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The Formation of *trans*-Fused Macrocycles from N^3,$N^{3'}$-Polymethylenebis-(hydantoins) by Ring-Closing Metathesis

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A straightforward ring transformation giving polymethylenebis(hydantoins) was extended, as these are HMBA analogues. Firstly, ethyl or allyl pyroglutamate was carbamoylated with a diisocyanate. Upon treatment with KO*t*Bu in allyl alcohol the bis(carbamoyllactam) rearranged to give the hydantoin, which was followed by the ring-opening of the pyrrolidinone with formation of the allyl ester. These compounds were subsequently ring-closed in the presence of second-generation Grubbs' catalyst to form macrocycles containing the ester functionality in the ring. It was established by HSQC experiments with inverse detection that only the *E* isomers were formed in the cases of the 24- and 26-membered heterocycles.

Introduction

Hydantoins, first identified as products of undesired side-reactions in peptide chemistry, have attracted much interest in drug discovery because of their wide range of therapeutic properties, which include, among others, antiarrhythmic,[1] anticonvulsant,[2] antitumour,[3] antidiabetic[4] and antimuscarinic[5] activities. Several clinically important pharmaceuticals, such as phenytoin (**1**, Figure 1), which is used to treat certain types of epileptic seizures,[6] and nilutamide (**2**), an antiandrogen medication used in the treatment of prostate cancer, are based upon this heterocyclic scaffold. Hydantoins are useful not only for human medicine, but also in agriculture. Hydantocidin (**3**) is a naturally occurring spirohydantoin with herbicidal activities,[7] while iprodion (**4**) is a commercially used fungicide.

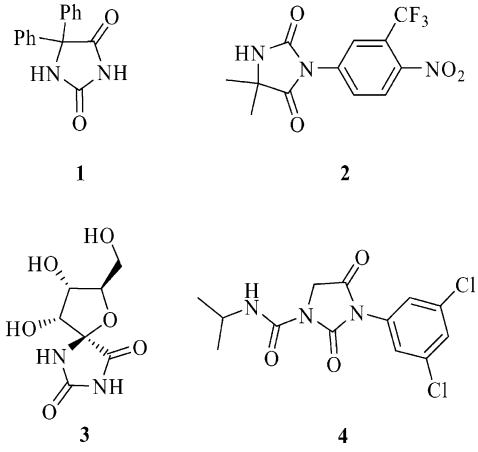

Figure 1. Phenytoin (**1**), nilutamide (**2**), hydantocidin (**3**) and iprodion (**4**).

Hydantoins may be regarded as cyclic ureides of α-amino acids, and these two types of compounds are readily interconvertible. A number of methods to synthesise hydantoins exist.[8,9] Treatment of α-amino acids, nitriles or amides with alkali cyanates is used mainly for the preparation of hydantoins with substituents at their C-5 positions, but also for N^1-substituted hydantoins. Treatment of free α-amino acids, esters or nitriles with isocyanates is valuable when hydantoins substituted at their N-3 positions are desired. Urea can be treated with α-amino acids, α-hydroxy acids, α-hydroxy nitriles, α-dicarbonyl compounds or unsaturated acids. Further, a range of other methods starting from amino acids or derivatives with carbonic acid derivatives such as phosgene, alkyl chloroformates or 1,1′-carbonyldiimidazole (CDI) have been described, while another general method is the Bucherer–Bergs synthesis of 5-substituted hydantoins from aldehydes and ketones through the action of potassium cyanide and ammonium carbonate. New synthetic methods are still being developed or older ones further investigated; they include palladium-catalysed reactions,[10] rearrangement reactions of 2,3-epoxydiaryl ketones[11] and modified Bucherer–Bergs reactions with nitriles and organometallic reagents.[12] In solid-phase synthesis the hydantoins are mostly synthesised from natural and unnatural acyclic α-amino acids or dipeptides as starting materials.[13]

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Several N^3,$N^{3'}$-polymethylenebis(hydantoins) have been evaluated as hexamethylenebis(acetamide) (HMBA) analogues. HMBA is a compound that induces cancer cells to differentiate to a less malignant phenotype, which provides an attractive area for the development of new anticancer drugs. These differentiation agents are expected to exhibit reduced toxicity relative to conventional chemotherapeutic agents, since the mechanism is not primarily based on cytotoxity. HMBA had some modest success in a phase II clinical trial.[14] Relatively high drug concentrations, of the order of 5 mM, are required, but HMBA suffers from dose-related toxicity and has a short biological lifetime as it undergoes rapid deacetylation and rapid renal clearance.[15] The bis(hydantoin) **5a** (Figure 2) was about 10 times more potent than HMBA. The phenytoin analogue **5b** was very insoluble, which may have limited its activity.[16,17]

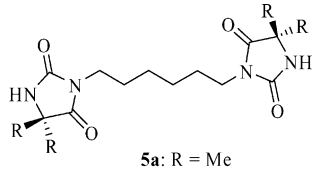


Figure 2. Bis(hydantoins) as HMBA analogues.

The bis(hydantoins) were synthesised through *N*-3-selective alkylation of the hydantoins with 1,6-dihalohexanes. The associated problems of selectivity and the low yields can be circumvented using the protocol described below.

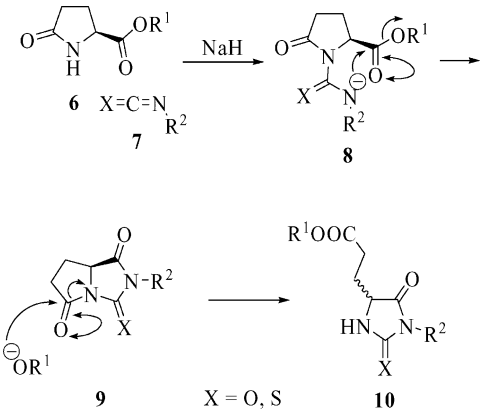
Recently we reported on the pyroglutamate–hydantoin rearrangement:[18] when a solution of pyroglutamate and iso(thio)cyanate is treated with NaH in THF, ring-closure to the hydantoin occurs, with simultaneous ring-opening of the pyrrolidinone (Scheme 1). With this reaction in ether as a solvent, the intermediate sodium salt of the *N*-carbamoylated pyroglutamate precipitates and can be easily isolated. These products of the double ring-transformation can be converted into bicyclic hydantoin derivatives[18] and macrocycles.[19]

In view of the promising results of earlier biotesting by chick heart invasion assay,[20] in which some bis(hydantoins) with hexa- and octamethylene spacers showed anti-invasive activity at a concentration of 10 μM,[21] the allyl esters of the bis(hydantoins) were synthesised and further ring-closed by ring-closing metathesis (RCM).[22,23] In this library of compounds, the ester function is incorporated in the macrocyclic ring, endowing the molecule with lower polarity. Esterification is also a bioreversible chemical derivatisation and is most popular for drugs containing carboxy or hydroxy functions. This was used in, for example, the synthesis of prodrugs to D-prolines, where ester derivatives as well as further macrocyclic ring-closed products were evaluated.[24]

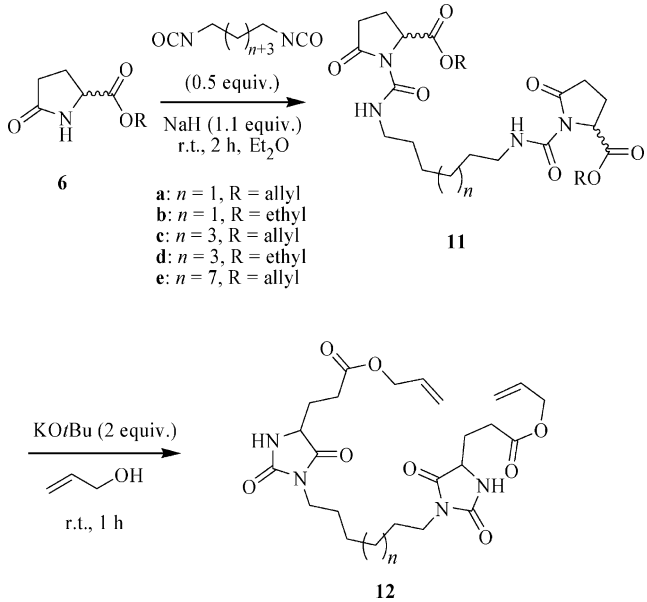
For the macrocycles that we have previously synthesised it was shown that only the *trans* isomers were formed.[19] This was also evaluated for the 24- and 26-membered rings described below. As these ring structures are symmetrical entities, $^3J_{H,H}$ coupling constants do not appear in the ^{1}H NMR spectra of these compounds, but can be recovered by using ^{1}H- and ^{13}C-correlated spectra obtained by inverse detection techniques.[25]

Results and Discussion

The hydantoins **11** were synthesised by the previously described two-step protocol,[19] since the more straightforward one-step ring-closing ring-opening (Scheme 1) did not go to completion in THF and some side reactions resulting from the attack of the alkoxide anions on the isocyanates occurred. NaH was therefore added to a mixture of allyl pyroglutamate, synthesised by a Dean–Stark esterification reaction, and diisocyanate in dry ether (Scheme 2). Almost immediately after the addition of the base, a white precipitate was formed. The reaction was quenched with saturated NH_4Cl solution after two hours. Stirring of the bis(carbamoyllactam) **11a** in allyl alcohol with 2.1 equiv. KO*t*Bu afforded the bis(hydantoin) **12a**.



Scheme 1.



Scheme 2.

It was investigated whether one could start from ethyl pyroglutamate and perform a transesterification simultaneously with the pyroglutamate–hydantoin rearrangement (Table 1). For this purpose the ethyl pyroglutamate was carbamoylated in ether with 1,6-diisocyanatohexane and then rearranged in allyl alcohol by treatment with KO*t*Bu. This sequence resulted in pure bis(hydantoin) **12b** in a slightly higher yield – 85% in comparison with 71% – for the complete sequence in Scheme 2. Unfortunately, though, this protocol could not be used successfully for diisocyanates with longer alkyl chains, since not only carbamoylation, but also rearrangement had started even during the intended preparation of **11d**. This is in contrast with our previous results with short-chain alkylisocyanates and arylisocyanates, which did not rearrange even after stirring overnight in ether. After workup, the hydantoin, which in this case is the side-product, could be precipitated in diethyl ether (34% yield) while the carbamoylated product had to be purified by column chromatography (48% yield, **11d**). The rearrangement resulted in **12d** in high yield.

Table 1. Yields of carbamoylation and rearrangement of pyroglutamate **6**.

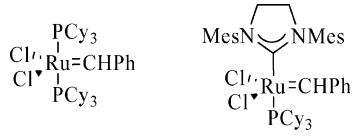
n	Path A, R = allyl		Path B, R = ethyl	
	Carbamoylation	Rearrangement	Carbamoylation	Rearrangement
1	**11a** 83%	**12a** 86%	**11b** 93%	**12b** 91%
3		**12c** 86%[a]	**11d** 48%[b]	**12d** 96%
7	**11e** 91%	**12e** 49%[c]		

[a] Product **11c** was not purified from the mixture with **12c**. [b] Drop in yield due to purification of **11d** from the crude mixture with the hydantoin by column chromatography. [c] Purified by column chromatography.

Also in the case of allyl pyroglutamate, prolonged stirring in ether causes the sodium salts of the carbamoylated lactams (**11c** and **11e**) to rearrange partially to the hydantoins (**12c** and **12e**), though the crude mixtures could be further used for the rearrangement in allyl alcohol. The rearrangement in ether can be limited by shortening the reaction time to 30 minutes and by using a 0.1 to 0.2 M concentration of the pyroglutamate. The limited reaction time is important, as side reactions occur with, for example, the nucleophilic alkoxide anions. Moreover, it is very important to work under dry conditions, as the presence of water leads to the formation of carbamic acids, which after decarboxylation produce amines, which add to isocyanates to form urea derivatives. These can be precipitated in ether, but column chromatography is needed to achieve complete purity.

The obtained hydantoins can be further derivatised by alkylation at nitrogen (Scheme 3). To introduce *N*-benzyl groups, the imidazolidinediones **12** were heated at reflux overnight in acetone with an excess of electrophile (mostly the corresponding bromide) and finely ground K_2CO_3. The alkylation had a 100% conversion, but the chromatographic removal of the excess of electrophile caused the yield to drop. For the methylation, iodomethane and NaH in DMF were used. The yields presented in Scheme 3 are those after purification of **13**.

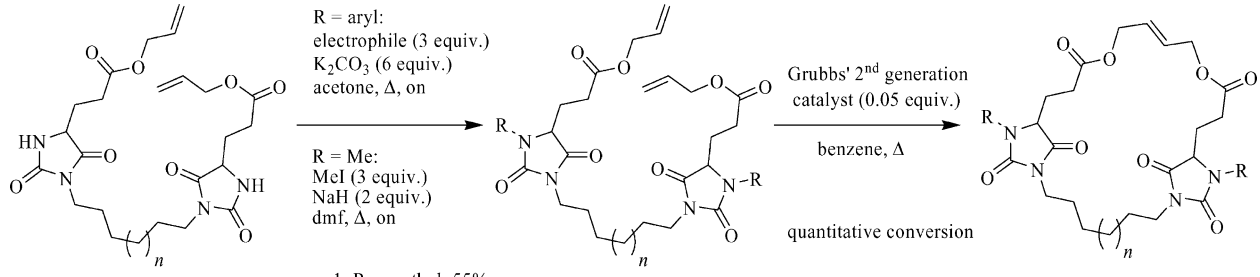
The *N*-alkylation also serves as protection methodology for the *N*-lactam to prevent deactivation of the catalyst used for the cyclisation. RCM is a powerful method to synthesise macrocyclic products; substrates devoid of any conformational constraints can be cyclised by it. Neither the conformational predisposition of the substrates nor the ring-size play a decisive role, but the presence of polar relay substituents, their distance from the alkene groups and low steric hindrance close to the double bond are important.[26] The ring-closure was carried out by use of 5 mol-% of second-generation Grubbs' catalyst **16** (Figure 3).[27] Simply heating the compounds at reflux overnight together with the ruthenium catalyst resulted in quantitative conversion to the macrocycles.



15 **16**

Figure 3. First- and second-generation Grubbs' catalysts.

Usually RCM results in mixtures of *E* and *Z* isomers, but in some cases only *E* isomers have been formed.[28] The use of the fully saturated second-generation Grubbs' catalyst **16** affords much higher *E*/*Z* ratios than the use of the standard Grubbs' carbene **15**.[29] This is caused by the ability of **16** to isomerise the initial product under the reaction



12 **13** **14**

a: *n* = 1, R = methyl, 55%
b: benzyl, 73%
c: *p*-bromobenzyl, 78%
d: *n* = 3, R = *p*-chlorobenzyl, 68%
e: *p*-bromobenzyl, 54%
f: *n* = 7, R = benzyl, 55%

Scheme 3.

conditions, thereby progressively enriching the mixture in the thermodynamically favoured *E* isomer.[30]

Also in this case, two separate signals for the alkene protons of derivatives **14** were observed. Since these macrocycles **14** have two chiral centres, these can be diastereomers as well. Usually the *E* and *Z* isomers are distinguished through their $^3J_{H,H}$ NMR coupling constants, but these are absent as the macrocycles are symmetrical. These $^3J_{H,H}$ coupling constants, however, can be recovered when an H,C-inverse-detection spectrum is acquired without carbon-decoupling during acquisition. In the inverse-detected H,C-correlation spectra, the major component due to signals coming from H bonded to ^{12}C, which represents 99% of the total number of C atoms in normal ^1H NMR spectra, is suppressed. By doing this, the $^3J_{H,H}$ coupling constants between equivalent protons can be observed.[25]

The diastereomers of **14a** and **14c** were separated by preparative thin-layer chromatography (TLC), though chromatography again caused a large drop in yield. For **14c**, coupling constants of 17.4 and 18.1 Hz were observed, pointing to *trans* geometries for both isomers.

Further evidence that a mixture of diastereomers rather than *E* and *Z* isomers is formed was provided by an experiment in which one of the diastereomers of **13e** was isolated in pure form by column chromatography. This so-called "diastereomer" is actually a mixture of two enantiomers, which cannot be distinguished in the NMR spectra. Heating of this diastereomer at reflux with Grubbs' catalyst **16** gave one product in the ^{13}C NMR spectrum, so only the *E* or the *Z* isomer was formed, as otherwise two products should have been observed in the ^{13}C NMR spectrum. The coupling constant of **14e** was 17.7 Hz, again pointing to the formation of the *E* isomer.

Conclusions

The pyroglutamate hydantoin rearrangement has been used to construct $N^3,N^{3'}$- polymethylenebis(hydantoins), which are HMBA analogues and showed anti-invasive activity in the chick heart assay. The biological data will be published in due course. After *N*-alkylation or *N*-arylation, the bis(hydantoins) were ring-closed to form 24- to 30-membered macrocycles, again indicating the power of ring-closing metathesis. The use of second-generation Grubbs' catalyst **16** resulted in exclusive formation of the *trans* isomers, as was confirmed by undecoupled HSQC.

Experimental Section

General Remarks: High-resolution ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run with a Jeol EX300 Eclipse NMR spectrometer. Peak assignments were obtained with the aid of 2D-HSQC, 2D-HMBC and 2D-COSY spectra. The compounds were diluted in deuterated solvents, and the solvent used is indicated for each compound. Low-resolution mass spectra were recorded with an Agilent 1100 Series VS (ES = 4000 V) mass spectrometer. IR spectra were obtained with a Perkin–Elmer Spectrum One infrared spectrometer. The samples were collected by preparing a thin film of compound between two sodium chloride plates. Crystalline compounds were mixed with KBr and pressed in a transparent plate. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and have not been corrected. The elemental analysis was performed with a Perkin–Elmer 2400 Elemental Analyzer. The purification of reaction mixtures was performed by column chromatography in a glass column with silica gel (Across, particle size 0.035–0.070 mm, pore diameter ca. 6 nm). Removal of the Grubbs' catalyst was achieved by preparative thin-layer chromatography.

In the next part the procedures and spectroscopic data are given for the different types of reaction. The amounts in grams were used for the synthesis of the products that are given just underneath the procedures.

Typical Experimental Procedure for the Carbamoylation of Pyroglutamates at Nitrogen: The pyroglutamate ester (2.48 g, 14.66 mmol) was dissolved in dry diethyl ether (70 mL, freshly distilled from Na metal), the diisocyanate (1.24 g, 7.37 mmol) was added by syringe, and the mixture was briefly stirred. After addition of NaH (0.36 g, 15.00 mmol) the reaction mixture was stirred under nitrogen for 0.5 to 2 hours, while a white precipitate formed. The reaction was then quenched with saturated NH_4Cl solution until the pH was neutral or slightly acidic. The mixture was extracted three times with EtOAc, and the organic layers were dried with $MgSO_4$ and filtered. Compound **11c** was further purified by column chromatography. The allyl ester derivatives can be used without purification in the subsequent rearrangement reaction, as they appear with the rearranged product.

Allyl 1-{6-[(2-Allyloxycarbonyl-5-oxopyrrolidin-1-ylcarbonyl)-amino]hexylcarbamoyl}-5-oxopyrrolidine-2-carboxylate (11a): Yield 83%, 3.08 g. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.40 (m, 4 H, CH_2CH_2), 1.50–1.60 (m, 4 H, $2\times CH_2CH_2N$), 2.01–2.11 (m, 2 H, $2\times CH_aH_b$, ring), 2.28–2.42 (m, 2 H, $2\times CH_aH_b$, ring), 2.57 (ddd, J = 17.7, 9.4, 3.3 Hz, 2 H, $2\times CH_aH_bCO$), 2.75 (dt, J = 17.7, 9.9 Hz, 2 H, $2\times CH_aH_bCO$), 3.18–3.37 (m, 4 H, $2\times NCH_2$), 4.68 (br d, J = 5.7 Hz, 4 H, $2\times OCH_2$), 4.82 (dd, J = 9.6, 2.8 Hz, 2 H, $2\times CH$), 5.26 (ddd, J_{cis} = 10.5, 2.3, 1.1 Hz, 2 H, $2\times =CH_aH_b$), 5.35 (ddd, J_{trans} = 17.3, 2.3, 1.4 Hz, 2 H, $2\times =CH_aH_b$), 5.92 (ddt, J_{trans} = 17.3 Hz, J_{cis} = 10.5 Hz and J_{vic} = 5.7 Hz, 2 H, $2\times CH=CH_2$), 8.28 (t, J = 5.2 Hz, 2 H, $2\times NH$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.25 ($2\times CH_2$, ring), 26.46 (CH_2CH_2), 29.47 ($2\times CH_2CH_2N$), 31.83 ($2\times CH_2CO$), 39.80 ($2\times NCH_2$), 58.10 ($2\times CH$), 66.14 ($2\times OCH_2$), 118.89 ($2\times =CH_2$), 131.43 ($2\times CH=CH_2$), 152.18 ($2\times C$=O, urea), 171.17 ($2\times C$=O, ester), 176.32 ($2\times C$=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1651 (C=C), 1689 (C=O), 1719 (C=O), 1745 (C=O), 3317 (NH) cm^{-1}. MS: *m/z* (%) = 507 (100) $[M + H]^+$. $C_{24}H_{34}N_4O_8$ (506.55): calcd. C 56.91, H 6.77, N 11.06; found C 57.14, H 6.41, N 11.38.

Ethyl 1-{6-[(2-Ethoxycarbonyl-5-oxopyrrolidin-1-ylcarbonyl)-amino]hexylcarbamoyl}-5-oxopyrrolidine-2-carboxylate (11b): Yield 93%, 1.43 g, white powder, m.p. 79 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.2 Hz, 6 H, $2\times CH_3$), 1.32–1.38 (m, 4 H, CH_2CH_2), 1.50–1.59 (m, 4 H, $2\times CH_2CH_2N$), 1.99–2.09 (m, 2 H, $2\times CH_aH_b$, ring), 2.27–2.41 (m, 2 H, $2\times CH_aH_b$, ring), 2.57 (ddd, J = 17.6, 9.4, 3.3 Hz, 2 H, $2\times CH_aH_bCO$), 2.74 (dt, J = 17.6, 9.9 Hz, 2 H, $2\times CH_aH_bCO$), 3.18–3.37 (m, 4 H, $2\times NCH_2$), 4.24 (q, J = 7.2 Hz, 4 H, $2\times OCH_2$), 4.78 (dd, J = 9.4, 2.8 Hz, 2 H, $2\times CH$), 8.28 (t, J = 5.5 Hz, 2 H, $2\times NH$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.21 ($2\times CH_3$), 21.37 ($2\times CH_2$, ring), 26.58 (CH_2CH_2), 29.60 ($2\times CH_2CH_2N$), 31.98 ($2\times CH_2CO$), 39.91 ($2\times NCH_2$), 58.26 ($2\times CH$), 61.80 ($2\times OCH_2$), 152.32 ($2\times C$=O, urea), 171.61 ($2\times C$=O, ester), 176.49 ($2\times C$=O, lactam) ppm. IR

(NaCl): $\tilde{\nu}_{max}$ = 1693 (C=O), 1722 (C=O), 1742 (C=O), 3320 (NH) cm^{-1}. MS: *m*/*z* (%) = 483 (100) [M + H]$^+$. $C_{22}H_{34}N_4O_8$ (482.53): calcd. C 54.76, H 7.10, N 11.61; found C 54.47, H 7.26, N 11.45.

The mixture of **11c** and the rearranged product was used without purification.

Ethyl 1-{6-[(2-Ethoxycarbonyl-5-oxopyrrolidin-1-ylcarbonyl)-amino]octylcarbamoyl}-5-oxopyrrolidine-2-carboxylate (11d): Yield 48%, 0.50 g; the rearranged product was also formed. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26–1.32 (m, 14 H, 2×C*H*$_3$, CH_2CH_2), 1.50–1.58 (m, 4 H, 2×CH_2CH_2N), 2.00–2.10 (m, 2 H, 2×CH_aH$_b$, ring), 2.28–2.42 (m, 2 H, 2×CH$_a$*H*$_b$, ring), 2.57 (ddd, *J* = 17.6, *J* = 9.4, 3.3 Hz, 2 H, 2×CH_aH$_b$CO), 2.75 (dt, *J* = 17.6, 9.9 Hz, 2 H, 2×CH$_a$*H*$_b$CO), 3.19–3.36 (m, 4 H, 2×NCH_2), 4.24 (q, *J* = 7.2 Hz, 4 H, 2×OCH_2), 4.77 (dd, *J* = 9.4, 2.8 Hz, 2 H, 2×C*H*), 8.29 (t, *J* = 5.5 Hz, 2 H, 2×N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.08 (2×*C*H$_3$), 21.22 (2×*C*H$_2$, ring), 26.70 (*C*H$_2$CH$_2$), 29.09 (*C*H$_2$CH$_2$CH$_2$*C*H$_2$), 29.51 (2×*C*H$_2$CH$_2$N), 31.85 (2×*C*H$_2$CO), 39.85 (2×N*C*H$_2$), 58.14 (2×*C*H), 61.62 (2×O*C*H$_2$), 152.19 (2×*C*=O, urea), 171.48 (2×*C*=O, ester), 176.39 (2×*C*=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1692 (C=O), 1721 (C=O), 1744 (C=O), 3316 (NH) cm^{-1}. MS: *m*/*z* (%) = 511 (100) [M + H]$^+$. Chromatography: R_f = 0.20 (PE/EtOAc, 1:1). $C_{24}H_{38}N_4O_8$ (510.58): calcd. C 56.46, H 7.50, N 10.97; found C 56.59, H 7.51, N 11.04.

Allyl 1-{6-[(2-Allyloxycarbonyl-5-oxopyrrolidin-1-ylcarbonyl)-amino]dodecylcarbamoyl}-5-oxopyrrolidine-2-carboxylate (11e): Yield 91%, 0.63 g. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.36 [m, 16 H, 2×N(CH$_2$)$_2$(CH_2)$_4$], 1.49–1.56 (m, 4 H, 2×CH_2CH$_2$N), 2.07 (ddt, *J* = 13.1, *J* = 9.8, 2.9 Hz, 2 H, 2×CH_aH$_b$, ring), 2.28–2.42 (m, 2 H, 2×CH$_a$*H*$_b$, ring), 2.57 (ddd, *J* = 17.6, *J* = 9.3, 3.2 Hz, 2 H, 2×CH_aH$_b$CO), 2.75 (dt, *J* = 17.6, 9.8 Hz, 2 H, 2×CH$_a$*H*$_b$CO), 3.19–3.37 (m, 4 H, 2×NCH_2), 4.66–4.69 (m, 4 H, 2×OCH_2), 4.82 (dd, *J* = 9.6, 2.9 Hz, 2 H, 2×C*H*), 5.27 (dbrq, *J* = 10.6, 1.4 Hz, 2 H, 2×=CH_aH$_b$), 5.35 (dbrq, J_{trans} = 17.2, 1.4 Hz, 2 H, 2×=CH$_a$*H*$_b$), 5.92 (ddt, J_{trans} = 17.2, J_{cis} = 10.6, J_{vic} = 5.7 Hz, 2 H, 2×C*H*=CH$_2$), 8.28 (t, *J* = 5.2 Hz, 2 H, 2×N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.25 (2×*C*H$_2$, ring), 26.86 (*C*H$_2$CH$_2$), 29.27 (2×*C*H$_2$), 29.51 (2×*C*H$_2$), 29.54 (2×*C*H$_2$), 29.57 (2×*C*H$_2$CH$_2$N), 31.86 (2×*C*H$_2$CO), 39.99 (2×N*C*H$_2$), 58.11 (2×*C*H), 66.14 (2×O*C*H$_2$), 118.91 (2×=*C*H$_2$), 131.41 (2×*C*H=CH$_2$), 152.16 (2×*C*=O, urea), 171.20 (2×*C*=O, ester), 176.32 (2×*C*=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1695 (C=O), 1722 (C=O), 1745 (C=O), 3323 (NH) cm^{-1}. MS: *m*/*z* (%) = 591 (100) [M + H]$^+$. $C_{30}H_{46}N_4O_8$ (590.71): calcd. C 61.00, H 7.85, N 9.48; found C 60.62, H 7.62, N 9.41.

Typical Experimental Procedure for the Rearrangement of Carbamoylated Pyroglutamates 11 to Hydantoins 12: The pyroglutamate ester **11** (1.40 g, 2.76 mmol) was dissolved in allyl alcohol (20 mL) and KO*t*Bu (0.65 g, 5.79 mmol) was added. The mixture was stirred at room temperature for 1 hour, protected from moisture with a $CaCl_2$ tube. The reaction mixture was quenched with a saturated NH_4Cl solution, extracted with EtOAc, dried with $MgSO_4$ and filtered. Removal of the solvent yielded the product. Product **12a** was crystallised from EtOAc, **12b** and **12c** were crystallised from dry acetone, and **12e** was further purified by column chromatography.

Allyl 3-(1-{6-[4-(2-Allyloxycarbonylethyl)-2,5-dioxoimidazolidin-1-yl]hexyl}-2,5-dioxoimidazolidin-4-yl)propionate (12a and 12b): Yield 86%, 1.20 g and 91%, 0.42 g, white crystals, m.p. 99–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28–1.39 (m, 4 H, CH_2CH_2), 1.56–1.68 (m, 4 H, 2×CH_2CH$_2$N), 1.98–2.10 (m, 2 H, 2×CH_aH$_b$CH$_2$CO), 2.17–2.29 (m, 2 H, 2×CH$_a$*H*$_b$CH$_2$CO), 2.51 (t, *J* = 7.2 Hz, 4 H, 2×CH_2CO), 3.48 (t, *J* = 7.2 Hz, 4 H, 2×NCH_2), 4.10 (brt, *J* = 5.8 Hz, 2 H, 2×C*H*), 4.60 (d, *J* = 5.8 Hz, 4 H, 2×OCH_2), 5.26 (dq, J_{cis} = 10.5, 1.1 Hz, 2 H, 2×=CH_aH$_b$), 5.32 (dq, J_{trans} = 17.1, 1.5 Hz, 2 H, 2×=CH$_a$*H*$_b$), 5.91 (ddt, J_{trans} = 17.1, J_{cis} = 10.5, J_{vic} = 5.8 Hz, 2 H, 2×C*H*=CH$_2$), 6.00 (brs, 2 H, 2×N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.12 (*C*H$_2$*C*H$_2$), 26.81 (2×*C*H$_2$CH$_2$CO), 27.82 (2×*C*H$_2$CH$_2$N), 29.68 (2×*C*H$_2$CO), 38.51 (2×N*C*H$_2$), 56.25 (2×*C*H), 65.65 (2×O*C*H$_2$), 118.83 (2×=*C*H$_2$), 131.78 (2×*C*H=CH$_2$), 157.28 (2×*C*=O, urea), 172.45 (2×*C*=O, ester), 173.54 (2×*C*=O, lactam) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1650 (C=C), 1732 (C=O), 1771 (C=O), 3234 (NH) cm^{-1}. MS: *m*/*z* (%) = 505 (100) [M + H]$^+$. $C_{24}H_{34}N_4O_8$ (506.55): calcd. C 56.91, H 6.77, N 11.06; found C 56.82, H 6.82, N 10.99.

Allyl 3-(1-{8-[4-(2-Allyloxycarbonylethyl)-2,5-dioxoimidazolidin-1-yl]octyl}-2,5-dioxoimidazolidin-4-yl)propionate (12c and 12d): Yield 86%, 1.05 g from **6a** and 96%, 50 mg, white powder, m.p. 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.35 [m, 8 H, 2×N(CH$_2$)$_2$-(CH_2)$_2$], 1.54–1.64 (m, 4 H, 2×NCH$_2$CH_2), 1.99–2.10 (m, 2 H, 2×CH_aH$_b$CH), 2.18–2.29 (m, 2 H, 2×CH$_a$*H*$_b$CH), 2.51 (t, *J* = 7.2 Hz, 4 H, 2×CH_2CO), 3.47 (t, *J* = 7.3 Hz, 4 H, 2×NCH_2), 4.10 (brt, *J* = 5.4 Hz, 2 H, 2×C*H*), 4.59 (brd, *J* = 5.8 Hz, 4 H, 2×OCH_2), 5.26 (dq, J_{cis} = 10.4, 1.4 Hz, 2 H, 2×=CH_aH$_b$), 5.32 (dq, J_{trans} = 17.2, 1.4 Hz, 2 H, 2×=CH$_a$*H*$_b$), 5.91 (ddt, J_{trans} = 17.2, J_{cis} = 10.4, J_{vic} = 5.8 Hz, 2 H, 2×C*H*=CH$_2$), 6.31 (s, 2 H, 2×N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.64 [2×N(CH$_2$)$_3$-*C*H$_2$], 26.93 (2×*C*H$_2$CH), 28.06 (2×NCH$_2$*C*H$_2$), 29.02 [2×N(CH$_2$)$_2$*C*H$_2$], 29.69 (2×*C*H$_2$CO), 38.79 (2×N*C*H$_2$), 56.32 (2×*C*H), 65.74 (2×O*C*H$_2$), 118.90 (2×=*C*H$_2$), 131.91 (2×*C*H=CH$_2$), 157.65 (2×*C*=O, urea), 172.54 (2×*C*=O, ester), 173.73 (2×*C*=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1649 (C=C), 1706 (C=O), 1774 (C=O), 3310 (NH) cm^{-1}. MS: *m*/*z* (%) = 535 (100) [M + H]$^+$. $C_{26}H_{38}N_4O_8$ (534.60): calcd. C 58.41, H 7.16, N 10.48; found C 58.14, H 7.33, N 10.39.

Allyl 3-(1-{12-[4-(2-Allyloxycarbonylethyl)-2,5-dioxoimidazolidin-1-yl]dodecyl}-2,5-dioxoimidazolidin-4-yl)propionate (12e): Yield 49%, 0.16 g, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.28 [m, 16 H, 2×N(CH$_2$)$_2$(CH_2)$_4$], 1.47–1.64 (m, 4 H, 2×CH_2CH$_2$N), 1.99–2.11 (m, 2 H, 2×CH_aH$_b$CH), 2.17–2.30 (m, 2 H, 2×CH$_a$*H*$_b$CH), 2.51 (t, *J* = 7.3 Hz, 4 H, 2×CH_2CO), 3.47 (t, *J* = 7.2 Hz, 4 H, 2×NCH_2), 4.11 (t, *J* = 5.9 Hz, 2 H, 2×C*H*), 4.59 (brd, *J* = 5.8 Hz, 4 H, 2×OCH_2), 5.25 (dq, J_{cis} = 10.4, 1.4 Hz, 2 H, 2×=CH_aH$_b$), 5.32 (dq, J_{trans} = 17.1, 1.4 Hz, 2 H, 2×=CH$_a$*H*$_b$), 5.91 (ddt, J_{trans} = 17.1, J_{cis} = 10.4, J_{vic} = 5.8 Hz, 2 H, 2×C*H*=CH$_2$), 6.74 (s, 2 H, 2×N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.74 [2×N(CH$_2$)$_2$-*C*H$_2$], 26.87 (2×*C*H$_2$CH), 28.09 (2×*C*H$_2$CH$_2$N), 29.16 [2×N(CH$_2$)$_3$*C*H$_2$], 29.49 [2×*C*H$_2$CO and 2×N(CH$_2$)$_4$(*C*H$_2$)$_2$], 38.78 (2×N*C*H$_2$), 56.21 (2×*C*H), 65.62 (2×O*C*H$_2$), 118.72 (2×=*C*H$_2$), 131.88 (2×*C*H=CH$_2$), 157.84 (2×*C*=O, urea), 172.40 (2×*C*=O, ester), 173.78 (2×*C*=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1651 (C=C), 1710 (C=O), 1733 (C=O), 1774 (C=O), 3337 (NH) cm^{-1}. MS: *m*/*z* (%) = 591 (100) [M + H]$^+$. Chromatography: R_f = 0.01 (PE/EtOAc, 5:2). $C_{30}H_{46}N_4O_8$ (590.71): calcd. C 61.00, H 7.85, N 9.48; found C 61.19, H 7.87, N 9.30.

Typical Procedure for the *N*-Alkylation of Hydantoins. Synthesis of 13a: The bis(hydantoin) (0.12 g, 0.24 mmol) was dissolved in THF (7 mL). Iodomethane (0.10 g, 0.70 mmol) was added by syringe, followed by NaH (0.02 g, 0.83 mmol). The mixture was stirred overnight, protected from moisture with a $CaCl_2$ tube. The reaction was quenched with a saturated NH_4Cl solution, extracted with EtOAc, dried with $MgSO_4$, filtered and coated on silica for column chromatography.

Allyl 3-(1-{6-[4-(2-Allyloxycarbonylethyl)-3-methyl-2,5-dioxoimidazolidin-1-yl]hexyl}-3-methyl-2,5-dioxoimidazolidin-4-yl)propionate (13a): Yield 55%, 71 mg, yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27–1.37 (m, 4 H, CH_2CH_2), 1.54–1.64 (m, 4 H, 2×CH_2CH$_2$N), 2.02–2.19 (m, 2 H, 2×CH_aH$_b$CH$_2$CO), 2.20–2.34 (m, 2 H, 2×CH$_a$$H_bCH_2$CO), 2.30–2.53 (m, 4 H, 2×CH_2CO), 2.93 (s, 6 H, 2×NCH_3), 3.47 (brt, J = 7.3 Hz, 4 H, 2×NCH_2), 3.91 (dd, J = 6.5, 3.2 Hz, 2 H, 2×CH), 4.58 (brd, J = 5.8 Hz, 4 H, 2×OCH_2), 5.25 (dbrq, J = 10.5, 1.2 Hz, 2 H, 2×=CH_aH$_b$), 5.32 (dbrq, J = 17.2, 1.2 Hz, 2 H, 2×=CH$_a$$H_b$), 5.90 (ddt, J_{trans} = 17.2, J_{cis} = 10.5, J_{vic} = 5.8 Hz, 2 H, 2×CH=CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.73 (2×CH$_2$CH$_2$CO), 26.18 (CH$_2$$CH_2$), 27.85 (2×$CH_3$), 27.93 (2×$CH_2CH_2$N), 28.11 (2×$CH_2$CO), 38.78 (2×NCH$_2$, alkyl), 60.05 (2×$C$H), 65.55 (2×OCH$_2$), 118.68 (2×=$CH_2$), 131.89 (2×$C$H=CH$_2$), 156.62 (2×$C$=O, urea), 171.98 (2×$C$=O, ester), 172.36 (2×$C$=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1709 (C=O), 1732 (C=O), 1770 (C=O) cm^{-1}. MS: m/z (%) = 535 (100) [M + H]$^+$. Chromatography: R_f = 0.01 (PE/EtOAc, 4:1). $C_{26}H_{38}N_4O_8$ (534.60): calcd. C 58.41, H 7.16, N 10.48; found C 58.37, H 7.18, N 10.14.

Typical Procedure for the *N*-Alkylation of Hydantoins. Synthesis of 13b–e: The bis(hydantoin) (0.32 g, 0.63 mmol) was dissolved in dry acetone (6 mL, dried with K_2CO_3 and distilled). The aryl bromide (0.32 g, 1.87 mmol) and K_2CO_3 (0.52 g, 3.76 mmol) were added and the mixture was heated at reflux overnight, protected from moisture with a $CaCl_2$ tube. The solution was cooled to room temperature, and the precipitate was filtered and coated on silica for column chromatography.

Allyl 3-(1-{6-[4-(2-Allyloxycarbonylethyl)-3-benzyl-2,5-dioxoimidazolidin-1-yl]hexyl}-3-benzyl-2,5-dioxoimidazolidin-4-yl)propionate (13b): Yield 73%, 0.52 g, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.42 (m, 4 H, CH_2CH_2), 1.58–1.68 (m, 4 H, 2×CH_2CH$_2$N), 2.01–2.13 (m, 2 H, 2×CH_aH$_b$CH$_2$CO), 2.16–2.27 (m, 2 H, 2×CH$_a$$H_bCH_2$CO), 2.25–2.42 (m, 4 H, 2×CH_2CO), 3.51 (brt, J = 7.2 Hz, 4 H, 2×NCH_2, alkyl), 3.82 (dd, J = 6.2, 2.9 Hz, 2 H, 2×CH), 4.10 (d, J = 15.3 Hz, 2 H, 2×NCH_aH$_b$, benzyl), 4.55 (brd, J = 5.8 Hz, 4 H, 2×OCH_2), 4.97 (d, J = 15.3 Hz, 2 H, 2×NCH$_a$$H_b$, benzyl), 5.23 (dbrq, J_{cis} = 10.5, 1.2 Hz, 2 H, 2×=CH_aH$_b$), 5.30 (dbrq, J_{trans} = 17.2, 1.2 Hz, 2 H, 2×=CH$_a$$H_b$), 5.89 (ddt, J_{trans} = 17.2, J_{cis} = 10.5, J_{vic} = 5.8 Hz, 2 H, 2×CH=CH$_2$), 7.25–7.37 (m, 10 H, 10×CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.45 (2×CH$_2$CH$_2$CO), 26.13 (CH$_2$$CH_2$), 27.86 (2×$CH_2CH_2$N or 2×$CH_2$CO), 27.95 (2×$CH_2CH_2$N or 2×$CH_2$CO), 38.79 (2×NCH$_2$, alkyl), 44.59 (2×NCH$_2$, benzyl), 57.31 (2×$C$H), 65.42 (2×OCH$_2$), 118.54 (2×=$CH_2$), 128.09 (2×$CH_{ar}$), 128.20 (4×$CH_{ar}$), 128.96 (4×$CH_{ar}$), 131.90 (2×$C$H=CH$_2$), 135.59 (2×$C_{ar,quat.}$), 156.63 (2×$C$=O, urea), 171.84 (2×$C$=O, ester), 172.28 (2×$C$=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1649 (C=C), 1707 (C=O), 1734 (C=O), 1768 (C=O) cm^{-1}. MS: m/z (%) = 687 (100) [M + H]$^+$. Chromatography: R_f = 0.02 (PE/EtOAc, 4:1). $C_{38}H_{46}N_4O_8$ (686.79): calcd. C 66.45, H 6.75, N 8.16; found C 66.10, H 6.46, N 8.09.

Allyl 3-(1-{6-[4-(2-Allyloxycarbonylethyl)-3-(4-bromobenzyl)-2,5-dioxoimidazolidin-1-yl]hexyl}-3-(4-bromobenzyl)-2,5-dioxoimidazolidin-4-yl)propionate (13c): Yield 78%, 0.17 g, yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.40 (m, 4 H, CH_2CH_2), 1.57–1.67 (m, 4 H, 2×CH_2CH$_2$N), 1.97–2.09 (m, 2 H, 2×CH_aH$_b$CH$_2$CO), 2.16–2.25 (m, 2 H, 2×CH$_a$$H_bCH_2$CO), 2.25–2.45 (m, 4 H, 2×CH_2CO), 3.50 (brt, J = 7.2 Hz, 4 H, 2×NCH_2, alkyl), 3.82 (dd, J = 6.6, 3.0 Hz, 2 H, 2×CH), 4.10 (d, J = 15.3 Hz, 2 H, 2×NCH_aH$_b$, benzyl), 4.56 (brd, J = 5.8 Hz, 4 H, 2×OCH_2), 4.88 (d, J = 15.3 Hz, 2 H, 2×NCH$_a$$H_b$, benzyl), 5.22–5.28 (m, 2 H, 2×=CH_aH$_b$), 5.26–5.34 (m, 2 H, 2×=CH$_a$$H_b$), 5.89 (ddt, J_{trans} = 16.7, J_{cis} = 10.3, J_{vic} = 5.8 Hz, 2 H, 2×CH=CH$_2$), 7.16 (d, J = 8.4 Hz, 4 H, 4×CH_{ar}), 7.48 (d, J = 8.4 Hz, 4 H, 4×CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.81 (2×CH$_2$CH$_2$CO), 26.36 (CH$_2$$CH_2$), 28.10 (2×$CH_2CH_2$N), 28.20 (2×$CH_2$CO), 39.09 (2×NCH$_2$, alkyl), 44.34 (2×NCH$_2$, benzyl), 57.67 (2×$C$H), 65.78 (2×OCH$_2$), 118.93 (2×=$CH_2$), 122.44 (2×$C_{ar,quat.}$), 130.21 (4×$CH_{ar}$), 132.07 (2×$C$H=CH$_2$), 132.39 (4×$CH_{ar}$), 134.94 (2×$C_{ar,quat.}$), 156.88 (2×$C$=O, urea), 172.12 (2×$C$=O, ester), 172.40 (2×$C$=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1705 (C=O), 1732 (C=O), 1768 (C=O) cm^{-1}. MS: m/z (%) = 843/845/847 (100) [M + H]$^+$. Chromatography: R_f = 0.17 (PE/EtOAc, 5:3). $C_{38}H_{44}Br_2N_4O_8$ (844.59): calcd. C 54.04, H 5.25, N 6.63; found C 53.81, H 5.29, N 6.32.

Allyl 3-(1-{8-[4-(2-Allyloxycarbonylethyl)-3-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl]octyl}-3-(4-chlorobenzyl)-2,5-dioxoimidazolidin-4-yl)propionate (13d): Yield 68%, 51 mg. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.34 [m, 8 H, 2×N(CH$_2$)$_2$(CH_2)$_2$], 1.56–1.66 (m, 4 H, 2×NCH$_2$CH_2), 1.98–2.10 (m, 2 H, 2×CH_aH$_b$CH), 2.17–2.26 (m, 2 H, 2×CH$_a$$H_b$CH), 2.24–2.45 (m, 4 H, 2×CH_2CO), 3.50 (td, J = 7.4, 1.8 Hz, 4 H, 2×NCH_2, alkyl), 3.81 (dd, J = 6.5, 2.9 Hz, 2 H, 2×CH), 4.11 (d, J = 15.3 Hz, 2 H, 2×NCH_aH$_b$, benzyl), 4.56 (d, J = 5.8 Hz, 4 H, 2×OCH_2), 4.90 (d, J = 15.3 Hz, 2 H, 2×NCH$_a$$H_b$, benzyl), 5.25 (brd, J_{cis} = 10.8 Hz, 2 H, 2×=CH_aH$_b$), 5.31 (brd, J_{trans} = 16.9 Hz, 2 H, 2×=CH$_a$$H_b$), 5.89 (ddt, J_{trans} = 16.9, J_{cis} = 10.8, J_{vic} = 5.8 Hz, 2 H, 2×CH=CH$_2$), 7.22 (d, J = 8.3 Hz, 4 H, 4×CH_{ar}), 7.32 (d, J = 8.3 Hz, 4 H, 4×CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.63 (2×CH$_2$CH), 26.71 [2×N(CH$_2$)$_3$$CH_2$], 28.03 (2×NCH$_2$$CH_2$ or 2×CH$_2$CO), 28.09 (2×NCH$_2$$CH_2$ or 2×CH$_2$CO), 29.03 [2×N(CH$_2$)$_2$$CH_2$], 39.13 (2×NCH$_2$, alkyl), 44.12 (2×NCH$_2$, benzyl), 57.51 (2×$C$H), 65.65 (2×OCH$_2$), 118.78 (2×=$CH_2$), 129.29 (4×$CH_{ar}$), 129.76 (4×$CH_{ar}$), 131.93 (2×$C$H=CH$_2$), 134.19 (2×$C_{ar,quat.}$), 134.31 (2×$C_{ar,quat.}$), 156.80 (2×$C$=O, urea), 172.01 (2×$C$=O, ester or lactam), 172.30 (2×C=O, lactam or ester) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1708 (C=O), 1733 (C=O), 1769 (C=O) cm^{-1}. MS: m/z (%) = 781/783/785 (100) [M – H]$^+$. Chromatography: R_f = 0.37 (PE/EtOAc, 4:3). $C_{40}H_{48}Cl_2N_4O_8$ (783.74): calcd. C 61.30, H 6.17, N 7.15; found C 61.23, H 6.44, N 6.84.

Allyl 3-(1-{8-[4-(2-Allyloxycarbonylethyl)-3-(4-bromobenzyl)-2,5-dioxoimidazolidin-1-yl]octyl}-3-(4-bromobenzyl)-2,5-dioxoimidazolidin-4-yl)propionate (13e): Yield 54%, 0.16 g. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24–1.38 [m, 8 H, 2×N(CH$_2$)$_2$(CH_2)$_2$], 1.56–1.66 (m, 4 H, 2×NCH$_2$CH_2), 1.98–2.10 (m, 2 H, 2×CH_aH$_b$CH), 2.17–2.26 (m, 2 H, 2×CH$_a$$H_b$CH), 2.24–2.45 (m, 4 H, 2×CH_2CO), 3.43–3.57 (m, 4 H, 2×NCH_2, alkyl), 3.82 (dd, J = 6.6, 3.0 Hz, 2 H, 2×CH), 4.10 (d, J = 15.4 Hz, 2 H, 2×NCH_aH$_b$, benzyl), 4.56 (dt, J = 5.8, 1.4 Hz, 4 H, 2×OCH_2), 4.89 (d, J = 15.4 Hz, 2 H, 2×NCH$_a$$H_b$, benzyl), 5.25 (dq, J_{cis} = 10.5, 1.2 Hz, 2 H, 2×=CH_aH$_b$), 5.31 (dq, J_{trans} = 17.1, 1.4 Hz, 2 H, 2×=CH$_a$$H_b$), 5.89 (ddt, J_{trans} = 17.1, J_{cis} = 10.5, J_{vic} = 5.8 Hz, 2 H, 2×CH=CH$_2$), 7.16 (d, J = 8.4 Hz, 4 H, 4×CH_{ar}), 7.47 (d, J = 8.4 Hz, 4 H, 4×CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.53 (2×CH$_2$CH), 26.60 [2×N(CH$_2$)$_3$$CH_2$], 27.93 (2×NCH$_2$$CH_2$ or 2×CH$_2$CO), 27.97 (2×NCH$_2$$CH_2$ or 2×CH$_2$CO), 28.92 [2×N(CH$_2$)$_2$$CH_2$], 39.01 (2×NCH$_2$, alkyl), 44.08 (2×NCH$_2$, benzyl), 57.41 (2×$C$H), 65.52 (2×OCH$_2$), 118.66 (2×=$CH_2$), 122.18 (2×$C_{ar,quat.}$), 129.98 (4×$CH_{ar}$), 131.84 (2×$C$H=CH$_2$), 132.13 (4×$CH_{ar}$), 134.74 (2×$C_{ar,quat.}$), 156.68 (2×$C$=O, urea), 171.87 (2×$C$=O, ester or lactam), 172.15 (2×C=O, lactam or ester) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1706 (C=O), 1734 (C=O), 1769 (C=O) cm^{-1}. MS: m/z (%) = 871/873/875 (100)

$[M + H]^+$. Chromatography: R_f = 0.11 (PE/EtOAc, 2:1). $C_{40}H_{48}Br_2N_4O_8$ (872.64): calcd. C 55.05, H 5.54, N 6.42; found C 55.45, H 5.93, N 6.05.

Allyl 3-(1-{12-[4-(2-Allyloxycarbonylethyl)-3-benzyl-2,5-dioxoimidazolidin-1-yl]dodecyl}-3-benzyl-2,5-dioxoimidazolidin-4-yl)propionate (13f): Yield 55%, 52 mg, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.34 [m, 16 H, 2× N(CH_2)$_2$(CH_2)$_4$], 1.57–1.67 (m, 4 H, 2× CH_2CH$_2$N), 2.01–2.13 (m, 2 H, 2× CH_aH$_b$CH), 2.17–2.28 (m, 2 H, 2× CH$_a$$H_b$CH), 2.30–2.26 (m, 4 H, 2× CH_2CO), 3.51 (td, J = 7.4, 2.2 Hz, 4 H, 2× NCH_2), 3.81 (dd, J = 6.2, 3.2 Hz, 2 H, 2× CH), 4.08 (d, J = 15.3 Hz, 2 H, 2× NCH_aH$_b$, benzyl), 4.56 (dt, J = 5.8, 1.4 Hz, 4 H, 2× OCH_2), 5.00 (d, J = 15.3 Hz, 2 H, 2× NCH$_a$$H_b$, benzyl), 5.24 (dq, J_{cis} = 10.5, 1.4 Hz, 2 H, 2× =CH_aH$_b$), 5.30 (dq, J_{trans} = 17.1, 1.4 Hz, 2 H, 2× =CH$_a$$H_b$), 5.91 (ddt, J_{trans} = 17.1, J_{cis} = 10.5, J_{vic} = 5.8 Hz, 2 H, 2× CH=CH$_2$), 7.24–7.38 (m, 10 H, 10× CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.47 (2× CH$_2$CH), 26.75 [2× N(CH_2)$_2$-CH$_2$], 27.99 (2× CH$_2$CO), 28.08 (2× CH$_2$CH$_2$N), 29.15 [2× N(CH_2)$_3$$CH_2$], 29.50 [2× N($CH_2$)$_4$($CH_2$)$_2$], 39.09 (2× NC$H_2$, alkyl), 44.63 (2× NC$H_2$, benzyl), 57.32 (2× CH), 65.50 (2× OCH_2), 118.60 (2× =CH$_2$), 128.16 (2× C$H_{ar, para}$), 128.24 (4× CH_{ar}), 129.02 (4× CH$_{ar}$), 131.90 (2× CH=CH$_2$), 135.63 (2× $C_{ar,quat.}$), 156.76 (2× C=O, urea), 171.93 (2× C=O, ester), 172.38 (2× C=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1709 (C=O), 1735 (C=O), 1769 (C=O) cm^{-1}. MS: m/z (%) = 771 (100) $[M + H]^+$. Chromatography: R_f = 0.29 (PE/EtOAc, 2:1). $C_{44}H_{58}N_4O_8$ (770.95): calcd. C 68.55, H 7.58, N 7.27; found C 68.47, H 7.90, N 7.19.

Typical Procedure for the Ring-Closing Metathesis Reaction of Bis(hydantoins) 14: Bis(hydantoin) **14** (0.11 g, 0.16 mmol) was dissolved in benzene (20 mL) and brought to reflux temperature. Then the second-generation Grubbs' catalyst (0.0068 g, 0.008 mmol) was added. The reaction was heated at reflux overnight, shielded from moisture with a $CaCl_2$ tube. Traces of catalyst were removed by preparative thin layer chromatography (TLC) and in the cases of compounds **14a** and **14c** diastereomers were separated; **14d** yielded one single diastereomer.

10,25-Dimethyl-15,20-dioxa-1,8,10,25-tetraazatricyclo[22.2.1.1^{8,11}]-octacos-17-ene-9,14,21,26,27,28-hexaone (14a): Yield (before TLC) 99%, 80 mg.

Diastereomer 1: Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27–1.40 (m, 4 H, CH_2CH_2), 1.54–1.69 (m, 4 H, 2× CH_2CH$_2$N), 2.14–2.49 (m, 8 H, 2× CH_2CH_2CO), 2.87 (s, 6 H, 2× NCH_3), 3.39–3.49 (m, 2 H, 2× NCH_aH$_b$, alkyl), 3.51–3.62 (m, 2 H, 2× NCH$_a$$H_b$, alkyl), 3.89 (t, J = 3.7 Hz, 2 H, 2× CH), 4.55 (brd, J = 10.9 Hz, 2 H, 2× OCH_aH$_b$), 4.63 (brd, J = 10.9 Hz, 2 H, 2× OCH$_a$$H_b$), 5.76 (t, J = 2.9 Hz, 2 H, 2× =CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.42 (2× CH$_2$CH$_2$CO), 26.55 (CH$_2$CH_2), 27.83 (2× CH$_2$CH$_2$N), 28.06 and 28.18 (2× CH$_3$, 2× CH$_2$CO), 39.09 (2× CH$_2$N), 60.81 (2× CH), 63.94 (2× OCH_2), 127.73 (2× = CH), 156.90 (2× C=O, urea), 172.03 (2× C=O, ester), 172.25 (2× C=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1706 (C=O), 1732 (C=O), 1768 (C=O) cm^{-1}. MS: m/z (%) = 507 (100) $[M + H]^+$. Chromatography: R_f = 0.26 (EtOAc/Et_2O, 1:1). $C_{24}H_{34}N_4O_8$ (506.55): calcd. C 56.91, H 6.77, N 11.06; found C 57.26, H 7.11, N 10.71.

Diastereomer 2: Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28–1.37 (m, 4 H, CH_2CH_2), 1.51–1.70 (m, 4 H, 2× CH_2CH$_2$N), 2.23–2.38 (m, 8 H, 2× CH_2CH_2CO), 2.90 (s, 6 H, 2× NCH_3), 3.41–3.59 (m, 4 H, 2× NCH_2, alkyl), 3.88–3.91 (m, 2 H, 2× CH), 4.50–4.66 (m, 4 H, 2× OCH_2), 5.78 (brt, J = 2.9 Hz, 2 H, 2× =CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) by difference spectrum reaction mixture and first fraction: δ = 23.48 (2× CH$_2$CH$_2$CO), 26.52 (CH$_2$CH_2), 27.96 (2× CH$_2$CH$_2$N or 2× CH$_3$ or 2× CH$_2$CO), 28.08 (2× CH$_2$CH$_2$N or 2× CH$_3$ or 2× CH$_2$CO), 38.96 (2× NCH_2, alkyl), 60.49 (2× CH), 63.88 (2× OCH_2), 127.49 (2× =CH), 156.73 (2× C=O, urea), 171.95 (2× C=O, ester), 172.30 (2× C=O, lactam) ppm. IR (NaCl) of the reaction mixture: $\tilde{\nu}_{max}$ = 1708 (C=O), 1733 (C=O), 1769 (C=O) cm^{-1}. MS: m/z (%) = 507 (100) $[M + H]^+$. Chromatography: R_f = 0.21 (EtOAc/Et_2O, 1:1). $C_{24}H_{34}N_4O_8$ (506.55): calcd. C 56.91, H 6.77, N 11.06; found C 57.14, H 6.88, N 10.73.

10,25-Dibenzyl-15,20-dioxa-1,8,10,25-tetraazatricyclo[22.2.1.1^{8,11}]-octacos-17-ene-9,14,21,26,27,28-hexaone (14b): Mixture of diastereomers. Yield 95%, 0.10 g, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28–1.43 (m, 4 H, CH_2CH_2), 1.56–1.74 (m, 4 H, 2× CH_2CH$_2$N), 2.14–2.41 (m, 8 H, 2× CH_2CH_2CO), 3.41–3.65 (m, 4 H, 2× NCH_2, alkyl), 3.78–3.81 (m, 2 H, 2× CH), 3.98 (dd, J = 15.3, 8.1 Hz, 2 H, 2× NCH_aH$_b$, benzyl), 4.54–4.72 (m, 4 H, 2× OCH_2), 5.00 (brd, J = 15.3 Hz, 2 H, 2× NCH$_a$$H_b$, benzyl), 5.79 (t, J = 2.8 Hz, 2 H, 2× =CH), 7.22–7.38 (m, 10 H, 10× CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.07 and 23.16 (2× CH$_2$CH$_2$CO), 26.55 (CH$_2$CH_2), 27.83 and 27.93 (2× CH$_2$CH$_2$N), 28.08 and 28.22 (2× CH$_2$CO), 39.04 and 39.16 (2× NCH_2, alkyl), 44.45 and 44.52 (2× NCH_2, benzyl), 57.38 and 57.47 (2× CH), 63.85 and 63.96 (2× OCH_2), 127.47 and 127.75 (2× =CH), 128.19, 128.32 and 128.34 (6× CH_{ar}), 129.03 (4× CH$_{ar}$), 135.47 (2× $C_{ar,quat.}$), 156.73 and 156.83 (2× C=O, urea), 172.00 and 172.12 (2× C=O, ester), 172.30 (2× C=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1708 (C=O), 1733 (C=O), 1768 (C=O) cm^{-1}. MS: m/z (%) = 659 (100) $[M + H]^+$. Chromatography: R_f = 0.6 (PE/EtOAc, 1:4). $C_{36}H_{42}N_4O_8$ (658.74): calcd. C 65.64, H 6.43, N 8.51; found C 65.79, H 6.76, N 8.15.

10,25-Bis(4-bromobenzyl)-15,20-dioxa-1,8,10,25-tetraazatricyclo-[22.2.1.1^{8,11}]octacos-17-ene-9,14,21,26,27,28-hexaone (14c): Yield (before TLC) 99%, 83 mg.

Diastereomer 1: Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.43 (m, 4 H, CH_2CH_2), 1.56–1.72 (m, 4 H, 2× CH_2CH$_2$N), 2.11–2.46 (m, 8 H, 2× CH_2CH_2CO), 3.43–3.52 (m, 2 H, 2× NCH_aH$_b$, alkyl), 3.55–3.66 (m, 2 H, 2× NCH$_a$$H_b$, alkyl), 3.76–3.80 (m, 2 H, 2× CH), 3.95 (d, J = 15.3 Hz, 2 H, 2× NCH_aH$_b$, benzyl), 4.57 (brd, J = 11.6 Hz, 2 H, 2× OCH_aH$_b$), 4.67 (brd, J = 11.6 Hz, 2 H, 2× OCH$_a$$H_b$), 4.92 (d, J = 15.3 Hz, 2 H, 2× NCH$_a$$H_b$, benzyl), 5.78 (t, J = 2.9 Hz, 2 H, 2× =CH), 7.12 (d, J = 8.3 Hz, 4 H, 4× CH_{ar}), 7.47 (d, J = 8.3 Hz, 4 H, 4× CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.05 (2× CH$_2$CH$_2$CO), 26.51 (CH$_2$CH_2), 27.77 (2× CH$_2$CH$_2$N or 2× CH$_2$CO), 28.17 (2× CH$_2$CH$_2$N or 2× CH$_2$CO), 39.19 (2× NCH_2, alkyl), 43.85 (2× NCH_2, benzyl), 57.50 (2× CH), 63.99 (2× OCH_2), 122.28 (2× $C_{ar,quat.}$), 127.72 (2× = CH), 130.07 (4× CH_{ar}), 132.21 (4× CH$_{ar}$), 134.47 (2× $C_{ar,quat.}$), 156.80 (2× C=O, urea), 172.12 (4× C=O, ester and lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1706 (C=O), 1733 (C=O), 1768 (C=O) cm^{-1}. Chromatography: R_f = 0.29 (PE/EtOAc, 1:1).

Diastereomer 2: Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.41 (m, 4 H, CH_2CH_2), 1.56–1.72 (m, 4 H, 2× CH_2CH$_2$N), 2.15–2.40 (m, 8 H, 2× CH_2CH_2CO), 3.45–3.62 (m, 4 H, 2× NCH_2, alkyl), 3.79 (t, J = 3.9 Hz, 2 H, 2× CH), 3.99 (d, J = 15.4 Hz, 2 H, 2× NCH_aH$_b$, benzyl), 4.59–4.60 (m, 4 H, 2× OCH_2), 4.91 (d, J = 15.4 Hz, 2 H, 2× NCH$_a$$H_b$, benzyl), 5.78 (brt, J = 2.8 Hz, 2 H, 2× =CH), 7.14 (d, J = 8.3 Hz, 4 H, 4× CH_{ar}), 7.48 (d, J = 8.3 Hz, 4 H, 4× CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.16 (2× CH$_2$CH$_2$CO), 26.46 (CH$_2$CH_2), 27.88 (2× CH$_2$CH$_2$N or 2× CH$_2$CO), 28.02 (2× CH$_2$CH$_2$N or 2× CH$_2$CO), 39.06 (2× NCH_2, alkyl), 43.96 (2× NCH_2, benzyl), 57.45 (2× CH), 63.90 (2× OCH_2), 122.28 (2× $C_{ar,quat.}$), 127.43 (2× =CH), 130.04 (4× CH_{ar}), 132.22 (4× CH_{ar}), 134.51 (2× $C_{ar,quat.}$), 156.71

(2× *C*=O, urea), 171.98 (2× *C*=O, ester), 172.12 (2× *C*=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1706 (C=O), 1733 (C=O), 1768 (C=O) cm^{-1}. Chromatography: R_f = 0.23 (PE/EtOAc, 1:1). MS: *m/z* (%) = 813/815/817 (100) $[M - H]^+$. $C_{36}H_{40}Br_2N_4O_8$ (816.53): calcd. C 52.95, H 4.94, N 6.86; found C 53.34, H 5.23, N 6.54.

12,27-Bis(4-chlorobenzyl)-17,22-dioxa-1,10,12,27-tetraazatricyclo-[24.2.1.1^{10,13}]triacont-19-ene-11,16,23,28,29,30-hexaone (14d): Mixture of diastereomers. Yield (before TLC) 99%, 39 mg. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.37 [m, 8 H, 2× $N(CH_2)_2(CH_2)_2$], 1.58–1.68 (m, 4 H, 2× NCH_2CH_2), 2.14–2.37 (m, 8 H, 2× CH_2CH_2CO), 3.43–3.55 (m, 2 H, 2× NCH_aH_b, alkyl), 3.52–3.66 (m, 2 H, 2× NCH_aH_b, alkyl), 3.80 (brs, 2 H, 2× *CH*), 3.99 (brd, *J* = 15.3 Hz, 2 H, 2× NCH_aH_b, benzyl), 4.47–4.71 (m, 4 H, 2× OCH_2), 4.94 (dd, *J* = 15.3, 2.6 Hz, 2 H, 2× NCH_aH_b, benzyl), 5.80 (t, *J* = 2.9 Hz, 2 H, 2× =CH), 7.19 (d, *J* = 7.8 Hz, 4 H, 4× CH_{ar}), 7.32 (d, *J* = 7.8 Hz, 4 H, 4× CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.02 (2× CH_2CH), 26.87 [2× $N(CH_2)_3CH_2$], 27.81 (2× NCH_2CH_2 or 2× CH_2CO), 27.97 (2× NCH_2CH_2 or 2× CH_2CO), 29.19 [2× $N(CH_2)_2CH_2$], 39.30 (2× NCH_2, alkyl), 43.94 (2× NCH_2, benzyl), 57.54 (2× *C*H), 64.21 (2× OCH_2), 127.79 (2× =*C*H), 129.35 (4× CH_{ar}), 129.82 (4× CH_{ar}), 134.08 (2× $C_{ar,quat.}$), 134.29 (2× $C_{ar,quat.}$), 156.89 (2× *C*=O, urea), 172.10 (4× *C*=O, lactam and ester) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1707 (C=O), 1735 (C=O), 1769 (C=O) cm^{-1}. MS: *m/z* (%) = 755/757/759 (100) $[M + H]^+$. Chromatography: R_f = 0.3 (PE/EtOAc, 1:1). $C_{38}H_{44}Cl_2N_4O_8$ (755.68): calcd. C 60.40, H 5.87, N 7.41; found C 60.76, H 6.14, N 7.12.

12,27-Bis(4-bromobenzyl)-17,22-dioxa-1,10,12,27-tetraazatricyclo-[24.2.1.1^{10,13}]triacont-19-ene-11,16,23,28,29,30-hexaone (14e): One diastereomer. Yield (before TLC) 99%, 0.12 g, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.37 [m, 8 H, 2× $N(CH_2)_2(CH_2)_2$], 1.57–1.69 (m, 4 H, 2× NCH_2CH_2), 2.14–2.35 (m, 8 H, 2× CH_2CH_2CO), 3.43–3.52 (m, 2 H, 2× NCH_aH_b, alkyl), 3.55–3.64 (m, 2 H, 2× NCH_aH_b, alkyl), 3.80 (brs, 2 H, 2× *CH*), 3.97 (brd, *J* = 15.2 Hz, 2 H, 2× NCH_aH_b, benzyl), 4.47–4.70 (m, 4 H, 2× OCH_2), 4.92 (dd, *J* = 15.2, 2.3 Hz, 2 H, 2× NCH_aH_b, benzyl), 5.80 (t, *J* = 2.9 Hz, 2 H, 2× =CH), 7.13 (d, *J* = 8.4 Hz, 4 H, 4× CH_{ar}), 7.47 (d, *J* = 8.4 Hz, 4 H, 4× CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.89 (2× CH_2CH), 26.77 [2× $N(CH_2)_3CH_2$], 27.71 (2× NCH_2CH_2 or 2× CH_2CO), 27.86 (2× NCH_2CH_2 or 2× CH_2CO), 29.09 [2× $N(CH_2)_2CH_2$], 39.19 (2× NCH_2, alkyl), 43.87 (2× NCH_2, benzyl), 57.42 (2× *C*H), 64.11 (2× OCH_2), 122.28 (2× $C_{ar,quat.}$), 127.67 (2× =*C*H), 130.04 (4× CH_{ar}), 132.21 (4× CH_{ar}), 134.47 (2× $C_{ar,quat.}$), 156.77 (2× *C*=O, urea), 171.98 (4× *C*=O, lactam and ester) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1710 (C=O), 1737 (C=O), 1769 (C=O) cm^{-1}. MS: *m/z* (%) = 843/845/847 (100) $[M + H]^+$. Chromatography: R_f = 0.35 (PE/EtOAc, 1:1). $C_{38}H_{44}Br_2N_4O_8$ (844.59): calcd. C 54.04, H 5.25, N 6.63; found C 54.31, H 5.48, N 6.25.

16,31-Dibenzyl-21,26-dioxa-1,14,16,31-tetraazatricyclo-[28.2.1.1^{14,17}]tetratriacont-23-ene-15,20,27,32,33,34-hexaone (14f): Mixture of diastereomers. Yield (before TLC) 99%, 54 mg, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.34 [m, 16 H, 2× $N(CH_2)_2(CH_2)_4$], 1.59–1.69 (m, 4 H, 2× CH_2CH_2N), 2.14–2.33 (m, 8 H, 2× CH_2CH_2CO), 3.45–3.63 (m, 4 H, 2× NCH_2), 3.79–3.81 (m, 2 H, 2× *CH*), 4.08 (d, *J* = 15.1 Hz, 2 H, 2× NCH_aH_b, benzyl), 4.49–4.67 (m, 4 H, 2× OCH_2), 5.00 (brd, *J* = 15.1 Hz, 2 H, 2× NCH_aH_b, benzyl), 5.81 (t, *J* = 2.8 Hz, 2 H, 2× =CH), 7.23–7.37 (m, 10 H, 10× CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.08 (2× CH_2CH), 26.47 [2× $N(CH_2)_2CH_2$], 27.67 (2× CH_2CO), 27.88 (2× CH_2CH_2N), 28.98 [2× $N(CH_2)_3CH_2$], 29.02 and 29.12 [2× $N(CH_2)_4(CH_2)_2$], 39.09 (2× NCH_2, alkyl), 44.61 (2× NCH_2, benzyl), 57.35 (2× *C*H), 64.22 (2× OCH_2), 128.06 and 128.26 (2× =*C*H), 128.38 and 129.10 (10× CH_{ar}), 135.55 (2× $C_{ar,quat.}$), 156.92 (2× *C*=O, urea), 171.96 (2× *C*=O, ester), 172.30 (2× *C*=O, lactam) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 1709 (C=O), 1736 (C=O), 1769 (C=O) cm^{-1}. MS: *m/z* (%) = 743 (100) $[M + H]^+$. Chromatography: R_f = 0.3 (PE/EtOAc, 1:1). $C_{42}H_{54}N_4O_8$ (742.90): calcd. C 67.90, H 7.33, N 7.54; found C 68.17, H 7.55, N 7.28.

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