NH-8; 7.98–7.90*, m, N*H*Ac; 7.93, br s, NH_2 and ArH-21; 7.84, s, ArH-21; 7.81, s, ArH-20; 7.75–7.68, m, NH-8; 7.70, s, ArH-20; 7.40–7.22, m, 2H, ArH-2 and ArH-19; 7.22–7.04, m, 2H, ArH-3 and ArH-18; 4.93*, br s, NCH-6; 4.51*, br s, NCH-6; 4.36, br s, NCH-6; 4.29*, br s, NCH-9; 4.19, br s, NCH-9; 4.07, br s, NCH-9; 3.90, br s, NCH-12; 3.86, br s, NCH-12; 3.61, br s, OCH_3; 3.55*, s, OCH_3; 3.28–2.79, m, 2H, ArCH$_2$-5; 2.80–2.48, m, 2H, ArC*H*$_2$(CH$_2$)$_3$; 2.70–2.52, m, 2H, NC*H*$_2$(CH$_2$)$_3$; 2.38–2.20, m, 2H, Ar(CH$_2$)$_3$C*H*$_2$; 1.93, s, $COCH_3$; 1.88, s, $COCH_3$; 1.80–1.65, m, 2H, NCH$_2$C*H*$_2$(CH$_2$)$_2$; 1.80–1.28, m, 2H, N(CH$_2$)$_3$C*H*$_2$; 1.78–1.50, m, 2H, ArCH$_2$C*H*$_2$(CH$_2$)$_2$; 1.76*, s, $COCH_3$; 1.70*, s, $COCH_3$; 1.40–1.15, m, Ar(CH$_2$)$_2$-C*H*$_2$CH$_2$; 1.10–0.78, m, 2H, N(CH$_2$)$_2$C*H*$_2$CH$_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.5*, *C*OOCH$_3$; 172.4*, *C*OOCH$_3$; 172.2, *C*OOCH$_3$; 171.8, CO-10; 171.7, CO-10; 171.6, *C*OOCH$_3$; 169.7, CO-7 and *C*OCH$_3^*$; 169.5, CO-7; 169.1, *C*OCH$_3$; 169.0, *C*OCH$_3$; 138.8, ArC-1a; 138.5*, ArC-1a; 138.4*, ArC-19a; 138.2, ArC-19a; 138.1, ArC-19a; 132.1*, ArC-17; 130.4, ArC-17; 127.2*, ArC-4; 126.8, ArCH-3; 126.6, ArCH-18; 126.6*, ArCH-3; 126.4*, ArCH-18; 126.1, ArC-4; 122.4*, ArC-20a and ArC-20b; 122.3, ArC-20a and ArC-20b; 120.4, ArCH-21; 119.1, ArCH-20; 118.9, ArCH-20; 118.7*, ArCH-21; 110.8, ArCH-19; 110.6*, ArCH-2; 110.5, ArCH-2; 57.0, NCH-6; 55.9*, NCH-6; 55.7*, NCH-6; 54.0, NCH-12; 53.9, NCH-12; 52.2*, NCH-6; 52.1*, NCH-9; 51.9, OCH_3; 51.8*, OCH_3; 50.9, NCH-9; 38.6, N*C*H$_2$(CH$_2$)$_3$; 38.5*, N*C*H$_2$(CH$_2$)$_3$; 38.3, ArCH$_2$-5; 36.0*, ArCH$_2$-5; 35.3*, Ar*C*H$_2$(CH$_2$)$_3$; 35.2*, Ar*C*H$_2$(CH$_2$)$_3$; 33.2, N(CH$_2$)$_3$*C*H$_2$; 32.9, N(CH$_2$)$_3$*C*H$_2$; 32.0, Ar*C*H$_2$(CH$_2$)$_3$; 31.9, Ar*C*H$_2$(CH$_2$)$_3$; 29.3, Ar(CH$_2$)$_3$-*C*H$_2$; 29.1, ArCH$_2$*C*H$_2$(CH$_2$)$_2$; 26.6*, Ar(CH$_2$)$_2$*C*H$_2$CH$_2$; 26.4, Ar(CH$_2$)$_2$*C*H$_2$CH$_2$; 23.2*, NCH$_2$*C*H$_2$(CH$_2$)$_2$; 22.8, CO*C*H$_3$; 22.7, CO*C*H$_3$; 22.6, NCH$_2$*C*H$_2$(CH$_2$)$_2$; 22.4*, CO*C*H$_3$; 22.1*, N(CH$_2$)$_2$*C*H$_2$CH$_2$; 21.3, N(CH$_2$)$_2$*C*H$_2$CH$_2$. Mass spectrum (ES$^+$) *m*/*z* 550 (100%) [MH$^+$]. HRMS (ES$^+$) calcd for $C_{30}H_{39}N_5O_5$+H: 550.3029; found: 550.3032.

4.2.5. (6*R*/*S*,9*S*,12*S*)-6-Acetamido-8,11-diaza-9-[3-(guanidino)propyl]-12-methoxy-carbonyl-7,10-dioxo-[12](4,17)carbazolophane hydrochloride (15c). A cream solid, mp 220–222°C. ^{13}C NMR [500 MHz, $(CD_3)_2SO$] δ 11.00, br s, ArN*H*; 10.97*, br s, ArN*H*; 8.46, br s, NH-8* and NH-11; 8.38, br d, *J*=8.0 Hz, NH-11; 8.35–8.20, m, N*H*Ac; 7.83–7.14, m, NH-8; 7.80–7.60, m, N*H*CH$_2$; 7.61*, s, ArH-21; 7.58, s, ArH-21 and ArH-20; 7.53–7.40*, m, N*H*Ac; 7.40–7.25, m, 2H, ArH-2 and ArH-19; 7.28–7.08, m, ArH-3 and ArH-18; 7.09–6.98*, m, ArH-3; 7.00–6.70, m, NH(C=N*H*)N*H*$_2$; 4.79*, br s, NCH-6; 4.54, br d, *J*=5.0 Hz, NCH-6*, NCH-9* and NCH-12; 4.38, br s, NCH-9; 4.32, br s, NCH-6; 3.64, s, OCH_3; 3.56*, s, OCH_3; 3.21–2.82, m, 2H, ArCH$_2$-5; 3.19–2.85, m, 2H, NC*H*$_2$(CH$_2$)$_2$; 2.99–2.87, m, ArC*H*$_2$(CH$_2$)$_3$; 2.78–2.68, m, ArC*H*$_2$(CH$_2$)$_3$; 2.03–1.88, m, 2H, ArCH$_2$C*H*$_2$(CH$_2$)$_2$; 1.94*, s, $COCH_3$; 1.89, s, $COCH_3$; 1.82–1.65, m, 2H, Ar(CH$_2$)$_3$C*H*$_2$; 1.82–1.35, m, 2H, N(CH$_2$)$_2$C*H*$_2$; 1.52–1.22, m, 2H, NCH$_2$C*H*$_2$CH$_2$; 1.37–1.21, m, Ar(CH$_2$)$_2$C*H*$_2$CH$_2$. ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 172.9, CO-10; 172.3*, CO-10; 172.1*, *C*OOCH$_3$; 171.6, *C*OOCH$_3$; 170.0, CO-7; 169.5*, CO-7; 169.2, *C*OCH$_3$; 169.0*, *C*OCH$_3$; 156.8, C=N; 138.9, ArC-1a and ArC-19a; 132.0*, ArC-17; 130.2, ArC-17; 127.2, ArCH-18; 126.9, ArCH-3; 126.5*, ArC-4; 126.3, ArC-4; 122.4, ArC-20a; 122.3, ArC-20b; 119.9, ArCH-21; 119.6*, ArCH-21; 117.3, ArCH-20; 117.1*, ArCH-20; 110.9, ArCH-19; 110.8, ArCH-2; 110.4*, ArCH-2 and ArCH-19; 57.3, NCH-6, 55.2*, NCH-6; 53.1*, NCH-6; 52.1, OCH_3; 51.9*, OCH_3; 51.4, NCH-12; 51.3, NCH-12; 50.9*, NCH-9; 50.4, NCH-9; 40.4, N*C*H$_2$(CH$_2$)$_2$; 40.2, N*C*H$_2$(CH$_2$)$_2$; 38.5, ArCH$_2$-5; 37.5, ArCH$_2$-5; 33.1, Ar*C*H$_2$(CH$_2$)$_3$; 32.8, Ar*C*H$_2$(CH$_2$)$_3$; 31.2, N(CH$_2$)$_2$*C*H$_2$; 31.0, N(CH$_2$)$_2$*C*H$_2$; 30.5, Ar(CH$_2$)$_3$*C*H$_2$; 26.7, ArCH$_2$*C*H$_2$(CH$_2$)$_2$; 24.8, NCH$_2$-*C*H$_2$CH$_2$; 24.4, NCH$_2$*C*H$_2$CH$_2$; 23.3, Ar(CH$_2$)$_2$*C*H$_2$CH$_2$; 23.1, Ar(CH$_2$)$_2$*C*H$_2$CH$_2$; 22.8, CO*C*H$_3$; 22.4, CO*C*H$_3$. Mass spectrum (ES$^+$) *m*/*z* 578 (100%) [MH$^+$]. HRMS (ES$^+$) calcd for $C_{30}H_{39}N_7O_5$+H: 578.3091; found: 578.3088.

4.2.6. (6*R*/*S*,9*R*,12*S*)-6-Acetamido-8,11-diaza-9-(3-guanidinopropyl)-12-methoxycarbonyl-7,10-dioxo-[12](4,17)-carbazolophane hydrochloride (15d). A cream solid, mp ca. 194°C (dec). NMR analysis was not possible due to paramagnetic impurities. Mass spectrum (ES$^+$) *m*/*z* 578 (29%) [MH$^+$]. HRMS (ES$^+$) calcd for $C_{30}H_{39}N_7O_5$+H: 578.3091; found: 578.3096.

4.2.7. Methyl (2*S*,5*R*,8*R*/*S*)-8-Acetamido-5-(4-aminobutyl)-3,6-diaza-4,7-dioxo-2-propyl-9-(6-propyl-9*H*-carbazol-3-yl)nonanoate hydrochloride (16a). A cream solid,

mp 160–162°C. R_f: 0.59 in MeOH/NEt_3 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$, isomer ratio 69:31] δ 11.16, br s, 0.7H, ArN*H*; 11.07*, br s, 0.3H, ArN*H*; 8.36, br d, *J*=6.5 Hz, 0.7H, N*H*Ac; 8.32, br d, *J*=8.0 Hz, 0.7H, NH-6; 8.29*, br d, *J*=7.5 Hz, 0.3H, NH-3; 8.21*, br d, *J*=8.0 Hz, 0.3H, N*H*Ac; 8.21*, br d, *J*=8.5 Hz, 0.3H, NH-6; 8.06*, br s, 0.6H, NH_2; 8.02, br d, *J*=8.0 Hz, 0.7H, NH-3; 7.99, br s, 1.4H, NH_2; 7.96*, s, 0.3H, ArH-4; 7.93, s, 0.7H, ArH-4; 7.81, s, 0.7H, ArH-5; 7.79*, s, 0.3H, ArH-5; 7.37*, d, *J*=8.0 Hz, 0.3H, ArH-8; 7.35, d, *J*=8.5 Hz, 1.4H, ArH-1 and ArH-8; 7.32*, d, *J*=8.5 Hz, 0.3H, ArH-1; 7.27*, d, *J*=8.5 Hz, 0.3H, ArH-2; 7.25, d, *J*=8.5 Hz, 0.7H, ArH-2; 7.17, d, *J*=8.0 Hz, 1H, ArCH-7; 4.57*, m, 0.3H, NCH-8; 4.53, dt, *J*=7.0, 7.5 Hz, 0.7H, NCH-8; 4.34*, dt, *J*=5.5, 8.0 Hz, 0.3H, NCH-5; 4.22, m, 1H, NCH-2; 4.09, m, 0.7H, NCH-5; 3.60, s, 3H, OCH_3; 3.18*, dd, *J*=13.5, 4.0 Hz, 0.3H, ArC*H*H-9; 3.05, dd, *J*=13.2, 7.5 Hz, 0.7H, ArC*H*H-9; 2.96, dd, *J*=13.2, 8.5 Hz, 0.7H, ArCH*H*-9; 2.89*, dd, *J*=13.2, 10.5 Hz, 0.3H, ArCH*H*-9; 2.73*, br d, *J*=5.5 Hz, 0.6H, $NCH_2(CH_2)_3$; 2.68, t, *J*=7.5 Hz, 2H, $ArCH_2CH_2CH_3$; 2.45, br s, 1.4H, $NCH_2(CH_2)_3$; 1.79, s, 2.1H, $COCH_3$; 1.76*, s, 0.9H, $COCH_3$; 1.71–1.51, m, 2.6H, $CHCH_2CH_2CH_3$ and $N(CH_2)_3CH_2^*$; 1.69–1.58, m, 2H, $ArCH_2CH_2CH_3$; 1.61–1.52*, m, 0.6H, $NCH_2CH_2(CH_2)_2$; 1.61–1.48, m, 0.7H, $N(CH_2)_3CH_2$; 1.41–1.26, m, 2.7H, $N(CH_2)_3CH_2$, $NCH_2CH_2(CH_2)_2$ and $N(CH_2)_2CH_2CH_2^*$; 1.32–1.18, m, 2H, $CHCH_2CH_2CH_3$; 0.91, t, *J*=7.0 Hz, 3H, $Ar(CH_2)_2CH_3$; 0.90–0.82, m, 1.4H, $N(CH_2)_2CH_2CH_2$; 0.82, t, *J*=7.0 Hz, 2.1H, $CH(CH_2)_2CH_3$; 0.81*, t, *J*=7.0 Hz, 0.9H, $CH(CH_2)_2CH_3$. ^{13}C NMR [75 MHz, $(CD_3)_2SO$] δ 172.3, *C*$OOCH_3$; 171.6, CO-7; 171.5*, CO-4; 171.4, CO-4; 171.3*, CO-7; 169.6, *C*OCH_3; 169.2*, *C*OCH_3; 138.7, ArC-9a; 138.3, ArC-8a; 131.8, ArC-6; 127.6*, ArC-3; 126.9, ArC-3; 126.6, ArCH-2; 126.0, ArCH-7; 122.2, ArC-4b; 122.1, ArC-4a; 120.3, ArCH-4; 120.2*, ArCH-4; 119.0, ArCH-5; 110.6, ArCH-8; 110.5*, ArCH-8; 110.3, ArCH-1; 110.2*, ArCH-1; 55.7, NCH-8; 55.1*, NCH-8; 52.4, NCH-5; 51.8, OCH_3; 51.5, NCH-2; 38.5*, $NCH_2(CH_2)_3$; 38.3, $NCH_2(CH_2)_3$; 37.5, $ArCH_2$-9 and $ArCH_2CH_2CH_3$; 32.9*, $CHCH_2CH_2CH_3$; 32.7, $CHCH_2CH_2CH_3$; 31.7*, $N(CH_2)_3CH_2$; 30.9, $N(CH_2)_3CH_2$; 26.5*, $NCH_2CH_2(CH_2)_2$; 26.4, $NCH_2CH_2(CH_2)_2$; 24.9, $ArCH_2CH_2CH_3$; 22.6*, $COCH_3$; 22.4, $COCH_3$; 22.2*, $N(CH_2)_2CH_2CH_2$; 22.1, $N(CH_2)_2CH_2CH_2$; 18.6, $CHCH_2CH_2CH_3$; 13.8, $Ar(CH_2)_2CH_3$; 13.5, $CH(CH_2)_2CH_3$. Mass spectrum (ES^+) *m/z* 580 (100%) [MH^+]. HRMS (ES^+) calcd for $C_{32}H_{45}N_5O_5$+H: 580.3512; found: 580.3499.

4.2.8. Methyl (2*S*,5*R*,8*R*/*S*)-8-Acetamido-3,6-diaza-5-(3-guanidinopropyl)-4,7-dioxo-2-propyl-9-(6-propyl-9*H*-carbazol-3-yl)nonanoate hydrochloride (16b). A cream solid, mp 210°C (dec). R_f: 0.54 in MeOH/NEt_3 20:1 (RP). ^{13}C NMR [500 MHz, $(CD_3)_2SO$, isomer ratio 69:31] δ 11.16*, br s, 0.3H, ArN*H*; 10.99, br s, 0.7H, ArN*H*; 8.33, br d, *J*=8.0 Hz, 0.7H, NH-6; 8.30, br d, *J*=6.5 Hz, 0.7H N*H*Ac; 8.25*, br d, *J*=7.5 Hz, 0.3H, NH-3; 8.21–8.11*, m, 0.6H, NH-6 and N*H*Ac; 8.07, br d, *J*=7.5 Hz, 0.7H, NH-3; 7.94, s, 1H, ArCH-4; 7.81, s, 1H, ArCH-5; 7.62–7.53*, m, 0.3H, N*H*CH_2; 7.45, br s, 0.7 N*H*CH_2; 7.35, m, 2H, ArH-1 and ArH-8; 7.26, d, *J*=8.5 Hz, 1H, ArH-2; 7.17, d, *J*=8.0 Hz, 1H, ArH-7; 6.85, v br s, 3H, NH(C=N*H*)NH_2; 4.56, m, 1H, NCH-8; 4.37*, dt, *J*=6.0, 7.5 Hz, 0.3H, NCH-5; 4.30–4.16, m, 1.7H, NCH-2 and NCH-5; 3.61, s, 3H, OCH_3; 3.20–3.11*, m, 0.3H, ArC*H*H-9; 3.15–3.05*, m, 0.6H, $NCH_2(CH_2)_2$; 3.11–3.03, m, 0.7H, ArC*H*H-9; 2.98–2.88, m, 0.7H, ArCH*H*-9; 2.93–2.83, m, 1.4H, $NCH_2(CH_2)_2$; 2.88–2.82*, m, 0.3H, ArCH*H*-9; 2.69, t, *J*=7.5 Hz, 2H, $ArCH_2CH_2CH_3$; 1.77, s, 2.1H, $COCH_3$; 1.75*, s, 0.9H, $COCH_3$; 1.68–1.54, m, 2H, $CHCH_2CH_2CH_3$; 1.67–1.58*, m, 0.6H, $C(CH_2)_2CH_2$; 1.65, m, 2H, $ArCH_2CH_2CH_3$; 1.52–1.38*, m, 0.6H, $NCH_2CH_2CH_2$; 1.48–1.36, m, 1.4H, $N(CH_2)_2CH_2$; 1.34–1.17, m, 2H, $CHCH_2CH_2CH_3$; 1.25–1.13, m, 1.4H, $NCH_2CH_2CH_3$; 0.91, t, *J*=7.0 Hz, 3H, $Ar(CH_2)_2CH_3$; 0.83, t, *J*=7.0 Hz, 3H, $CH(CH_2)_2CH_3$. ^{13}C NMR [75 MHz, $(CD_3)_2SO$] δ 172.3, *C*$OOCH_3$; 171.7, CO-7; 171.4*, CO-7; 171.2, CO-4; 169.6, *C*OCH_3; 169.3*, *C*OCH_3; 156.5, C=N; 138.7, ArC-9a; 138.3, ArC-8a; 131.8, ArC-6; 127.1, ArC-3; 126.6, ArCH-2; 126.0, ArCH-7; 122.2, ArC-4b; 122.1, ArC-4a; 120.2, ArCH-4; 120.1*, ArCH-4; 119.0, ArCH-5; 110.6, ArCH-8; 110.4, ArCH-1; 55.6, NCH-8; 55.0*, NCH-8; 52.1, NCH-5; 51.8, OCH_3; 51.6, NCH-2; 40.4*, $NCH_2(CH_2)_2$; 40.2, $NCH_2(CH_2)_2$; 37.5, $ArCH_2$-9 and $ArCH_2CH_2CH_3$; 32.9*, $CHCH_2CH_2CH_3$; 32.8, $CHCH_2CH_2CH_3$; 29.6*, $N(CH_2)_2CH_2$; 28.9, $N(CH_2)_2CH_2$; 25.0*, $NCH_2CH_2CH_3$; 24.9, $ArCH_2CH_2CH_3$; 24.8, $NCH_2CH_2CH_3$; 22.5*, $COCH_3$; 22.4, $COCH_3$; 18.6, $CHCH_2CH_2CH_3$; 13.8, $Ar(CH_2)_2CH_3$; 13.5, $CH(CH_2)_2CH_3$. Mass spectrum (ES^+) *m/z* 608 (31%) [MH^+]. HRMS (ES^+) calcd for $C_{32}H_{45}N_7O_5$+H: 608.3560; found: 608.3558.

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