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Synthesis of *N*(3),*N*′(3)-Polymethylene-bis-hydantoins and Their Macrocyclic Derivatives

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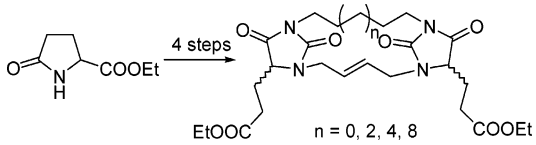

An efficient and straightforward two-step approach toward *N*(3),*N*′(3)-polymethylene-bis-hydantoins was developed. As a first step, a pyroglutamate is reacted with a diisocyanate to produce a bis-carbamoyllactam. The second step is a double-ring transformation by treatment of this bis-carbamoyllactam with KO*t*Bu in ethanol. In this fashion N(3),N′(3)-polymethylene-bis-hydantoins are produced in two quantitative steps and under very mild conditions. When properly derivatized, these compounds can be converted to their macrocyclic derivatives upon treatment with 5 mol % of second-generation Grubbs' catalyst. These macrocyclic derivatives are so far not described in the literature. It was proven that exclusively (*E*)-isomers are formed.

Introduction

The exploration of privileged structures in drug discovery has gained significant popularity in pharmaceutical chemistry over the years. Hydantoins (or imidazolidine-2,4-diones, **1**) have been extensively studied and are reported to possess a wide range of biological activities (Figure 1). Phenetoin (5,5-diphenylhydantoin, **2**), for example, was already synthesized in 1908[1] and is now still the drug of choice for the treatment of certain types of epileptic seizures.[2] They have proven useful not only in human medicine (antiarrhythmic,[3] anticonvulsant,[4] antitumor,[5] antidiabetic,[6] and antimuscarinic activity,[7] etc.) but also in the agrochemical sector (herbicidal and fungicidal activity).[8] In recent years, many new synthetic approaches have been developed toward this interesting heterocycle.[9−15]

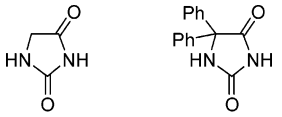

FIGURE 1. Hydantoin nucleus **1** and phenetoin **2**.

Recently, we described the pyroglutamate−hydantoin rearrangement.[16] It was found that treating pyroglutamates **3** with NaH in the presence of isocyanates or isothiocyanates in THF

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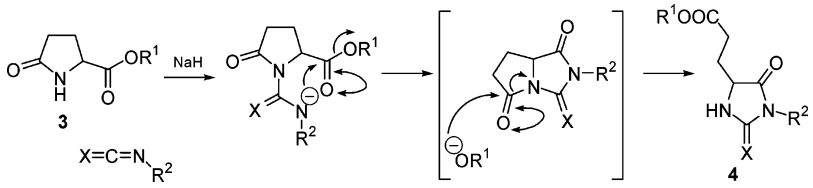
SCHEME 1



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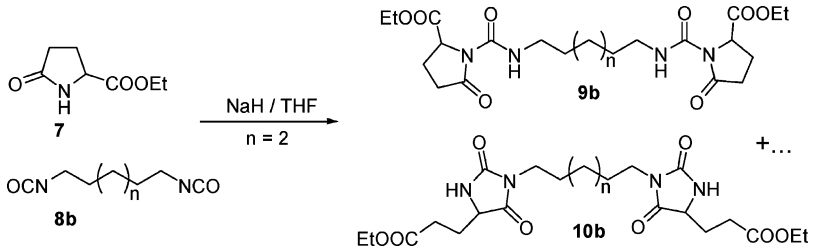


produces hydantoins **4** in high yield via a ring-closing−ring-opening sequence (Scheme 1).

In this paper, we disclose the application of this ring transformation for the synthesis of *N*(3),*N*′(3)-polymethylene-bis-hydantoins. Several of these bis-hydantoins **5** have been evaluated as hexamethylenebis(acetamide) analogues (HMBA, **6**) (Figure 2). HMBA is an agent that induces differentiation of certain types of tumor cells to nonmalignant phenotypes. This implies that it works not by killing the cancer cells but by inducing them to differentiate and to express characteristics of the normal nontransformed counterpart. This is a promising approach to cancer therapy, potentially without many of the disadvantages of cytotoxic agents. HMBA has even had some modest success in clinical trials. The doses required to achieve sufficient blood levels in human patients, however, led to some undesirable side effects. It was found that compounds **5a** and **5d** were 10 times more potent than HMBA itself, but the activity of **5b** however was low, probably due to its insolubility.[17−19] Compound **5c** was found to show antiepileptic activity in the maximal electroshock seizure test.[20]

The synthesis of these compounds usually involves the reaction of a hydantoin with a *ω*-dihaloalkane under basic conditions. The problem with this reaction is the need for N(3)-selective alkylation and the yield which is usually quite low. Starting from pyroglutamates would avoid the problem of N(3)-selectivity and also allows the synthesis of highly functionalized derivatives since pyroglutamates can easily be derivatized.[16,21−24]

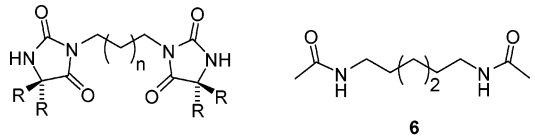
Results and Discussion

Following our protocol for the ring transformation of pyroglutamates, a mixture of ethylpyroglutamate **7** and diisocyanate **8b** in THF was treated with NaH (Scheme 2). It was found, however, that a mixture of compounds was obtained. Besides the desired compound **10b**, the dicarbamoyllactam **9b** was observed in the ^{1}H NMR of the crude reaction mixture accompanied by a variety of compounds probably resulting from the attack of the formed alkoxide anion on the second isocyanate after reaction with the first isocyanate functionality.

To avoid these undesired reactions, it seemed necessary to make a short synthetic detour. Previous observations had shown that the formed sodium salt of the carbamoylated lactam precipitates from diethyl ether, effectively preventing it from reacting further.[25] Thus, it would be possible to isolate the carbamoylated intermediate and attempt the ring transformation in a separate step. As expected, the double sodium salts **11** precipitates from solution after treating a mixture of **7** and **8** with NaH in ether and provided derivatives **9** in quantitative yield and good purity after acidic workup (Scheme 3).

The double-ring transformation from **9** to **10** did not proceed as smoothly as anticipated. Treatment of **9** with strong bases such as NaH and KO-*t*-Bu in THF at room temperature or at reflux did not result in the desired conversion. Switching to ethanol as a solvent in combination with NaOH or KO-*t*-Bu as a base however, resulted in clean and complete double transformation to the bis-hydantoins **10** within 1 h at room temperature (Scheme 4). Derivatives **10** are obtained as a viscous oil after acidic workup but can be crystallized from THF to afford white powders.

Special attention is required when distinguishing between 1-carbamoyl-2-pyrrolidines **9** and hydantoins **10**. Indeed, from their structures it is obvious that straightforward ^{1}H NMR and



5a n = 4, R = Me
5b n = 4, R = Ph
5c n = 0, R = Ph
5d n = 3, R = Me

FIGURE 2. Bis-hydantoins **5** and HMBA **6**.

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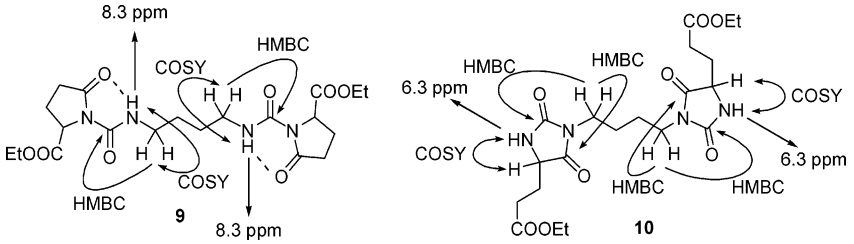

FIGURE 3. Most important COSY and HMBC couplings in **9a** and **10a**.

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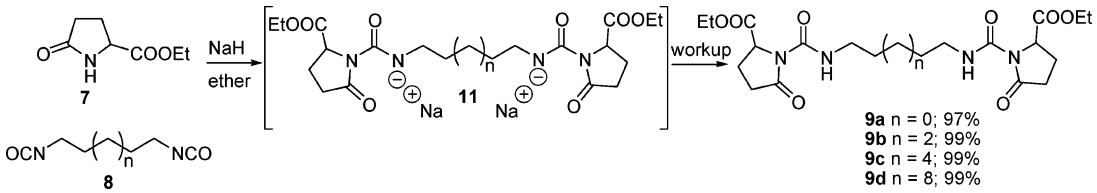

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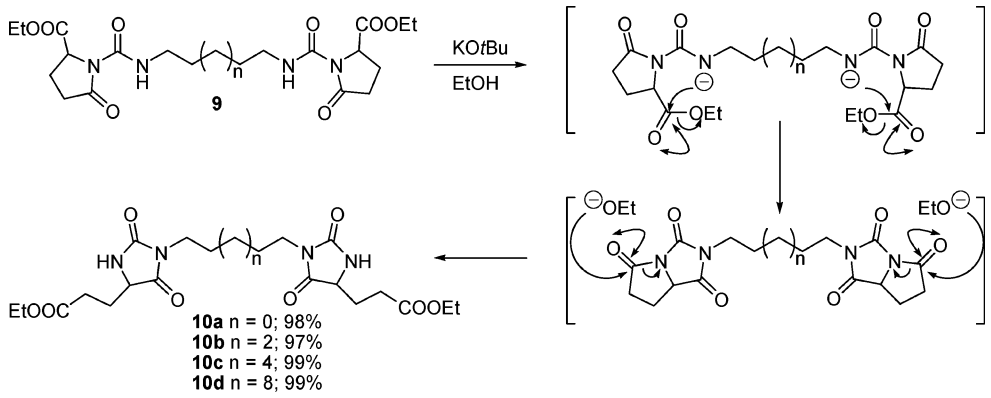

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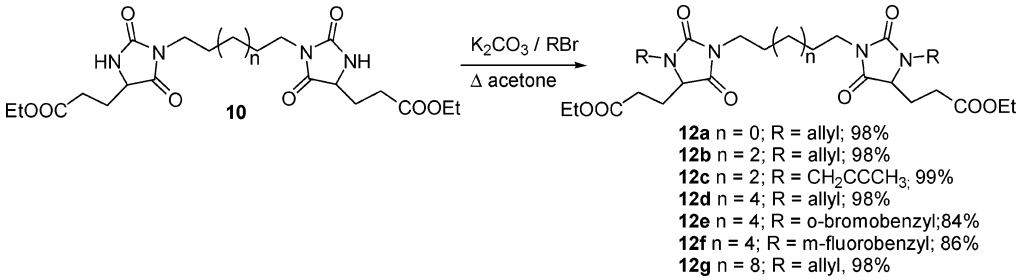

^{13}C NMR measurements are not sufficient to distinguish between the two. However, having both compounds in hand, two-dimensional spectroscopy clearly allowed the unambiguous determination (Figure 3). In the case of **9**, there is a coupling in the COSY spectrum between the NH protons and the CH_2 next to the nitrogen. On the other hand, the NH protons of **10** show a coupling to the proton next to the carbonyl and not to the CH_2, proving that this methylene is connected to a tertiary nitrogen. Furthermore, the protons of the CH_2 next to nitrogen of **9** only couple to the urea carbonyl in the HMBC (heteronuclear multiple bound correlation) spectrum, whereas in the case of **10** they couple to both the urea and the lactam carbonyl. Another distinctive feature is the shift of the NH-protons. Intramolecular hydrogen bridge formation in **9** to the lactam carbonyl causes a downfield shift, resulting in a typical value of 8.3 ppm, whereas the value in the case of **10** is typically around 6.3 ppm.

As we reported before, the hydantoins can easily be further functionalized by refluxing in acetone with a proper electrophile in the presence of finely ground K_2CO_3.[16] The same conditions proved to work perfectly on the dimers, and in this fashion several derivatives could be prepared in near-quantitative yields (Scheme 5). The only losses occur during purification by flash chromatography, which is only necessary to remove the excess of electrophile in the case of **12e** and **12f**. For all other derivatives, it is sufficient to filter off the solids and evaporate the volatiles in vacuo.

One of the challenges of medicinal chemistry is the enhancement of the affinity of a given ligand for its target by decreasing its degrees of freedom, thereby reducing the cost in entropy. To prevent free rotation around the central polymethylene axis, we wanted to evaluate the possibility to use ring-closing metathesis (RCM) for the macrocyclization of derivatives

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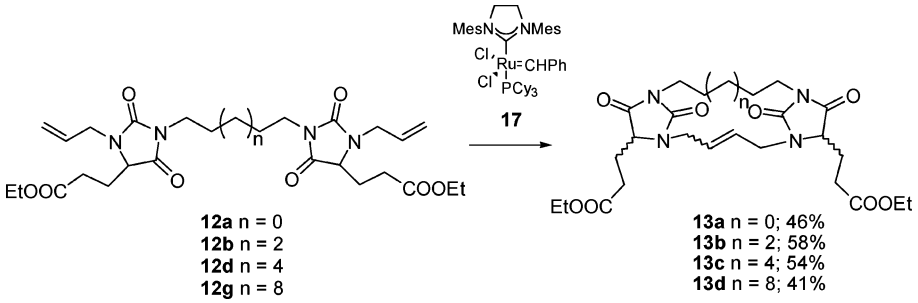

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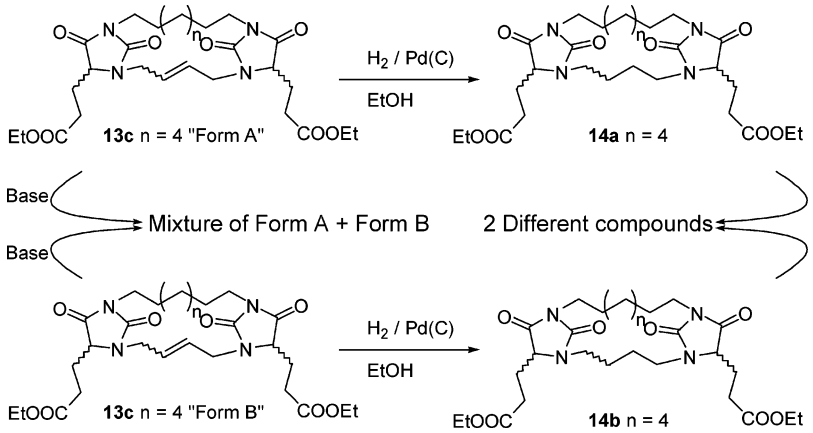

12a,**b**,**d**,**g**.[26,27] Fürstner and co-workers have proven that substrates devoid of any conformational constraints can be efficiently cyclized by RCM to macrocyclic products and that neither the conformational predisposition nor the ring size formed is a major concern. The decisive parameters are the presence of polar relay substituents, their proper distance to the alkene groups, and the low steric hindrance close to the double bonds.[28] Since all of these requirements are met in these substrates, macrocyclization was expected to pose no special problems. Indeed, it was found that treating derivatives **12a**,**b**,**d**,**g** with a catalytic amount of the second-generation Grubbs' catalyst **17** (5 mol %) resulted in quantitative conversion to macrocyclic derivatives **13** after 16 h of reflux in CH_2Cl_2 (Scheme 6). A significant drop in yield, however, was observed during purification by flash chromatography, probably caused by the high polarity of these compounds.

It is known that when using RCM as a macrocyclization method, usually (*E*,*Z*) mixtures of cyclized compounds are formed. In this case, two separate signals (1:1 ratio) were observed for the alkene protons of derivatives **13**. This, however, does not mean that an (*E*,*Z*) mixture is formed, since in this particular case, both **12** and **13** have two racemic centers and, thus, the two observed signals could belong to another diastereoisomer. Moreover, $^3J_{HH}$ coupling constants, which are normally used to distinguish *trans* and *cis* isomers, are absent since the macrocycles are symmetrical entities and as a consequence the two alkene protons do not couple with each other. They appear as small triplets. It was, however, possible to separate the two forms of compound **13c** by flash chromatography. Now it was possible to prove whether form A and form B were diastereoisomers or (*E*,*Z*)-isomers. First, it was observed that treatment with base of one form of **13c** resulted in equilibration to the mixture of both forms (Scheme 7). Second, hydrogenation of form A and form B gave two different compounds. This can only be the case if the two compounds were diastereoisomers since the (*E*,*Z*)-isomers should have produced the same hydrogenation product.

The question rose whether the *trans*- or *cis*-fused cycles were produced. The presence of only one isomer around the double bound can be explained by secondary metathesis reactions. In a kinetic study, Grubbs has proven that macrocycles isomerize to produce a thermodynamically controlled (*E*/*Z*) ratio regardless the stereochemistry of the initial alkene.[29] Although usually a mixture of both isomers is isolated, Fürstner has already reported that only the (*E*)-isomer is formed in some cases.[30] A stereoselective approach to macrocyclic (*E*)- and (*Z*)-isomers is possible using ring-closing alkyne metathesis (RCAM).[31] In the first case, the macrocyclic alkyne is converted to the (*E*)-isomer

(26) For our previous work on using RCM for the synthesis of azaheterocycles, see: (a) Dieltiens, N.; Stevens, C. V.; De Vos, D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.*, **2004**, *45*, 8995−8998. (b) Dieltiens, N.; Stevens, C. V.; Allaert, B.; Verpoort, F. *Arkivoc* **2005**, *i*, 92−97.

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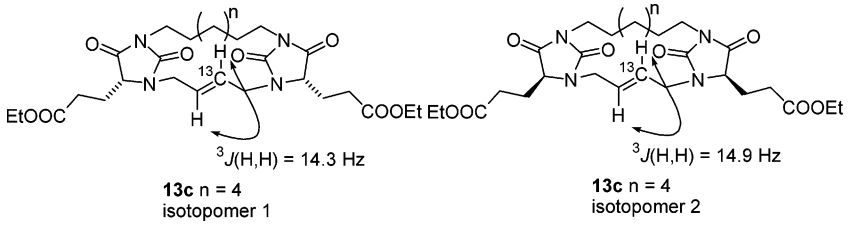
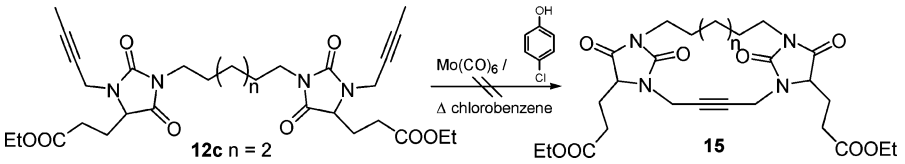


FIGURE 5. $^3J_{H,H}$ coupling of the ^{13}C satellites of both isotopomers of **13c**.

SCHEME 8



by *trans*-selective hydrosilylation and subsequent protodesilylation.[32] In the second case, the macrocyclic alkyne is converted to the (*Z*)-isomer by Lindlar reduction.[33] In this perspective, derivative **12c** was prepared and was treated with a mixture of $Mo(CO)_6$ and *p*-chlorophenol as an "instant" catalyst system under an Ar atmosphere (Scheme 8).[34] Unfortunately, even after prolonged reaction times only starting material could be recovered.

In a further attempt to selectively synthesize the *trans*- and the *cis*-isomer, derivative **10c** was refluxed in two separate experiments with *trans*-1,4-dichloro-2-butene and *cis*-1,4-dichloro-2-butene. Only in the second case was some reaction observed, resulting in a mixture that was tentatively identified as a mixture of starting material, monoalkylated material, and cyclized material (<10%). The last two components proved impossible to separate, but a ^{13}C-spectrum of this mixture proved it to be different from compound **13c**, suggesting that the macrocycles produced by RCM are in the *trans*-geometry. The fact that these derivatives are so difficult to cyclize again proves the importance of RCM as the macrocyclization method and of the functional group as an essential relay in order to accomplish this.[35] Probably chelation complexes of type **16** are formed during metathesis, effectively bringing the two alkene moieties in the correct position (Figure 4).

A more decisive confirmation of the *trans*-geometry was obtained by looking at the ^{13}C satellites of the alkene protons of one pair of enantiomers of **13c** (Figure 5).[36] When one of the two alkene carbon atoms is a ^{13}C-isotope, the symmetry is lost due to the presence of a magnetically active ^{13}C in place of an inactive ^{12}C. In this case, the two isotopomers give two separate signals (br d, 5.14 ppm, 14.3 Hz and br d, 5.12 ppm, 14.9 Hz). They are not each others mirror image because of the two other chiral centers. A $^3J_{H,H}$ coupling of 14.3 and 14.9 Hz is observed, pointing to the *trans*-geometry.[37]

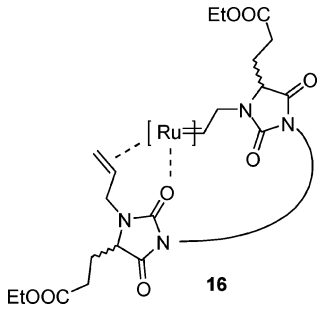


FIGURE 4. Possible chelation complex formed during metathesis.

Conclusions

A short and high-yield approach was developed to *N*(3),*N*′-(3)-polymethylene-bis-hydantoins. This two-step approach consists of carbamoylation of a pyroglutamate and subsequent double-ring transformation. After proper functionalization, these dimers can be cyclized by ring-closing metathesis using the second-generation Grubbs' catalyst. It was proven that only the *trans*-isomers are isolated.

Experimental Section

1. Synthesis of Derivatives 9. As a representative example, the synthesis of ethyl 1-({[4-({[2-(ethoxycarbonyl)-5-oxopyrrolidin-1-yl]carbonyl}amino)butyl]amino}carbonyl)-5-oxopyrrolidine-2-carboxylate **9a** is described. Ethyl pyroglutamate **7** (5 g, 31.8 mmol) was dissolved in diethyl ether (100 mL, freshly distilled from Na metal) and kept under a positive N_2-pressure. To this solution was added 1,4-diisocyanatobutane (2.23 g, 15.9 mmol) followed by NaH (0.92 g, 38.2 mmol, washed with hexanes). The reaction was allowed to stir under nitrogen atmosphere at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl until the pH was neutral. The mixture was extracted with EtOAc, and the organics were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo. Compound **9a** was obtained as a viscous oil in quantitative yield.

Ethyl 1-({[4-({[2-(ethoxycarbonyl)-5-oxopyrrolidin-1-yl]carbonyl}amino)butyl]amino}carbonyl)-5-oxopyrrolidine-2-carboxylate 9a: ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (6H, t, J = 7.2 Hz), 1.60 (4H, t, J = 3.0 Hz), 2.00−2.10 (2H, m), 2.25−2.45 (2H, m), 2.57 (2H, ddd, J = 17.6 Hz, J = 3.4 Hz, J = 9.5 Hz), 2.74 (2H, ddd, J = 17.6 Hz, J = 9.9 Hz, J = 9.9 Hz), 3.23−3.40 (4H,

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(36) For clarity the diastereoisomer with the two ester groups in a *cis* position is depicted.

(37) For articles concerning the recovery of $^3J_{H,H}$, see: (a) Mucci, A.; Parenti, F.; Schenetti, L. *Eur. J. Org. Chem.* **2002**, 938−940. (b) Janssen, C. E.; Krause, N. *Eur. J. Org. Chem.* **2005**, 2322−2329.

m), 4.24 (4H, q, $J = 7.2$ Hz), 4.77 (2H, dd, $J = 9.5$ Hz, $J = 2.6$ Hz), 8.31 (2H, t, $J = 5.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 21.3, 27.0, 31.9, 39.5, 58.2, 61.7, 152.3, 171.5, 176.5; IR (NaCl, cm^{-1}) ν_{max} 1694 (C═O), 1721 (br C═O), 3317 (NH); MS (70 eV) *m*/*z* 455.7 ($M^+ + 1$, 100); HRMS calcd for $C_{20}H_{30}N_4O_8$ ($M + H^+$) 455.2136, found 455.2148.

2. Synthesis of Derivatives 10. As a representative example, the synthesis of 3-(1-{4-[4-(2-ethoxycarbonylethyl)-2,5-dioxoimidazolidin-1-yl]butyl}-2,5-dioxoimidazolidin-4-yl)propionic acid ethyl ester **10a** is described. Compound **9a** (7.23 g, 15.9 mmol) was dissolved in absolute ethanol (75 mL) and kept under a positive N_2 pressure. To this solution was added KO-*t*-Bu (3.92 g, 35 mmol). The reaction was allowed to stir under nitrogen atmosphere at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous oxalic acid until the pH was acidic. The ethanol was removed in vacuo, and the residue was extracted with EtOAc, the organics were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo. For the crystallization, the product was dissolved in a minimal amount of boiling THF and hexane was added until the solution remained cloudy. The flask was put in the freezer and afterward the solids were filtered. This procedure was repeated until no more precipitate was formed. Compound **10a** was obtained in quantitative yield.

3-(1-{4-[4-(2-Ethoxycarbonylethyl)-2,5-dioxoimidazolidin-1-yl]butyl}-2,5-dioxoimidazolidin-4-yl)propionic acid ethyl ester 10a: white powder; mp 124−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (6H, t, $J = 7.2$ Hz), 1.63 (4H, br s), 2.03 (2H, ddt, $J = 13.9$ Hz, $J = 7.2$ Hz, $J = 7.3$ Hz), 2.20 (2H, ddt, $J = 13.9$ Hz, $J = 7.3$ Hz, $J = 6.3$ Hz), 2.47 (2H, t, $J = 7.3$ Hz), 3.52 (4H, br s), 4.14 (4H, q, $J = 7.2$ Hz), 4.10 (2H, dd, $J = 7.2$ Hz, $J = 6.3$ Hz), 6.29 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 25.2, 26.9, 29.9, 38.0, 56.4, 61.1, 157.4, 172.9, 173.7; IR (KBr, cm^{-1}) ν_{max} 1713 (br C═O), 1764 (C═O), 3249 (NH); MS (70 eV) *m*/*z* 455.7 ($M^+ + 1$, 100); HRMS calcd for $C_{20}H_{30}N_4O_8$ ($M + H^+$) 455.2136, found 455.2148.

3. Synthesis of Derivatives 12. As a representative example, the synthesis of 3-(3-allyl-1-{4-[3-allyl-4-(2-ethoxycarbonylethyl)-2,5-dioxoimidazolidin-1-yl]butyl}-2,5-dioxoimidazolidin-4-yl)propionic acid ethyl ester **12a** is described. Compound **10a** (7.23 g, 15.9 mmol) was dissolved in acetone (75 mL). To this solution were added K_2CO_3 (11 g, 79.5 mmol) and allyl bromide (7.70 g, 63.6 mmol). This mixture was refluxed until TLC showed complete consumption of the starting material. The mixture was filtered, and the solvent was removed in vacuo. Compound **12a** was obtained as a viscous oil in quantitative yield.

3-(3-Allyl-1-{4-[3-allyl-4-(2-ethoxycarbonylethyl)-2,5-dioxoimidazolidin-1-yl]butyl}-2,5-dioxoimidazolidin-4-yl)propionic acid ethyl ester 12a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (6H, t, $J = 7.2$ Hz), 1.64 (4H, br s), 2.00−2.12 (2H, m), 2.18−2.42 (6H, m), 3.53 (4H, br s), 3.62 (2H, dd, $J = 15.7$ Hz, $J = 7.4$ Hz), 4.01 (2H, dd, $J = 3.0$ Hz, $J = 6.6$ Hz), 4.13 (4H, q, $J = 7.2$ Hz), 4.34 (2H, dd, $J = 15.7$ Hz, $J = 5.0$ Hz), 5.24 (2H, d, $J = 4.7$ Hz), 5.28 (2H, s), 5.70−5.83 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 23.8, 25.3, 28.2, 38.3, 43.5, 57.8, 60.9, 119.5, 131.8, 156.3, 172.4, 172.6; IR (NaCl, cm^{-1}) ν_{max} 1645 (C═C), 1709 (br C═O), 1769 (C═O); MS (70 eV) *m*/*z* 535.7 ($M^+ + 1$, 100); HRMS calcd for $C_{26}H_{38}N_4O_8$ ($M + H^+$) 535.2762, found 535.2769.

4. Synthesis of Derivatives 13. As a representative example, the synthesis of 3-[18-(2-ethoxycarbonylethyl)-8,17,19,20-tetraoxo-1,6,9,16-tetraazatricyclo[14.2.1.1^{6,9}]icos-3-en-7-yl]propionic acid ethyl ester **13b** is described. Compound **12b** (0.2 g, 0.36 mmol) was dissolved in CH_2Cl_2 (20 mL, freshly distilled from CaH_2), and the second-generation Grubbs' catalyst (0.015 g, 0.018 mmol) was added. The reaction was allowed to reflux for 16 h under a N_2 atmosphere. The product was coated on silica gel by removal of the solvent in vacuo and purified by flash chromatography (silica gel; hexane/EtOAc). Compound **13a** is obtained as a 1:1 mixture of the two diastereoisomers (combined yield 46%) which can be separated and obtained as viscous oils.

3-[18-(2-Ethoxycarbonylethyl)-8,17,19,20-tetraoxo-1,6,9,16-tetraazatricyclo[14.2.1.1^{6,9}]icos-3-en-7-yl]propionic acid ethyl ester 13b, diastereoisomer 1: TLC R_f 0.42 (petroleum ether/ethyl acetate, 2:8); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.30 (4H, m), 1.24 (6H, t, $J = 7.2$ Hz), 1.62−1.74 (4H, m), 2.00−2.16 (2H, m), 2.17−2.52 (6H, m), 3.43−3.49 (4H, m), 3.57 (2H, ddd, $J = 13.8$ Hz, $J = 6.3$ Hz, $J = 3.9$ Hz), 4.04 (2H, dd, $J = 2.9$ Hz, $J = 6.5$ Hz), 4.11 (4H, q, $J = 7.2$ Hz), 4.35 (2H, d, $J = 16.0$ Hz), 5.35 (2H, t, $J = 2.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.6, 27.5, 27.8, 28.5, 39.6, 41.8, 57.7, 60.9, 126.3, 157.0, 172.6, 172.7; IR (NaCl, cm^{-1}) ν_{max}: 1709 (C═O), 1769 (C═O); MS (70 eV) *m*/*z* 535.2 ($M^+ + 1$, 100); HRMS calcd for $C_{26}H_{38}N_4O_8$ ($M + H^+$) 535.2762, found 535.2772.

Diastereoisomer 2: TLC R_f 0.38 (petroleum ether/ethyl acetate, 2:8); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.35 (4H, m), 1.26 (6H, t, $J = 7.2$ Hz), 1.58−1.75 (4H, m), 1.97−2.09 (2H, m), 2.13−2.55 (6H, m), 3.43−3.49 (4H, m), 3.48 (2H, ddd, $J = 13.3$ Hz, $J = 6.4$ Hz, $J = 3.8$ Hz), 3.58 (2H, ddd, $J = 13.3$ Hz, $J = 3.9$ Hz, $J = 3.8$ Hz), 3.68 (2H, dt, $J = 16.2$ Hz, $J = 2.4$ Hz), 4.04 (2H, dd, $J = 3.6$ Hz, $J = 7.2$ Hz), 4.09 (2H, d, $J = 16.2$ Hz), 4.14 (4H, q, $J = 7.2$ Hz), 5.63 (2H, t, $J = 2.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 24.3, 26.8, 27.6, 28.6, 38.9, 42.4, 58.1, 60.9, 128.2, 156.9, 172.7, 173.0; IR (NaCl, cm^{-1}) ν_{max} 1709 (C═O), 1768 (C═O); MS (70 eV) *m*/*z* 535.2 ($M^+ + 1$, 100); HRMS calcd for $C_{26}H_{38}N_4O_8$ ($M + H^+$) 535.2762, found 535.2779.

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Supporting Information Available: General information and spectroscopic data of all compounds synthesized with complete peak assignment. Copies of the ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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