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The Pyroglutamate Hydantoin Rearrangement

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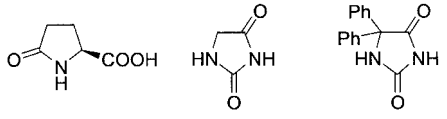
When a mixture of a pyroglutamate and an isocyanate in THF is treated with NaH, a ring transformation occurs leading to functionalised hydantoins. The novel reaction involves a ring-closing ring-opening sequence providing a new and straightforward access to an interesting class of heterocyclic compounds. Furthermore, starting from pyroglutamates allows the synthesis of highly substituted hydantoins under very mild conditions. This ring transformation in combination with ring-closing metathesis is used in a four-step reaction sequence for the synthesis of multi-functionalised bicyclic hydantoin derivatives.

Introduction

Pyroglutamates and their transformations have received a lot of attention over the years because of their importance in several domains. Pyroglutamic acid (**1**) (Figure 1) is a very useful and versatile starting material for the synthesis of both natural and unnatural products.[1] Intensive study of glutamate analogues resulted in specific inhibitors of different receptor types of the mammalian central nervous system.[2,3] It has also been used for the synthesis of pyrrolidine alkaloids,[4,5] kainoids,[6] (–)-bulgecinine,[7] (–)-domoic acid,[8] enantiomerically pure glycine and proline derivatives,[9] a wide variety of non-proteinogenic amino acids,[10] etc. During the last decade, hydantoins (or imidazolidine-2,4-diones, **2**) have been extensively studied and are reported to possess a wide range of biological activities. Phenetoin (5,5-diphenylhydantoin, **3**) for example was already synthesised in 1908[11] and is now still the drug of choice for the treatment of certain types of epileptic seizures.[12] They have not only proven useful in human medicine (antiarrhytmic,[13] anticonvulsant,[14,15] antitumour,[16] antidiabetic,[17,18] antimuscarinic,[19] ... activity), but also in the agrochemical sector (herbicidal and fungicidal activity).[20] In recent years many new synthetic approaches have been developed towards this interesting heterocycle.[21–27] In this article we wish to report on the single-step transformation of pyroglutamates to hydantoins, and the use of this ring transformation in combination with ring-closing metathesis for the synthesis of heavily substituted bicyclic hydantoin derivatives.



1 2 3

Figure 1. Pyroglutamic acid (**1**), the hydantoin nucleus (**2**) and phenetoin (**3**).

Results and Discussion

The Pyroglutamate Hydantoin Rearrangement

During our research on pyroglutamates for the development of agrochemicals and pharmaceutically interesting azaheterocyclic skeletons, we found that when the sodium salt of an alkyl pyroglutamate **4** is treated with 1 equivalent of an isocyanate, reaction occurs both on the N atom and on the C2 atom resulting in a complex mixture of different compounds. However, when a mixture of **4** with an isocyanate is treated with NaH in diethyl ether, a precipitate is formed during the reaction, which after workup proved to be the sodium salt of the expected carbamoyllactam **5** in high purity (Scheme 1). On the other hand, if the reaction is performed in THF no precipitate is formed, and after workup a compound was isolated which gave a different but very similar ^{1}H NMR spectrum. It was assumed that intermediate **5** (Scheme 1), which is apparently soluble in THF, reacts intramolecularly by a nucleophilic attack on

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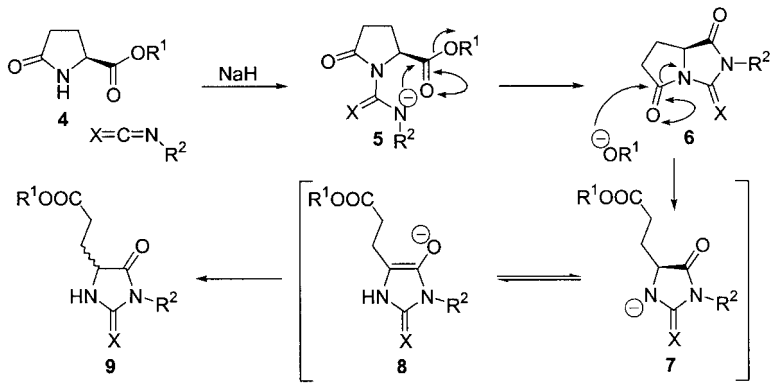


Scheme 1.

the carbonyl of the ester function followed by expulsion of an alkoxide anion resulting in the formation of the bicyclic intermediate **6**. The alkoxide anion in turn can open this bicyclic intermediate with formation of the anions **7** and **8**. These anions are in equilibrium with each other, causing racemisation of the chiral centre (this was proven by quenching the reaction with D_2O). Upon work up this resulted in the hydantoin derivatives **9** as a 1:1 mixture of its enantiomers.

In contrast, the isolated carbamoyllactams **10** (R^1 = Et, R^2 = Bn) and **11** (R^1 = Et, R^2 = Ph)[28] are still optically active. Because we now had both the carbamoyllactam **10** and the hydantoin derivative **9e** in hand, it was easy to compare all the spectroscopic data. From their structures it is obvious that they would have very similar ^{1}H NMR and ^{13}C NMR spectra, hence no conclusions could be made judging these spectra alone. The decisive proof was given by comparing both COSY (Correlated Spectroscopy) and HMBC (Heteronuclear Multiple Bound Correlation) coupled spectra (Figure 2). In the case of **10**, there is a coupling in the COSY spectrum between the proton on the N atom and the two protons of the benzyl group, the proton on nitrogen appears as an incompletely resolved triplet. In the case of **9e**, however, the proton on the N atom couples with the proton next to the carbonyl and not with the protons of the benzyl group, proving that the benzyl group is attached to a tertiary nitrogen. Furthermore, in the HMBC spectrum, the protons of the benzyl group of **10** only couple to the urea carbonyl (easily distinguishable from both other carbonyl groups), whereas in the case of **9e** they couple to both the urea and the lactam carbonyl.

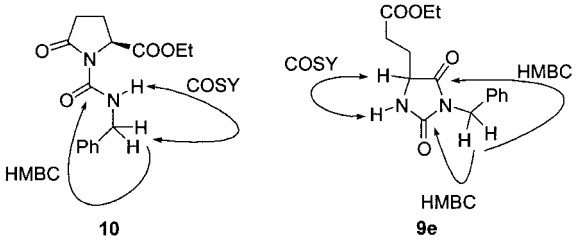
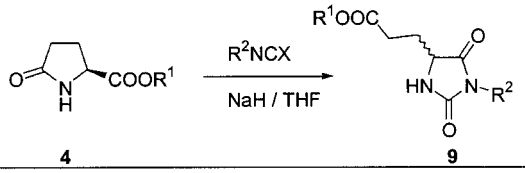
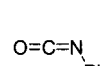
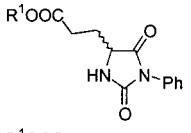
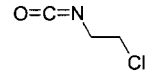
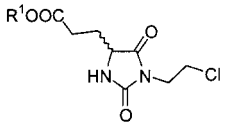
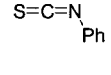
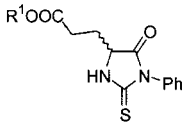
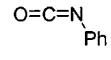
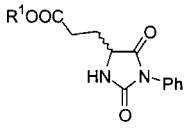
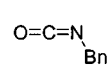
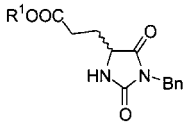
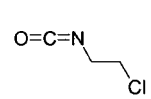
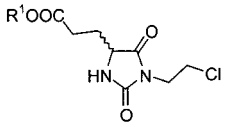
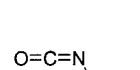
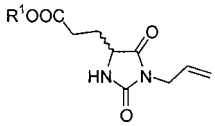
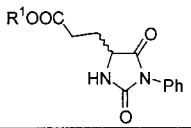


Figure 2. Characteristic COSY and HMBC couplings of **10** and **9e**.

Table 1. Synthesis of hydantoin derivatives **9** by ring transformation of pyroglutamates **4**.



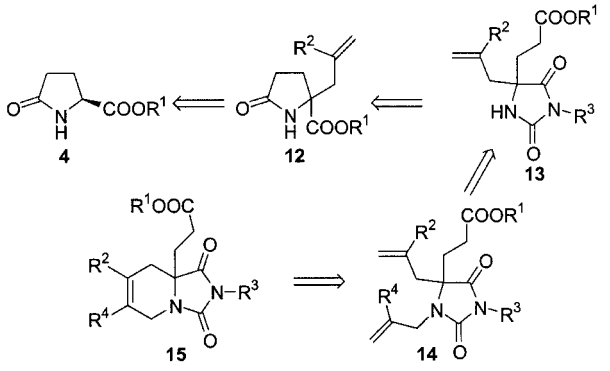
	R^1	Isocyanate	hydantoin	yield (%)
a	Bn			56
b	Bn			50
c	Bn			42
d	Et			89
e	Et			87
f	Et			81
g	Et			48
h	Me			81

Since it was established that the hydantoin was synthesised, the same methodology was performed on other combinations of pyroglutamate esters and isocyanates (Table 1).

We were pleased to find that different esters underwent the same reaction, although, in some cases, traces of carbamoyllactam could be observed due to the poor solubility of this intermediate in THF. This is probably the reason why the benzyl ester formed a hydantoin with phenyl isothiocyanate (Entry 3), whereas the ethyl ester only gave the thiocarbamoylated pyroglutamate.

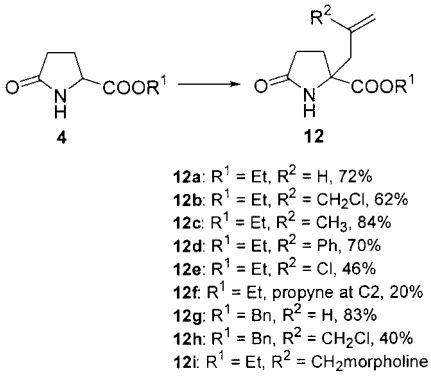
Synthesis of Bicyclic Hydantoin Derivatives

Having discovered this ring transformation and established its general nature, we wanted to use this reaction as the key step in the synthesis of more complex hydantoins. Our goal was the synthesis of a new series of more constrained bicyclic derivatives **15**. These compounds have attracted the attention of a number of research groups due to their potential biological application and as a template in organic synthesis.[29,30] Our strategy to synthesise this heterocyclic skeleton, started from a pyroglutamate ester **4** (Scheme 2). The first step is functionalisation at the C2 position, which afforded compound **12**. Next carbamoylation and immediate ring transformation would provide the hydantoin derivatives **13**. Subsequent *N*-alkylation to afford **14** and RCM would provide the envisaged compounds **15**.[31] This strategy provides the possibility of varying substituents at four positions and thus would be ideal to synthesise a library of highly functionalised molecules.



Scheme 2. Retrosynthetic analysis of bicyclic hydantoin derivatives **15**.

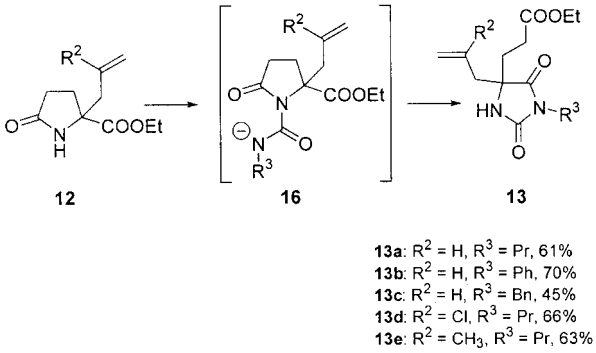
Although alkylation of pyroglutamates at the C2 position has been described before,[32] this method is rather unpractical with the need for stringent time and temperature control. It was found that excellent results can be obtained when a mixture of the pyroglutamate and the electrophile is treated with 2.1 equivalents of LiHMDS at –40 °C (Scheme 3). Even when using several equivalents of electrophile, no *N*-alkylation was observed. This methodology however, can not be followed if base-sensitive electrophiles are used (e.g. in case of **12e** and **12f**). When using the benzyl ester, however, small amounts of benzyl alcohol were formed caused by fragmentation of the ester. This kind of fragmentation has been observed before.[33] Therefore, all following reactions were carried out on the ethyl ester.



12a: R^1 = Et, R^2 = H, 72%
12b: R^1 = Et, R^2 = CH_2Cl, 62%
12c: R^1 = Et, R^2 = CH_3, 84%
12d: R^1 = Et, R^2 = Ph, 70%
12e: R^1 = Et, R^2 = Cl, 46%
12f: R^1 = Et, propyne at C2, 20%
12g: R^1 = Bn, R^2 = H, 83%
12h: R^1 = Bn, R^2 = CH_2Cl, 40%
12i: R^1 = Et, R^2 = CH_2morpholine

Scheme 3. Reagents and conditions: 4 equiv. electrophile, 2.1 equiv. LiHMDS, THF, 30 min at –40 °C, then 2 h at room temp.

The ring transformation was then performed using different isocyanates (Scheme 4). In almost all cases, small amounts of the carbamoyllactam **16** were formed together with the desired hydantoins **13** thus requiring purification. It was observed that bulky R^2 substituents (e.g. **12d** and **12i**) prevent the pyroglutamate from reacting with the isocyanate even under more drastic conditions (reflux in DMF). In these cases only unreacted starting material could be recovered. Also compound **12f**, with a propyne substituent at C2, gave a mixture of compounds upon reaction with isocyanates and was therefore not further used.



13a: R^2 = H, R^3 = Pr, 61%
13b: R^2 = H, R^3 = Ph, 70%
13c: R^2 = H, R^3 = Bn, 45%
13d: R^2 = Cl, R^3 = Pr, 66%
13e: R^2 = CH_3, R^3 = Pr, 63%

Scheme 4. Reagents and conditions: R^3NCO, NaH, THF, room temp., 16 h.

As is the case for the derivatives **9**, 2D-spectra confirm the structure of compounds **13** (Figure 3). An example is shown in Figure 3: In the HMBC spectrum of **13c**, the protons of the allyl substituent, of the benzyl group and on the N atom couple to the same carbon at δ = 175.0 ppm.

The hydantoins **13** obtained in this fashion proved to be rather poor nucleophiles. Treatment with strong bases did not lead to alkylation, but resulted in partial decomposition of the starting material. The only way to alkylate these com-

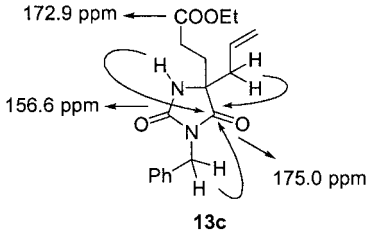
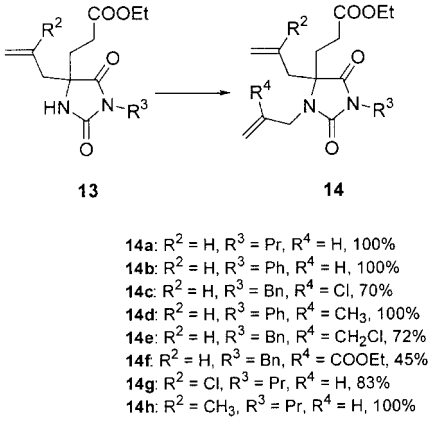


Figure 3. Characteristic HMBC couplings of **13c** and chemical shifts of the carbonyl carbon atoms.

pounds at N1 in good yield was to reflux them with 2 equivalents of electrophile and 5 equivalents of finely ground K_2CO_3 in acetone for several days (Scheme 5).

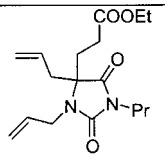
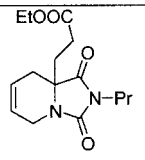
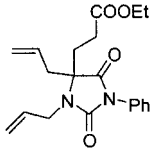
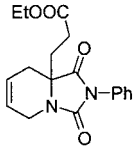
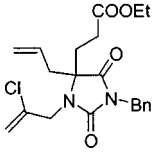
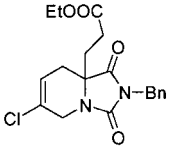
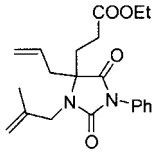
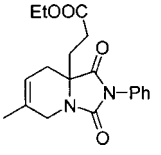
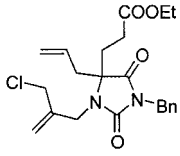
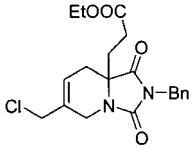
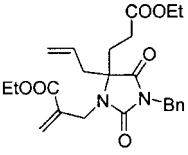
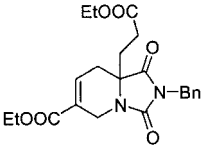
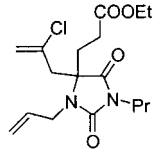
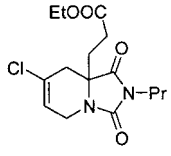
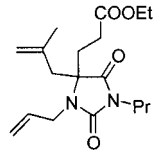
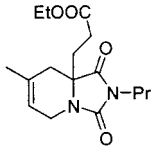


Scheme 5. Reagents and conditions: electrophile, K_2CO_3, acetone, reflux.

Finally, ring-closing metathesis on substrates **14** provided the envisaged bicyclic structures **15** in excellent yields (Table 2). The second-generation Grubbs' catalyst **16**[34] and Hoveyda–Grubbs' catalyst **17**[35] (Figure 4) provide the possibility of performing RCM on a variety of substrates with different substituents on the double bond. Substrates with a vinylic or allylic chloride (**15c**, **15e**, **15g**) or an extra ester functionality (**15f**) thus provide the possibility of further functionalisation.[36]

Figure 5 shows the structure obtained by X-ray analysis of derivative **15b**. As expected, the five-membered cycle is planar with the typical C=O bonds of 1.21 Å. The observed torsion angle of 44.05° between the five-membered and the phenyl rings (C3–N4–C7–C12) confirms the non-coplanar configuration of these molecular fragments. The annelated partially saturated six-membered ring (C1–N2–C14–C15–C16–C17) has the pseudo-envelope conformation in which

Table 2. Synthesis of bicyclic hydantoin derivatives using RCM.

	substrate **14**	RCM product **15**	Yield (%)
a			93
b			88
c			75
d			79
e			85
f			55
g			77
h			86

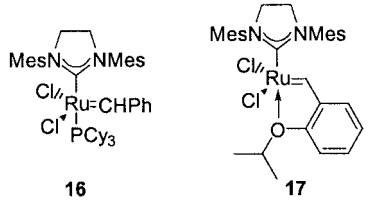


Figure 4. Second-generation Grubbs' catalyst **16** and Hoveyda-Grubbs' catalyst **17**.

all atoms but C1 are in the same plane with the observed C15–C14–N2–C1 torsion angle of 39.07°. An observed C15–C16 bond length of 1.371 Å clearly indicates the presence of the double bond between these atoms formed by the RCM reaction. The ester fragment adopts a typical zigzag conformation with the expected bond lengths. Finally, we were not able to find any significant intra- and intermolecular interactions in the crystal packing of the compound **15b**.

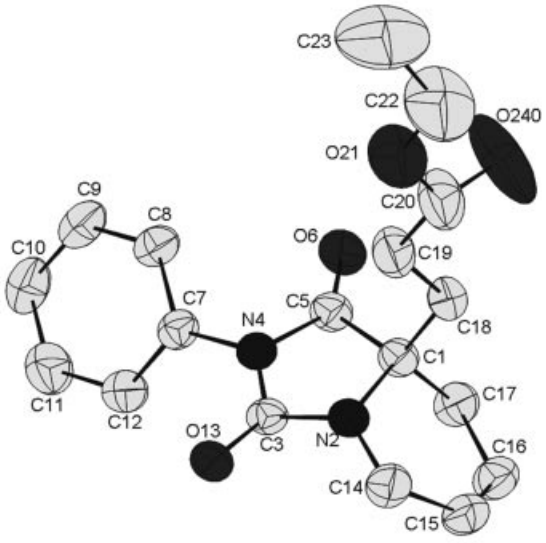


Figure 5. X-ray structure of bicyclic derivative **15b**.[37]

Conclusions

In the present study we have described a new ring transformation of pyroglutamates leading to hydantoins in one step in good to high yields. This rearrangement proceeds through a ring-closing ring-opening sequence. Furthermore, the general nature of this rearrangement was proven using different pyroglutamate esters and isocyanates. The rearrangement was used in a reaction sequence in combination with ring-closing metathesis for the synthesis of multifunctionalised bicyclic hydantoins, expanding the synthetic scope and utility of pyroglutamates.

Experimental Section

General Remarks: High-resolution ^{1}H NMR (270 MHz) and ^{13}C NMR (68 MHz) spectra were run with a Jeol JNM-EX 270 NMR spectrometer or with a Jeol JNM-EX 300 NMR spectroscopy. Peak assignments were obtained with the aid of DEPT, 2D-HETCOR, 2D-COSY spectra. The compounds were diluted in deuterated solvents and the used solvent 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. For liquid samples the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and are uncorrected. The elemental analysis was performed with a Perkin–Elmer 2400 Elemental Analyzer. The purification of reaction mixtures was performed by flash chromatography using a glass column with silica gel (Across, particle size 0.035–0.070 mm, pore diameter ca. 6 nm). Single crystals of compound **15b** as colourless plates were grown by slow evapouration of its $CDCl_3$ solution. The X-ray data were collected with a Rigaku AFC-7R diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) at 293 K. Psi-scan absorption corrections were applied to the data using TeXsan 10.3b program.[38] The structures were solved by direct methods (SIR-92) and refined by full-matrix least-squares on F^2 using Crystals for Windows program.[39] All of the non-hydrogen atoms were refined anisotropically. Selected data: **15b:** $C_{18}H_{20}N_2O_4$, M = 328.37, triclinic, space group $P\bar{1}$, a = 8.2050(16), b = 9.5970(19), c = 12.045(2) Å; α = 77.59(3), β = 79.65(3), γ = 67.39(3)°, V = 850.2(4) Å ^{3}, Z = 2, T = 293 K, μ = 0.091 mm^{-1}, 4215 reflections measured, 3037 unique (R_{int} = 0.0832); final R_1 = 0.051, R_w = 0.129.

CCDC-287973 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Typical Experimental Procedure for the Alkylation of Pyroglutamates at the 2-Position: The pyroglutamate ester (12 mmol) was dissolved in THF (15 mL, freshly distilled from Na metal) and the alkyl halide (48 mmol) was added. The mixture was cooled to –40 °C under N_2. Over a period of 30–40 min, LiHMDS (25.2 mmol, solution in hexane) was added at this temperature. The mixture was stirred at room temperature for an additional 2 h and the reaction then quenched by 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.

Ethyl 2-Allyl-5-oxopyrrolidine-2-carboxylate (12a): Yield: 1.70 g (72%). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.07–2.17 (m, 1 H, $COCH_2CH_AH_B$), 2.35–2.51 (m, 4 H, $COCH_2CH_AH_B$ + CCH_AH_B), 2.63–2.71 (m, 1 H, CCH_AH_B), 4.22 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.14–5.21 (m, 2 H, $CH{=}CH_2$), 5.69 (dddd, J = 6.5 Hz, J = 7.9 Hz, J = 10.9 Hz, J = 16.2 Hz, 1 H, $CH{=}CH_2$), 6.35 (br s, 1 H, NH) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 14.20 (CH_2CH_3), 29.88 ($COCH_2CH_2$), 30.04 ($COCH_2$), 43.38 ($CH_2CH{=}CH_2$), 61.72 (CH_2CH_3), 65.35 (C_q), 120.41 ($CH{=}CH_2$), 131.19 ($CH{=}CH_2$), 173.19 (NHC=O), 177.25 (C=OO) ppm. MS: m/z (%) = 198 (100) [M + H$^+$]. IR: $\tilde{\nu}_{max}$ = 1711 (br C=O) cm^{-1}. $C_{10}H_{15}NO_3$ (197.23): calcd. C 60.90, H 7.67, N 7.10; found C 60.74, H 7.77, N 7.09.

Ethyl 5-Oxo-2-(2-chloromethylprop-2-enyl)pyrrolidine-2-carboxylate (12b): Yield: 1.83 g (62%). M.p. 55.4–56.6 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.12–2.22 (m, 1 H, $COCH_2CH_AH_B$), 2.37–2.54 (m, 3 H, $COCH_2CH_AH_B$), 2.54 (d, J =14.5 Hz, 1 H, CCH_AH_B), 2.94 (d, J =14.5 Hz, 1 H, CCH_AH_B), 4.00 (s, 2 H, CH_2Cl), 4.22 (q, J =7.1 Hz, 2 H, CH_2CH_3), 5.06 (s, 1 H, $C{=}CH_AH_B$), 5.33 (s, 1 H, $C{=}CH_AH_B$), 6.41 (br s, 1 H, NH) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 14.11 (CH_2CH_3), 29.69 ($COCH_2CH_2$), 31.23 ($COCH_2$), 41.74 (CCH_2), 48.41 (CH_2Cl), 61.99 (CH_2CH_3), 65.07 (C_q), 120.03 ($C{=}CH_2$), 139.91 ($C{=}CH_2$), 173.19 (NHC=O), 177.21 (C=OO) ppm. MS: m/z (%) = 246.0/248.0 (100) [M + H$^+$]. IR: $\tilde{\nu}_{max}$ = 1707 (C=O), 1741 (C=O) cm^{-1}. $C_{11}H_{16}ClNO_3$ (245.70): calcd. C 53.77, H 6.56, N 5.70; found C 53.73, H 6.43, N 5.66.

Ethyl 2-(2-Methylprop-2-enyl)-5-oxopyrrolidine-2-carboxylate (12c): Yield: 2.13 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.2 Hz, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 2.09–2.19 (m, 1 H, $COCH_AH_B$), 2.35–2.52 (m, 3 H, $COCHAH_BCH_2$), 2.37 (dd, J = 2.6 Hz, J = 13.7 Hz, 1 H, CCH_AH_BC), 2.69 (d, J = 13.7 Hz, 1 H, CCH_AH_BC), 4.21 (q, J = 7.2 Hz, 2 H, $CH_AH_BCH_3$), 4.76 (s, 1 H, $C{=}CH_AH_B$), 4.92 (s, 1 H, $C{=}CH_AH_B$), 6.27 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.19 (CH_2CH_3), 23.57 (CH_3), 29.69 ($COCH_2CH_2$), 31.66 ($COCH_2$), 47.11 (CCH_2C), 61.88 (CH_2CH_3), 65.02 (C_q), 116.11 ($C{=}CH_2$), 139.96 ($CH_3C{=}CH_2$), 173.52 (HNC=O), 176.72 (C=OO) ppm. IR: $\tilde{\nu}_{max}$ = 1647 (C=C), 1706 (C=O), 1735 (C=O), 3220 (br NH) cm^{-1}. MS: m/z (%) = 212.8

(100) [M + H$^+$]. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 8.11, N 6.63; found C 62.36, H 8.13, N 6.59.

Ethyl 5-Oxo-2-(2-phenylprop-2-enyl)pyrrolidine-2-carboxylate (12d): Yield: 2.30 g (70%). M.p. 73.4–74.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.2 Hz, 3 H, CH_3), 2.05–2.17 (m, 1 H, COCH_AH$_B$), 2.23–2.36 (m, 2 H, COCH$_2$CH_2), 2.23–2.49 (m, 1 H, COCH$_A$$H_B$), 2.86 (d, J = 13.6 Hz, 1 H, CCH_AH$_B$C), 3.21 (d, J = 12.1 Hz, 1 H, CCH$_A$$H_B$C), 3.75 (q, J = 7.2 Hz, 1 H, CH_AH$_B$CH$_3$), 3.76 (q, J = 7.2 Hz, 1 H, CH$_A$$H_BCH_3$), 5.15 (s, 1 H, C=C$H_AH_B$), 5.33 (d, J = 1.4 Hz, 1 H, C=CH$_A$$H_B$), 5.98 (br s, 1 H, NH), 7.29–7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.97 (CH_3), 29.60 (COCH$_2$$CH_2$), 31.49 (CO$CH_2$), 45.05 (C$CH_2$C), 61.69 ($CH_2CH_3$), 65.46 ($C_q$), 118.52 (C=$CH_2$), 126.69 ($CH_{ar}$), 128.15 ($CH_{ar}$), 128.55 ($CH_{ar}$), 140.54 ($C$=CH$_2$), 143.68 ($C_{q,ar}$), 172.87 (HNC=O), 176.42 (C=OO) ppm. IR: $\tilde{\nu}_{max}$ = 1728 (C=O), 1744 (C=O), 3203 (br NH) cm^{-1}. MS: m/z (%) = 274.3 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (4:6)]: R_f = 0.21. $C_{16}H_{19}NO_3$ (273.33): calcd. C 70.31, H 7.01, N 5.12; found C 70.10, H 7.04, N 5.04.

Benzyl 2-Allyl-5-oxopyrrolidine-2-carboxylate (12g): Yield: 2.58 g (83%). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.09–2.16 (m, 1 H, COCH$_2$CH_AH$_B$), 2.33–2.47 (m, 4 H, COCH_2CH$_A$$H_B$ + CCH_AH$_B$), 2.66 (dd, J = 6.4 Hz, J = 13.7 Hz, 1 H, CCH$_A$$H_B$), 5.09–5.16 (m, 2 H, CH=CH_2), 5.17 (s, 2 H, CH_2Ph), 5.61 (dddd, J = 6.6 Hz, J = 8.3 Hz, J = 10.4 Hz, J = 16.7 Hz, 1 H, CH=CH$_2$), 7.33–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 29.72 (COCH$_2$$CH_2$), 30.17 (CO$CH_2$), 43.45 (C$CH_2$), 65.28 ($C_q$), 67.53 ($CH_2$Ph), 120.81 (CH=$CH_2$), 128.41 ($CH_{ar}$), 128.71 ($CH_{ar}$), 130.78 ($CH$=CH$_2$), 135.09 ($C_{q,ar}$), 172.85 (NHC=O), 176.91 (C=OO) ppm. MS: m/z (%) = 260 (100) [M + H$^+$]. IR: $\tilde{\nu}_{max}$ = 1703 (C=O), 1736 (C=O) cm^{-1}. Chromatography [Hex/EtOAc (25:75)]: R_f = 0.31. $C_{15}H_{17}NO_3$ (259.30): calcd. C 69.48, H 6.61, N 5.40; found C 69.13, H 6.52, N 5.37.

Benzyl 5-Oxo-2-(2-chloromethylprop-2-enyl)pyrrolidine-2-carboxylate (12h): Yield: 1.48 g (40%). M.p. 47.3–50.3 °C.^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.17–2.24 (m, 1 H, COCH$_2$CH_AH$_B$), 2.37–2.50 (m, 3 H, COCH_2CH$_A$$H_B$), 2.57 (d, J =14.5 Hz, 1 H, CCH_AH$_B$), 2.96 (d, J =14.5 Hz, 1 H, CCH$_A$$H_B$), 3.96 (s, 2 H, CH$_2$Cl), 5.02 (s, 1 H, C=C$H_AH_B$), 5.20 (d, J =12.0 Hz, 1 H, CH_AH$_B$Ph), 5.23 (d, J =12.0 Hz, 1 H, CH$_A$$H_B$Ph), 5.30 (s, 1 H, C=CH$_A$$H_B$), 7.40 (s, 5 H, Ph) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 29.61 (COCH$_2$$CH_2$), 31.25 (CO$CH_2$), 41.71 (C$CH_2$), 48.37 ($CH_2$Cl), 65.14 ($C_q$), 67.65 ($CH_2$Ph), 120.09 (C=$CH_2$), 128.52 ($CH_{ar}$), 128.68 ($CH_{ar}$), 134.89 ($C_{q,ar}$), 139.67 ($C$=CH$_2$), 172.97 (NHC=O), 177.18 (C=OO) ppm. MS: m/z (%) = 308.0/310.0 (100) [M + H$^+$], 257 (7), 91 (7) [Bn$^+$]. IR: $\tilde{\nu}_{max}$ = 1701 (C=O), 1735 (C=O) cm^{-1}. Chromatography [Hex/EtOAc (25:75)]: R_f = 0.45. $C_{16}H_{18}ClNO_3$ (307.77): calcd. C 62.44, H 5.89, N 4.55; found C 62.28, H 5.78, N 4.47.

Typical Experimental Procedure for the Alkylation of Pyroglutamates at the 2-Position with Base Sensitive Electrophiles: The pyroglutamate ester (12 mmol) was dissolved in THF (15 mL, freshly distilled from Na metal) and the solution was cooled to –40 °C under N_2. LiHMDS (25.2 mmol, solution in hexane) was added at this temperature and the mixture was stirred for 20 min followed by addition of the alkyl halide (48 mmol, dissolved in 5 mL of dry THF). The mixture was stirred at room temperature for an additional 2 h and the reaction then quenched by 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, and the residue was purified by flash chromatography (silica gel; hexane/EtOAc).

Ethyl 2-(2-Chloroprop-2-enyl)-5-oxopyrrolidine-2-carboxylate (12e): Yield: 1.28 g (46%). M.p. 90.3° C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.2 Hz, 3 H, CH_3), 2.13–2.23 (m, 1 H, COCH_AH$_B$), 2.36–2.43 (m, 2 H, COCH$_2$CH_2), 2.46–2.56 (m, 1 H, COCH$_A$$H_B$), 2.71 (d, J = 14.3 Hz, 1 H, CCH_AH$_B$C), 3.05 (d, J = 14.3 Hz, 1 H, CCH$_A$$H_B$C), 4.22 (q, J = 7.2 Hz, 1 H, CH_AH$_B$CH$_3$), 4.23 (q, J = 7.2 Hz, 1 H, CH$_A$$H_BCH_3$), 5.25 (t, J = 0.7 Hz, 1 H, C=CH_AH$_B$), 5.35 (d, J = 1.4 Hz, 1 H, C=CH$_A$$H_B$), 6.29 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.18 (CH_3), 29.31 (COCH$_2$$CH_2$), 31.58 (CO$CH_2$), 48.13 (C$CH_2$C), 62.23 ($CH_2CH_3$), 64.72 ($C_q$), 117.85 (C=$CH_2$), 136.20 ($C$Cl=CH$_2$), 172.51 (HNC=O), 176.52 (C=OO) ppm. IR: $\tilde{\nu}_{max}$ = 1636 (.C=C), 1715 (C=O), 1741 (C=O), 3195 (br NH) cm^{-1}. MS: m/z (%) = 232.7/234.7 (100) [M + H$^+$]. $C_{10}H_{14}ClNO_3$ (231.68): calcd. C 51.84, H 6.09, N 6.05; found C 51.44, H 6.26, N 6.10.

Ethyl 5-Oxo-2-prop-2-ynylpyrrolidine-2-carboxylate (12f): Yield: 0.47 g (20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.2 Hz, 3 H, CH_3), 2.08 (t, J = 2.2 Hz, 1 H, CH), 2.12–2.52 (m, 4 H, COCH_2CH_2), 2.61 (dd, J = 14.3 Hz, J = 2.2 Hz, 1 H, CCH_AH$_B$C), 2.82 (dd, J = 14.3 Hz, J = 2.2 Hz, 1 H, CCH$_A$$H_B$C), 4.25 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 5.25 (t, J = 0.7 Hz, 1 H, C=CH_AH$_B$), 7.01 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.13 (CH_3), 29.09 (COCH$_2$$CH_2$), 29.79 (C$CH_2$C + CO$CH_2$), 62.15 ($CH_2CH_3$), 64.67 ($C_q$), 72.11 (CH), 78.21 (C), 172.33 (HNC=O), 177.36 (C=OO) ppm. IR: $\tilde{\nu}_{max}$ = 1705 (br C=O), 2120 (alkyne), 3283 (br NH) cm^{-1}. MS: m/z (%) = 391.7, (100) [2M + H$^+$]. Chromatography [Hex/EtOAc (2:8)]: R_f = 0.3. $C_{10}H_{13}NO_3$ (195.22): calcd. C 61.53, H 6.71, N 7.18; found C 61.73, H 6.77, N 7.13.

Ethyl 2-[2-(Morpholin-4-ylmethyl)prop-2-enyl]-5-oxopyrrolidine-2-carboxylate (12i): Ethyl 5-oxo-2-(2-chloromethylprop-2-enyl)pyrrolidine-2-carboxylate (4 mmol) was dissolved in THF (20 mL, freshly distilled from Na metal). Morpholine (10 mmol) was added and the mixture was refluxed until TLC analysis showed that all starting material was consumed. Then the mixture was cooled and aqueous $NaHCO_3$ (15 mL) was added. The mixture was extracted with EtOAc, and the organics were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography. Yield: 0.71 g (60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3 H, CH_3), 1.98–2.08 (m, 1 H, COCH_AH$_B$), 2.23 (d, J = 13.5 Hz, 1 H, CCH_AH$_B$C), 2.31–2.56 (m, 7 H, COCH$_A$$H_BCH_2$ + CH_2NCH_2), 2.75 (d, J = 12.1 Hz, 1 H, NCH_AH$_B$C), 2.94 (d, J = 12.1 Hz, 1 H, NCH$_A$$H_B$C), 2.98 (d, J = 13.5 Hz, 1 H, CCH$_A$$H_B$C), 3.68–3.87 (m, 4 H, C$H_2OCH_2$), 4.16 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 5.01 (s, 1 H, C=CH_AH$_B$), 5.07 (s, 1 H, C=CH$_A$$H_B$), 9.19 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.35 (CH_3), 30.26 (COCH$_2$$CH_2$), 32.76 (CO$CH_2$), 47.54 (C$CH_2$C), 53.31 ($CH_2NCH_2$), 61.49 ($CH_2CH_3$), 65.37 (C$CH_2$N), 65.94 ($C_q$), 66.73 ($CH_2OCH_2$), 122.43 (C=$CH_2$), 139.22 ($C$=CH$_2$), 173.71 (HNC=O), 176.77 (C=OO) ppm. IR: $\tilde{\nu}_{max}$ = 1705 (C=O), 1734 (C=O), 3270 (br NH) cm^{-1}. MS: m/z (%) = 297.8 (100) [M + H$^+$]. Chromatography: First 100% EtOAc until R_f = 0.27 then strip with CH_2Cl_2 + 5% MeOH. $C_{15}H_{24}N_2O_4$ (296.36): calcd. C 60.79, H 8.16, N 9.45; found C 60.46, H 8.16, N 9.39.

Typical Experimental Procedure for the Hydantoin Formation from Pyroglutamates: The pyroglutamate ester (5 mmol) was dissolved in THF (40 mL, freshly distilled from Na metal) and the isocyanate (5.5 mmol) was added followed by NaH (5.5 mmol, washed with hexanes). The mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of saturated aqueous NH_4Cl until the pH was neutral. Then the mixture was extracted with EtOAc, and the organics were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo, and the residue was purified by

recrystallisation in case of solids or by flash chromatography (silica gel; hexane/EtOAc) in case of liquids.

Benzyl 3-(2,5-Dioxo-1-phenyl-imidazolidin-4-yl)propanoate (9a): Yield: 0.95 g (56%). M.p. 144,5–145,4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10–2.22 (m, 1 H, CHCH_AH$_B$), 2.27–2.38 (m, 1 H, CHCH$_A$$H_B$), 2.59 (t, J = 7.1 Hz, 2 H, CH_2CO), 4.25 (br t, J = 5.6 Hz, 1 H, CHCO), 5.13 (s, 2 H, CH_2Ph), 6.36 (br s, 1 H, NH), 7.33–7.48 (m, 10 H, 2 × Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.43 (CH_2), 30.18 (CH_2), 56.68 (CH), 67.34 (OCH_2), 126.59 (CH_{arom}), 128.79 (CH_{arom}), 128.85 (CH_{arom}), 128.93 (CH_{arom}), 129.11 (CH_{arom}), 129.57 (CH_{arom}), 131.75 ($C_{q.\ arom}$) 135.86 ($C_{q.\ arom}$), 156.69 (NC=ON), 172.83 (C=O), 172.99 (C=O) ppm. MS (ES, Neg): m/z (%) = 337.2 (100) [M – H$^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 1699 (C=O), 1715 (C=O), 1781 (C=O), 3256 (br NH) cm^{-1}. $C_{19}H_{18}N_2O_4$ (338.36): calcd. C 67.36, H 5.36, N 8.28; found C 67.03, H 5.43, N 8.27.

Benzyl 3-[1-(2-Chloro-ethyl)-2,5-dioxo-imidazolidin-4-yl]propanoate (9b): Yield: 0.81 g (50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99–2.11 (m, 1 H, CHCH_AH$_B$), 2.14–2.28 (m, 1 H, CHCH$_A$$H_B$), 2.52 (t, J = 7.4 Hz, 2 H, CH_2CO), 3.68 (t, J = 5.9 Hz, 2 H, CH_2Cl), 3.77–3.82 (m, 2 H, NCH_2), 4.13 (br t, J = 6.1 Hz, 1 H, CH), 5.10 (s, 2 H, CH_2Ph), 7.12 (br s, 1 H, NH), 7.27–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.92 (CH_2), 29.54 (CH_2), 40.13 (CH_2N or CH_2Cl), 40.74 (CH_2N or CH_2Cl), 56.44 (CH), 66.90 (OCH_2), 128.44 (CH_{arom}), 128.59 (CH_{arom}), 128.83 (CH_{arom}), 135.77 ($C_{q.\ arom}$), 157.44 (NC=ON), 172.67 (C=O), 173.80 (C=O) ppm. MS (ES, Neg): m/z (%) = 323.3/325.2 (100) [M – H$^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 1714 (br, C=O), 1777 (C=O), 3320 (NH) cm^{-1}. $C_{15}H_{17}ClN_2O_4$ (324.76): calcd. C 55.48, H 5.28, N 8.63; found C 55.45, H 5.36, N 8.62.

Benzyl 3-(5-Oxo-1-phenyl-2-thioxo-imidazolidin-4-yl)propanoate (9c): Yield: 0.74 g (42%). M.p. 157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13–2.26 (m, 1 H, CHCH_AH$_B$), 2.33–2.44 (m, 1 H, CHCH$_A$$H_B$), 2.58–2.65 (m, 2 H, CH_2CO), 4.35 (dd, J = 5.1 Hz and J = 6.5 Hz, 1 H, CH), 5.16 (s, 2 H, CH_2Ph), 7.28–7.53 (m, 10 H, 2 × Ph), 7.66 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.61 (CH_2), 29.85 (CH_2), 59.00 (CH), 67.10 (OCH_2), 128.25 ($CH_{arom.}$), 128.50 ($CH_{arom.}$), 128.56 ($CH_{arom.}$), 128.69 ($CH_{arom.}$), 129.18 ($CH_{arom.}$), 129.32 ($CH_{arom.}$), 132.54 ($C_{q.\ arom.}$), 135.29 ($C_{q.\ arom.}$), 172.69 (C=O) 173.20 (C=O), 183.71 (C=S) ppm. MS (ES, Neg): m/z (%) = 353.2 (100) [M – H$^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 1697 (C=S), 1719 (C=O), 1750 (C=O), 3233 (NH) cm^{-1}. $C_{19}H_{18}N_2O_3S$ (354.42): calcd. C 64.39, H 5.12, N 7.90; found C 64.15, H 5.30, N 7.82.

Ethyl 3-(2,5-Dioxo-1-phenyl-imidazolidin-4-yl)propanoate (9d): Yield: 1.23 g (89%). M.p. 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 2.08–2.20 (m, 1 H, CHCH_AH$_B$), 2.26–2.37 (m, 1 H, CHCH$_A$$H_B$), 2.53 (t, J = 6.9 Hz, 2 H, $COCH_2$), 4.16 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 4.26 (dt, J = 1.3 Hz and J = 5.7 Hz, 1 H, CH), 6.31 (br s, 1 H, NH), 7.31–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.14 (CH_3), 26.96 (CH_2), 29.53 (CH_2), 56.20 (CH), 60.95 (OCH_2), 126.21 (CH_{arom}), 128.33 (CH_{arom}), 129.12 (CH_{arom}), 131.38 ($C_{q.\ arom}$), 156.62 (NC=ON), 172.62 (C=O), 172.67 (C=O) ppm. MS (70 eV, ES, Neg): m/z (%) = 275.3 (100) [M – H$^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 1713 (C=O), 1728 (C=O), 1774 (C=O), 3272 (NH) cm^{-1}. $C_{14}H_{16}N_2O_4$ (276.29): calcd. C 60.86, H 5.84, N 10.14; found C 60.84, H 5.76, N 10.05.

Ethyl 3-(1-Benzyl-2,5-dioxo-imidazolidin-4-yl)propanoate (9e): Yield: 1.26 g (87%). M.p. 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 3 H, CH_3), 1.93–2.06 (m, 1 H, CHCH_AH$_B$), 2.15–2.26 (m, 1 H, CHCH$_A$$H_B$), 2.42 (t, J = 7.2 Hz, 2 H, $COCH_2$), 4.07–4.08 (m, 1 H, CH), 4.12 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 4.64 (s, 2 H, CH_2Ph), 6.29 (br s, 1 H, NH), 7.25–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.12 (CH_3), 26.84 (CH_2), 29.51 (CH_2), 42.14 (CH_2N), 56.35 (CH), 60.86 (OCH_2), 127.89 (CH_{arom}), 128.39 (CH_{arom}), 128.65 (CH_{arom}), 135.96 ($C_{q.\ arom}$), 157.43 (NC=ON), 172.65 (C=O), 173.49 (C=O) ppm. MS (ES, Neg): m/z (%) = 289.2 (100) [M – H$^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 1708 (C=O), 1732 (C=O), 1778 (C=O), 3448 (br NH) cm^{-1}. $C_{15}H_{18}N_2O_4$ (290.31): calcd. C 62.02, H 6.25, N 9.65; found C 61.80, H 6.19, N 9.72.

Ethyl 3-[1-(2-Chloro-ethyl)-2,5-dioxo-imidazolidin-4-yl]propanoate (9f): Yield: 1.06 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3 H, CH_3), 2.01–2.13 (m, 1 H, CHCH_AH$_B$), 2.18–2.30 (m, 1 H, CHCH$_A$$H_B$), 2.49 (t, J = 7.4 Hz, 2 H, $COCH_2$), 3.75 (t, J = 6.1 Hz, 2 H, CH_2Cl), 3.84–3.89 (m, 2 H, NCH_2), 4.14 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 4.20 (t, J = 6.1 Hz, 1 H, CH), 7.18 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.37 (CH_3), 26.99 (CH_2), 29.58 (CH_2), 40.17 (CH_2N of CH_2Cl), 40.73 (CH_2N of CH_2Cl), 56.54 (CH), 61.14 (OCH_2), 157.42 (NC=ON), 172.93 (C=O), 173.91 (C=O) ppm. MS (ES, Neg): m/z (%) = 261.2/263.2 (100) [M – H$^+$]. IR (NaCl): $\tilde{\nu}_{max}$ = 1714 (C=O), 1778 (C=O) cm^{-1}. $C_{10}H_{15}ClN_2O_4$ (262.69): calcd. C 45.72, H 5.76, N 10.66; found C 45.70, H 5.71, N 10.63.

Ethyl 3-(1-Allyl-2,5-dioxo-imidazolidin-4-yl)propanoate (9g): Yield: 0.57 g (48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 6.9 Hz, 3 H, CH_3), 1.99–2.10 (m, 1 H, CHCH_AH$_B$), 2.17–2.28 (m, 1 H, CHCH$_A$$H_B$), 2.48 (t, J = 7.4 Hz, 2 H, $COCH_2$), 4.13 (q, J = 6.9 Hz, 2 H, CH_2CH$_3$), 4.11 (d, J = 13.9 Hz, 1 H, NCH_AH$_B$), 4.17 (d, J = 13.9 Hz, 1 H, NCH$_A$$H_B$), 4.09–4.19 (m, 1 H, CH), 5.17–5.24 (m, 2 H, HC=CH_2), 5.76–5.88 (m, 1 H, HC=CH$_2$), 7.25 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.31 (CH_3), 27.05 (CH_2), 29.60 (CH_2), 40.41 (NCH_2), 56.48 (CH), 61.02 (OCH_2), 117.94 (HC=CH$_2$), 131.34 (HC=CH$_2$), 157.65 (NC=ON), 172.81 (C=O), 173.70 (C=O) ppm. MS (ES, Neg): m/z (%) = 239.3 (100) [M – H$^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 1646 (C=C), 1719 (br C=O), 1775 (C=O), 3316 (NH) cm^{-1}. $C_{11}H_{16}N_2O_4$ (240.26): calcd. C 54.99, H 6.71, N 11.66; found C 54.63, H 6.73, N 11.63.

Methyl 3-(2,5-Dioxo-1-phenyl-imidazolidin-4-yl)propanoate (9h): Yield: 1.06 g (81%). M.p. 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–2.22 (m, 1 H, CHCH_AH$_B$), 2.25–2.39 (m, 1 H, CHCH$_A$$H_B$), 2.52–2.58 (m, 2 H, CH_2CO), 3.70 and 3.71 (2×s, 3 H, CH_3), 4.23–4.28 (m, 1 H, CH), 6.45–6.71 (1 H, br s, NH), 7.36–7.50 (5 H, m, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.35 (CH_2), 29.66 (CH_2), 52.41 (OCH_3), 56.54 (CH), 126.59 (CH_{arom}), 128.75 (CH_{arom}), 129.53 (CH_{arom}), 131.74 ($C_{q.\ arom}$), 157.04 (NC=ON), 172.98 (C=O), 173.48 (C=O) ppm. MS (ES, Pos): m/z (%) = 263.3 (100) [M + H$^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 1707 (C=O), 1725 (C=O), 1775 (C=O), 3233 (NH) cm^{-1}. $C_{13}H_{14}N_2O_4$ (262.26): calcd. C 59.54, H 5.38, N 10.68; found C 59.81, H 5.21, N 10.71.

Ethyl 3-(4-Allyl-2,5-dioxo-1-propylimidazolidin-4-yl)propanoate (13a): Yield: 0.86 g (61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.25 (t, J = 7.2 Hz, 3 H, CH_3), 1.63 (sext, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.03–2.29 (m, 4 H, $COCH_2CH_2$), 2.43 (dd, J = 14.0 Hz, J = 7.4 Hz, 1 H, CH_AH$_B$CH), 2.50 (dd, J = 14.0 Hz, J = 7.6 Hz, 1 H, CH$_A$$H_B$CH), 3.44 (t, J = 7.4 Hz, 2 H, CH_2CH$_2$CH$_3$), 4.13 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 5.16 (s, 1 H, HC=CH_AH$_B$), 5.20 (d, J = 3.3 Hz, 1 H, HC=CH$_A$$H_B$), 5.59–5.73 (m, 1 H, H$C$=CH$_2$), 5.88 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.23 ($CH_2CH_2CH_3$), 14.21 (CH_3), 21.52 ($CH_2CH_2CH_3$), 28.74 ($COCH_2$), 31.05 ($COCH_2CH_2$), 40.36 ($CH_2CH_2CH_3$), 41.57 (CCH_2), 61.04 (CH_2CH_3), 64.38 (C_q), 121.34 (HC=CH$_2$), 130.02 (HC=CH$_2$), 156.97 (NC=ON), 172.86 (C=OO), 175.29 (HNC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1642 (C=C), 1713 (br C=O),

1775 (C=O) cm^{-1}. MS: *m/z* (%) = 283.3 (100) $[M+H^+]$. Chromatography [Hex/EtOAc (1:1)]: R_f = 0.42. $C_{14}H_{22}N_2O_4$ (282.34): calcd. C 59.56, H 7.85, N 9.92; found C 59.16, H 7.75, N 9.89.

Ethyl 3-(4-Allyl-2,5-dioxo-1-phenylimidazolidin-4-yl)propanoate (13b): Yield: 1.11 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.12–2.30 (m, 2 H, $COCH_2CH_2$), 2.37–2.41 (m, 2 H, $COCH_2CH_2$), 2.51 (dd, *J* = 13.8 Hz, *J* = 7.2 Hz, 1 H, CH_AH_BCH), 2.62 (dd, *J* = 13.8 Hz, *J* = 7.7 Hz, 1 H, CH_AH_BCH), 4.15 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 5.23 (s, 1 H, $HC=CH_AH_B$), 5.27 (d, *J* = 1,9 Hz, 1 H, $HC=CH_ACH_B$), 5.70–5.84 (m, 1 H, $HC=CH_2$), 6.09 (br s, 1 H, NH), 7.32–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.24 (CH_3), 28.90 ($COCH_2$), 31.29 ($COCH_2CH_2$), 41.75 (CCH_2), 61.17 (CH_2CH_3), 64.49 (C_q), 121.73 ($HC=CH_2$), 126.32 ($CH_{arom.}$), 128.51 ($CH_{arom.}$), 129.24 ($CH_{arom.}$), 129.86 ($HC=CH_2$), 131.44 ($C_{q\ arom.}$) ppm. 155.76 (NC=ON), 172.84 (C=OO), 174.23 (HNC=O). IR: $\tilde{\nu}_{max}$ = 1719 (C=O), 1781 (C=O) cm^{-1}. MS: *m/z* (%) = 317.3 (100) $[M+H^+]$. Chromatography: Hex/EtOAc (1:1) R_f = 0.33. $C_{17}H_{20}N_2O_4$ (316.35): calcd. C 64.54, H 6.37, N 8.86; found C 64.42, H 6.46, N 8.76.

Ethyl 3-(4-Allyl-1-benzyl-2,5-dioxoimidazolidin-4-yl)propanoate (13c): Yield: 0.74 g (45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.05–2.20 (m, 4 H, $COCH_2CH_2$), 2.39 (dd, *J* = 14.0 Hz, *J* = 7.3 Hz, 1 H, CH_AH_BCH), 2.47 (dd, *J* = 14.0 Hz, *J* = 7.4 Hz, 1 H, CH_AH_BCH), 4.09 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 4.62 (s, 2 H, CH_2Ph), 5.02–5.12 (m, 2 H, $HC=CH_2$), 5.46–5.60 (m, 1 H, $HC=CH_2$), 6.05 (br s, 1 H, NH), 7.23–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.19 (CH_3), 28.67 ($COCH_2$), 31.08 ($COCH_2CH_2$), 41.52 (CCH_2), 42.35 (CH_2Ph), 61.01 (CH_2CH_3), 64.55 (C_q), 121.36 ($HC=CH_2$), 127.97 ($CH_{arom.}$), 128.55 ($CH_{arom.}$), 128.66 ($CH_{arom.}$), 129.83 ($HC=CH_2$), 136.03 ($C_{q\ arom.}$) ppm. 156.55 (NC=ON), 172.87 (C=OO), 175.04 (HNC=O). IR: $\tilde{\nu}_{max}$ = 1713 (C=O), 1774 (C=O) cm^{-1}. MS: *m/z* (%) = 331.2 (100) $[M+H^+]$. Chromatography [Hex/EtOAc (55:45)]: R_f = 0.22. $C_{18}H_{22}N_2O_4$ (330.38): calcd. C 65.44, H 6.71, N 8.48; found C 65.39, H 6.90, N 8.43.

Ethyl 3-[4-(2-Chloroprop-2-enyl)-2,5-dioxo-1-propylimidazolidin-4-yl]propanoate (13d): Yield: 1.05 g (66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.24 (t, *J* = 7.2 Hz, 1.5 H, CH_3), 1.25 (t, *J* = 7.2 Hz, 1.5 H, CH_3), 1.64 (sext, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.11–2.20 (m, 2 H, $COCH_2CH_2$), 2.23–2.35 (m, 2 H, $COCH_2CH_2$), 2.77 (d, *J* = 14.6 Hz, 1 H, CCH_AH_BC), 2.87 (d, *J* = 14.6 Hz, 1 H, CCH_AH_BCH), 3.45 (t, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 4.12 (q, *J* = 7.2 Hz, 1 H, $CH_AH_BCH_3$), 4.13 (q, *J* = 7.2 Hz, 2 H, $CH_AH_BCH_3$), 5.28 (s, 1 H, $HC=CH_AH_B$), 5.34 (d, *J* = 3.3 Hz, 1 H, $HC=CH_AH_B$), 6.48 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.28 ($CH_2CH_2CH_3$), 14.18 (CH_3), 21.35 ($CH_2CH_2CH_3$), 28.54 ($COCH_2$), 31.34 ($COCH_2CH_2$), 40.53 ($CH_2CH_2CH_3$), 45.97 (CCH_2), 61.05 (CH_2CH_3), 63.80 (C_q), 118.37 ($HC=CH_2$), 135.25 ($HC=CH_2$), 156.90 (NC=ON), 172.55 (C=OO), 174.75 (HNC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1633 (C=C), 1717 (br C=O), 1777 (C=O) cm^{-1}. MS: *m/z* (%) = 317.7/319.8 (100) $[M+H^+]$. Chromatography [Hex/EtOAc (6:4)]: R_f = 0.26. $C_{14}H_{21}ClN_2O_4$ (316.78): calcd. C 59.08, H 6.68, N 8.84; found C 58.97, H 6.78, N 8.74.

Ethyl 3-[4-(2-Methylprop-2-enyl)-2,5-dioxo-1-propylimidazolidin-4-yl]propanoate (13e): Yield: 0.93 g (63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.25 (t, *J* = 7.2 Hz, 1.5 H, CH_3), 1.26 (t, *J* = 7.2 Hz, 1.5 H, CH_3), 1.62 (sext, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 1.73 (s, 3 H, CCH_3), 2.08–2.28 (m, 4 H, $COCH_2CH_2$), 2.38 (d, *J* = 13.6 Hz, 1 H, CCH_AH_BC), 2.55 (d, *J* = 13.6 Hz, 1 H, CCH_AH_BCH), 3.43 (dt, *J* = 2.8 Hz, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 4.13 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.79 (s, 1 H, $C=CH_AH_B$), 4.91 (d, *J* = 1.1 Hz, 1 H, $C=CH_AH_B$), 6.04 (br s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.26 ($CH_2CH_2CH_3$), 14.19 (CH_3), 21.42 ($CH_2CH_2CH_3$), 24.30 (CH_3), 28.76 ($COCH_2$), 31.83 ($COCH_2CH_2$), 40.42 ($CH_2CH_2CH_3$), 44.62 (CCH_2), 61.07 (CH_2CH_3), 64.79 (C_q), 116.98 ($C=CH_2$), 138.75 ($C=CH_2$), 157.39 (NC=ON), 172.87 (C=OO), 175.46 (HNC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1646 (C=C), 1713 (br C=O), 1772 (C=O) cm^{-1}. MS: *m/z* (%) = 297.8 (100) $[M+H^+]$. Chromatography [Hex/EtOAc (4:6)]: R_f = 0.42. $C_{15}H_{24}N_2O_4$ (296.36): calcd. C 60.79, H 8.16, N 9.45; found C 60.54, H 8.00, N 9.36.

Typical Experimental Procedure for the Carbamoyllactam Formation from Pyroglutamates: The pyroglutamate ester (1.9 mmol) was dissolved in diethyl ether (10 mL, freshly distilled from Na metal) and the isocyanate (1.9 mmol) was added followed by NaH (2.09 mmol, washed with hexanes). The mixture was stirred at room temperature for 1 h. Then the reaction was quenched by addition of saturated aqueous NH_4Cl until the pH was neutral. The mixture was extracted with diethyl ether, and the organics were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo.

(2*S*) Ethyl 1-Benzylcarbamoyl-5-oxopyrrolidine-2-carboxylate (10): Yield: 0.38 g (69%). $[a]_D$ = –6.0 (*c* = 3.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.96–2.06 (m, 1 H, $CHCH_AH_B$), 2.22–2.36 (m, 1 H, $CHCH_AH_B$), 2.51 (ddd, *J* = 3.4 Hz, *J* = 9.4 Hz, *J* = 18.2 Hz, 1 H, $COCH_AH_B$), 2.70 (dt, *J* = 8.9, *J* = 18.2 Hz, 1 H, CH_AH_B), 4.22 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.45 (dd, *J* = 5.9 Hz, *J* = 15.3 Hz, 1 H, NCH_AH_B), 4.50 (dd, *J* = 5.9 Hz, *J* = 15.3 Hz, 1 H, NCH_AH_B), 4.77 (dd, *J* = 2.8 Hz, *J* = 9.6 Hz, 1 H, CH), 7.20–7.33 (m, 5 H, Ph), 8.70 (br t, *J* = 5.9 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.92 (CH_3), 21.07 ($CHCH_2$), 31.58 ($COCH_2$), 43.54 (NCH_2), 58.03 (CH), 61.54 (OCH_2), 127.19 (CH_{arom}), 127.29 (CH_{arom}), 128.45 (CH_{arom}), 137.97 ($C_{q,arom}$), 152.22 (NC=ON), 171.26 (COO), 176.37 (NC=O) ppm. MS (ES, Pos): *m/z* (%) = 291.3 (100) $[M+H^+]$. IR: $\tilde{\nu}_{max}$ = 1694 (C=O), 1723 (C=O), 1746 (C=O), 3314 (br NH) cm^{-1}. $C_{15}H_{18}N_2O_4$ (290.31): calcd. C 62.02, H 6.25, N 9.65; found C 61.69, H 5.93, N 9.68.

(2*S*) Ethyl 1-Fenylcarbamoyl-5-oxopyrrolidine-2-carboxylate (11): Yield: 0.47 g (89%). $[a]_D$ = –19.7 (*c* = 1.3, CH_2Cl_2). M.p. 104.2–107.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.11 (dddd, *J* = 2.9 Hz, *J* = 3.2 Hz, *J* = 9.6 Hz, *J* = 13.4 Hz, 1 H, $CHCH_AH_B$), 2.39 (dddd, *J* = 9.7 Hz, *J* = 9.7 Hz, *J* = 9.8 Hz, *J* = 13.4 Hz, 1 H, $CHCH_AH_B$), 2.65 (ddd, *J* = 3.2 Hz, *J* = 9.7 Hz, *J* = 17.7 Hz, 1 H, $COCH_AH_B$), 2.84 (ddd, *J* = 9.6 Hz, *J* = 9.8 Hz, *J* = 17.7 Hz, 1 H, $COCH_AH_B$), 4.26 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.87 (dd, *J* = 2.9 Hz, *J* = 9.7 Hz, 1 H, CH), 7.10–7.53 (m, 5 H, Ph), 10.42 (br s, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.11 (CH_3), 21.13 ($CHCH_2$), 31.96 ($COCH_2$), 58.20 (CH), 61.88 (OCH_2), 120.16 (CH_{arom}), 124.27 (CH_{arom}), 129.00 (CH_{arom}), 137.17 ($C_{q,arom}$), 149.57 (NC=ON), 171.19 (COO), 176.71 (NCO) ppm. MS (ES, Pos): *m/z* (%) = 277.2 (100) $[M+H^+]$. IR: $\tilde{\nu}_{max}$ = 1702 (C=O), 1717 (C=O), 1739 (C=O), 3300 (br NH) cm^{-1}. $C_{14}H_{16}N_2O_4$ (276.11): calcd. C 60.86, H 5.84, N 10.14; found C 61.48, H 5.69, N 10.21.

Typical Experimental Procedure for the *N*-Alkylation of Ethyl 3-[1,4-Dialkyl-2,5-dioxo-1-imidazolidin-4-yl]propanoates (13): The hydantoin (**13**) (3 mmol) was dissolved in acetone (10 mL) and the alkyl halide (9 mmol) was added followed by K_2CO_3 (15 mmol, finely ground). The mixture was refluxed until TLC analysis showed that all starting material was consumed. The mixture was filtered and the solvent was removed in vacuo. If necessary the

residue was purified by flash chromatography (silica gel; hexane/EtOAc).

Ethyl 3-(3,4-Diallyl-2,5-dioxo-1-propylimidazolidin-4-yl)propanoate (14a): Yield: 0.97 g (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.24 (t, J = 7.2 Hz, 3 H, CH_3), 1.61 (sext, J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 2.05–2.20 (m, 4 H, $COCH_2CH_2$), 2.46–2.60 (m, 2 H, CCH_2), 3.44 (dt, J = 7.4 Hz, J = 1.7 Hz, 2 H, NCH_2CH_2), 3.82 (dd, J = 15.6 Hz, J = 6.9 Hz, 1 H, NCH_AH_BCH), 4.01 (dd, J = 15.6 Hz, J = 6.5 Hz, 1 H, NCH_AH_BCH), 4.11 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 5.10–5.35 (m, 4 H, 2×HC=CH_2), 5.42–5.56 (m, 1 H, HC=CH_2), 5.85–5.99 (m, 1 H, HC=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.35 ($CH_2CH_2CH_3$), 14.22 (CH_3), 21.57 ($CH_2CH_2CH_3$), 28.33 ($COCH_2$), 29.77 ($COCH_2CH_2$), 39.54 (CCH_2CH), 40.58 ($CH_2CH_2CH_3$), 42.87 (NCH_2CH), 60.90 (CH_2CH_3), 68.09 (C_q), 118.93 (HC=CH_2), 121.01 (HC=CH_2), 129.88 (HC=CH_2), 133.32 (HC=CH_2), 156.39 (NC=ON), 172.05 (C=OO), 174.19 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1643 (C=C), 1709 (C=O), 1735 (C=O), 1768 (C=O) cm^{-1}. MS: m/z (%) = 323.3 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (6:4)]: R_f = 0.52. $C_{17}H_{26}N_2O_4$ (322.40): calcd. C 63.33, H 8.13, N 8.69; found C 62.98, H 8.01, N 8.66.

Ethyl 3-(3,4-Diallyl-2,5-dioxo-1-phenylimidazolidin-4-yl)propanoate (14b): Yield: 1.07 g (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 2.14–2.38 (m, 4 H, $COCH_2CH_2$), 2.60 (dd, J = 14.2 Hz, J = 6.5 Hz, 1 H, CCH_AH_B), 2.67 (dd, J = 14.2 Hz, J = 8.0 Hz, 1 H, CCH_AH_B), 3.91 (dd, J = 15.4 Hz, J = 6.9 Hz, 1 H, NCH_AH_BCH), 4.09 (dd, J = 15.4 Hz, J = 6.6 Hz, 1 H, NCH_AH_BCH), 4.13 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.19–5.40 (m, 4 H, 2×HC=CH_2), 5.57–5.71 (m, 1 H, HC=CH_2), 5.92–6.06 (m, 1 H, HC=CH_2), 7.32–7.48 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.24 (CH_3), 28.48 ($COCH_2$), 29.97 ($COCH_2CH_2$), 39.78 (CCH_2CH), 43.16 (NCH_2CH), 61.00 (CH_2CH_3), 68.18 (C_q), 119.28 (HC=CH_2), 121.42 (HC=CH_2), 126.22 ($CH_{arom.}$), 128.35 ($CH_{arom.}$), 129.13 ($CH_{arom.}$), 129.77 (HC=CH_2), 131.52 ($C_{q\ arom.}$) ppm. 133.04 (HC=CH_2), 155.22 (NC=ON), 171.99 (C=OO), 173.23 (NC=O). IR: $\tilde{\nu}_{max}$ = 1642 (C=C), 1717 (br C=O), 1772 (C=O) cm^{-1}. MS: m/z (%) = 357.2 (100) [M + H$^+$]. $C_{20}H_{24}N_2O_4$ (356.42): calcd. C 67.40, H 6.79, N 7.86; found C 67.08, H 6.74, N 7.84.

Ethyl 3-[4-Allyl-1-benzyl-3-(2-chloroprop-2-enyl)-2,5-dioxo-1-phenylimidazolidin-4-yl]propanoate (14c): Yield: 0.85 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.0 Hz, 3 H, CH_3), 2.00–2.28 (m, 4 H, $COCH_2CH_2$), 2.50 (dd, J = 14.5 Hz, J = 7.2 Hz, 1 H, CCH_AH_B), 2.58 (dd, J = 14.5 Hz, J = 7.3 Hz, 1 H, CCH_AH_B), 3.90 (d, J = 15.8 Hz, 1 H, NCH_AH_BC), 4.09 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.27 (d, J = 15.8 Hz, 1 H, NCH_AH_BC), 4.62 (d, J = 14.4 Hz, 1 H, NCH_AH_BPh), 4.68 (d, J = 14.4 Hz, 1 H, NCH_AH_BPh), 4.93–5.10 (m, 2 H, HC=CH_2), 5.28–5.39 (m, 1 H, HC=CH_2), 5.42 (d, J = 1.8 Hz, 1 H, C=CH_AH_B), 5.50 (d, J = 1.8 Hz, 1 H, C=CH_AH_B), 7.25–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.22 (CH_3), 28.33 ($COCH_2$), 29.95 ($COCH_2CH_2$), 39.54 (CCH_2CH), 42.79 (NCH_2Ph), 46.50 (NCH_2C), 60.84 (CH_2CH_3), 68.38 (C_q), 116.72 (C=CH_2), 121.28 (HC=CH_2), 128.06 ($CH_{arom.}$), 128.67 ($CH_{arom.}$), 128.75 ($CH_{arom.}$), 129.44 (HC=CH_2), 135.88 ($C_{q\ arom.}$) ppm. 137.45 (CCl), 156.52 (NC=ON), 172.03 (C=OO), 173.73 (NC=O). IR: $\tilde{\nu}_{max}$ = 1635 (C=C), 1713 (br C=O), 1772 (C=O) cm^{-1}. MS: m/z (%) = 405.2 (100) [M + H$^+$], 407.2 (29) [M + H$^+$]. Chromatography [Hex/EtOAc (7:3)]: R_f = 0.35. $C_{21}H_{25}ClN_2O_4$ (404.89): calcd. C 62.30, H 6.22, N 6.92; found C 62.55, H 6.14, N 6.86.

Ethyl 3-[4-Allyl-3-(2-methylprop-2-enyl)-2,5-dioxo-1-phenylimidazolidin-4-yl]propanoate (14d): Yield: 1.11 g (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 3 H, CH_3), 1.86 (s, 3 H, CCH_3), 2.18–2.38 (m, 4 H, $COCH_2CH_2$), 2.63–2.67 (m, 2 H, CH_2CH), 3.86 (d, J = 15.3 Hz, 1 H, NCH_AH_BC), 4.03 (d, J = 15.3 Hz, 1 H, NCH_AH_BC), 4.12 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 4.96 (s, 1 H, C=CH_AH_B), 5.02 (s, 1 H, C=CH_AH_B), 5.19 (d, J = 3.9 Hz, 1 H, HC=CH_AH_B), 5.24 (d, J = 10.7 Hz, 1 H, HC=CH_AH_B), 5.55–5.69 (m, 1 H, HC=CH_2), 7.31–7.48 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.23 (CH_3), 20.89 (CCH_3), 28.53 ($COCH_2$), 29.95 ($COCH_2CH_2$), 39.72 (CCH_2CH), 46.41 (NCH_2C), 60.97 (CH_2CH_3), 68.44 (C_q), 114.96 (C=CH_2), 121.42 (HC=CH_2), 126.17 ($CH_{arom.}$), 128.32 ($CH_{arom.}$), 129.12 ($CH_{arom.}$), 129.83 (HC=CH_2), 131.65 ($C_{q\ arom.}$) ppm. 141.50 (C=CH_2), 155.80 (NC=ON), 172.00 (C=OO), 173.33 (NC=O). IR: $\tilde{\nu}_{max}$ = 1717 (br C=O), 1773 (C=O) cm^{-1}. MS: m/z (%) = 371.2 (100) [M + H$^+$]. $C_{21}H_{26}N_2O_4$ (370.44): calcd. C 68.09, H 7.07, N 7.56; found C 67.93, H 6.97, N 7.55.

Ethyl 3-{4-Allyl-1-benzyl-3-[2-(chloromethyl)prop-2-enyl]-2,5-dioxoimidazolidin-4-yl}propanoate (14e): Yield: 0.90 g (72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3 H, CH_3), 2.01–2.20 (m, 4 H, $COCH_2CH_2$), 2.48 (dd, J = 14.5 Hz, J = 7.4 Hz, 1 H, CCH_AH_BCH), 2.56 (dd, J = 14.5 Hz, J = 6.9 Hz, 1 H, CCH_AH_BCH), 3.89–4.12 (m, 4 H, NCH_2CCH_2Cl), 4.09 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.64 (s, 2 H, NCH_2Ph), 4.79–5.08 (m, 2 H, HC=CH_2), 5.23 (s, 1 H, C=CH_AH_B), 5.23–5.37 (m, 1 H, HC=CH_2), 5.37 (s, 1 H, C=CH_AH_B), 7.25–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.22 (CH_3), 28.32 ($COCH_2$), 29.71 ($COCH_2CH_2$), 39.52 (CCH_2CH), 42.21 (NCH_2CH), 42.73 (NCH_2Ph), 45.98 (CH_2Cl), 60.89 (CH_2CH_3), 68.55 (C_q), 118.50 (C=CH_2), 121.27 (HC=CH_2), 128.06 ($CH_{arom.}$), 128.69 ($CH_{arom.}$), 128.78 ($CH_{arom.}$), 129.51 (HC=CH_2), 135.94 ($C_{q\ arom.}$) ppm. 140.87 (C=CH_2), 156.81 (NC=ON), 171.87 (C=OO), 173.94 (NC=O). IR: $\tilde{\nu}_{max}$ = 1710 (br C=O), 1769 (C=O) cm^{-1}. MS: m/z (%) = 419.2/421.3 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (6:4)]: R_f = 0.63. $C_{22}H_{27}N_2O_4$ (418.91): calcd. C 63.08, H 6.50, N 6.69; found C 62.94, H 6.55, N 6.72.

Ethyl 2-{[5-Allyl-3-benzyl-5-(3-ethoxy-3-oxopropyl)-2,4-dioxoimidazolidin-1-yl]methyl}acrylate (14f): Yield: 0.60 g (45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.32 (m, 6 H, 2×CH_2CH_3), 1.94–2.15 (m, 4 H, $COCH_2CH_2$), 2.60 (dd, J = 14.2 Hz, J = 6.5 Hz, 1 H, CCH_AH_B), 2.52 (d, J = 7.2 Hz, 2 H, CCH_2), 4.02–4.16 (m, 3 H, NCH_AH_B + CH_2CH_3), 4.19–4.26 (m, 3 H, NCH_AH_B + CH_2CH_3), 4.64 (s, 2 H, CH_2Ph), 4.91–5.07 (m, 2 H, HC=CH_2), 5.22–5.36 (m, 1 H, HC=CH_2), 5.99 (d, J = 0.8 Hz, 1 H, C=CH_AH_B), 6.42 (s, 1 H, C=CH_AH_B), 7.24–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.21 (2×CH_3), 28.36 ($COCH_2$), 29.75 ($COCH_2CH_2$), 39.40 (CCH_2CH), 39.75 (NCH_2CH), 42.67 (CH_2Ph), 60.79 (CH_2CH_3), 61.36 (CH_2CH_3), 68.43 (C_q), 121.09 (HC=CH_2), 128.00 ($CH_{arom.}$), 128.64 ($CH_{arom.}$), 128.73 ($CH_{arom.}$), 129.60 (C=CH_2), 129.67 (HC=CH_2), 136.02 ($C_{q\ arom.}$) ppm. 156.64 (NC=ON), 165.99 (CC=O), 171.85 (C=OO), 174.00 (NC=O). IR: $\tilde{\nu}_{max}$ = 1662 (C=C), 1711 (br C=O), 1770 (C=O) cm^{-1}. MS: m/z (%) = 443.2 (100) [M + H$^+$]. Chromatography [Hex/EtOAc/ether (9:1:2)]: R_f = 0.07. $C_{24}H_{30}N_2O_4$ (442.50): calcd. C 65.14, H 6.83, N 6.33; found C 65.09, H 6.85, N 6.23.

Ethyl 3-[3-Allyl-4-(2-chloroprop-2-enyl)-2,5-dioxo-1-propylimidazolidin-4-yl]propanoate (14g): Yield: 0.89 g (83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.24 (t, J = 7.1 Hz, 1.5 H, CH_3), 1.25 (t, J = 7.1 Hz, 1.5 H, CH_3), 1.63 (sext, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.01–2.25 (m, 4 H, $COCH_2CH_2$), 2.80 (d, J = 14.9 Hz, 1 H, CCH_AH_B), 2.95 (d, J = 14.9 Hz, 1 H, CCH_AH_B), 3.42 (dt, J = 7.4 Hz, J = 11.8 Hz, 1 H, $NCH_AH_BCH_2$), 3.48 (dt, J = 7.4 Hz, J = 11.8 Hz, 1 H, $NCH_AH_BCH_2$), 3.65 (dd, J = 15.6 Hz, J = 7.8 Hz, 1 H,

NCH_AH$_B$CH), 4.11 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.28 (dd, J = 15.6 Hz, J = 5.5 Hz, 1 H, NCH$_A$$H_B$CH), 5.19–5.35 (m, 4 H, C=CH_2 + HC=CH_2), 5.89–6.02 (m, 1 H, HC=CH$_2$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.32 (CH$_2$CH$_2$$CH_3$), 14.19 (CH$_3$), 21.32 (CH$_2$$CH_2CH_3$), 27.92 (CO$CH_2$), 30.32 (COCH$_2$$CH_2$), 40.70 ($CH_2CH_2CH_3$), 43.54 (C$CH_2$C + NCH$_2$CH), 60.84 ($CH_2CH_3$), 67.49 (C$_q$), 118.14 (C=$CH_2$), 119.02 (HC=$CH_2$), 133.13 (H$C$=CH$_2$), 135.09 ($C$=CH$_2$), 156.14 (NC=ON), 171.73 (C=OO), 173.45 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1632 (C=C), 1709 (C=O), 1735 (C=O), 1770 (C=O) cm^{-1}. MS: m/z (%) = 357.7/359.7 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (2:1)]: R_f = 0.43. C$_{17}$H$_{25}$ClN$_2$O$_4$ (356.84): calcd. C 57.22, H 7.06, N 7.85; found C 56.89, H 6.90, N 7.83.

Ethyl 3-[3-Allyl-4-(2-methylprop-2-enyl)-2,5-dioxo-1-propylimidazolidin-4-yl]propanoate (14h): Yield: 1.01 g (100%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, J = 7.4 Hz, 3 H, CH$_2$CH$_2$CH_3), 1.24 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.61 (sext, J = 7.4 Hz, 2 H, CH$_2$CH_2CH$_3$), 1.63 (s, 3 H, CCH$_3$), 1.96–2.22 (m, 4 H, COCH_2CH_2), 2.49 (d, J = 14.4 Hz, 1 H, CCH_AH$_B$), 2.57 (d, J = 14.4 Hz, 1 H, CCH$_A$$H_B$), 3.41 (dt, J = 7.4 Hz, J = 13.5 Hz, 1 H, NCH_AH$_B$CH$_2$), 3.45 (dt, J = 7.4 Hz, J = 13.5 Hz, 1 H, NCH$_A$$H_BCH_2$), 3.61 (dd, J = 15.4 Hz, J = 7.7 Hz, 1 H, NCH_AH$_B$CH), 4.11 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 4.21 (ddt, J = 15.4 Hz, J = 5.5 Hz, J = 1.4 Hz, 1 H, NCH$_A$$H_B$CH), 4.72 (d, J = 0.8 Hz, 1 H, C=CH_AH$_B$), 4.86 (t, J = 1.5 Hz, 1 H, C=CH$_A$$H_B$), 5.20 (dd, J = 9.9 Hz, J = 0.8 Hz, 1 H, HC=CH_AH$_B$), 5.31 (dq, J = 17.0 Hz, J = 1.4 Hz, 1 H, HC=CH$_A$$H_B$), 5.87–6.00 (m, 1 H, HC=CH$_2$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.34 (CH$_2$CH$_2$$CH_3$), 14.24 (CH$_3$), 21.45 (CH$_2$$CH_2CH_3$), 23.67 (C$CH_3$), 28.13 (CO$CH_2$), 30.88 (COCH$_2$$CH_2$), 40.58 ($CH_2CH_2CH_3$), 42.45 (C$CH_2$C), 43.23 (N$CH_2$CH), 60.82 ($CH_2CH_3$), 67.97 (C$_q$), 116.58 (C=$CH_2$), 118.96 (HC=$CH_2$), 133.19 (H$C$=CH$_2$), 138.77 ($C$=CH$_2$), 156.32 (NC=ON), 172.00 (C=OO), 174.39 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1645 (C=C), 1708 (C=O), 1735 (C=O), 1767 (C=O) cm^{-1}. MS: m/z (%) = 337.8 (100) [M + H$^+$]. C18 H$_{28}$N$_2$O$_4$ (336.43): calcd. C 64.26, H 8.39, N 8.33; found C 64.22, H 8.55, N 8.28.

Typical Experimental Procedure for the Synthesis of Ethyl 3-(2,6-Dialkyl-1,3-dioxo-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl)propanoates (15): The hydantoin **14** (0.6 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL, freshly distilled from CaH$_2$) and the second generation Grubbs' catalyst (0.03 mmol) was added. The mixture was refluxed under N$_2$ for 4 h. The residue was adsorbed onto silica gel by removal of the solvent in vacuo and purified by flash chromatography (silica gel; hexane/EtOAc).

Ethyl 3-[1,3-Dioxo-2-propyl-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl]propanoate (15a): Yield: 0.16 g (93%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.93 (t, J = 7.4 Hz, 3 H, CH$_3$ pr), 1.24 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3), 1.66 (sext, J = 7.4 Hz, 2 H, NCH$_2$CH_2), 2.05–2.33 (m, 6 H, COCH_2CH_2 and CCH_2), 3.49 (dt, J = 7.4 Hz, J = 1.6 Hz, 2 H, NCH_2CH$_2$), 3.56 (d, J = 18.2 Hz + small splitting, 1 H, NCH_AH$_B$), 4.10 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.41 (d, J = 18.2 Hz + small splitting, 1 H, NCH$_A$$H_B$), 5.78 (t, J = 1.9 Hz + small splitting, 2 H, HC=CH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.22 (CH$_3$ pr), 14.15 (CH$_2$$CH_3$), 21.53 (CH$_2$ pr), 28.43 (COCH$_2$), 28.80 (COCH$_2$$CH_2$), 31.65 (C$CH_2$CH), 37.71 (NCH$_2$), 40.37 (NCH$_2$ pr), 60.28 (C$_q$), 60.87 (CH$_2$CH$_3$), 121.59 (CH), 123.27 (CH), 155.15 (NC=ON), 172.39 (C=OO), 175.74 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1656 (C=C), 1709 (br C=O), 1771 (C=O) cm^{-1}. MS: m/z (%) = 295.2 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (6:4)]: R_f = 0.25. C$_{15}$H$_{22}$N$_2$O$_4$ (294.35): calcd. C 61.21, H 7.53, N 9.52; found C 60.92, H 7.62, N 9.48.

Ethyl 3-[1,3-Dioxo-2-phenyl-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl]propanoate (15b): Yield: 0.17 g (88%). M.p. 110–113 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.23 (t, J = 7.2 Hz, 3 H, CH$_2$CH_3), 2.19–2.56 (m, 6 H, COCH_2CH_2 and CCH_2), 3.65 (d, J = 19.9 Hz + small splitting, 1 H, NCH_AH$_B$), 4.12 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 4.48 (d, J = 19.9 Hz, 1 H, NCH$_A$$H_B$), 5.78 (m, 1 H, CH), 7.35–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.22 (CH$_2$$CH_3$), 28.94 (CO$CH_2$), 28.99 (COCH$_2$$CH_2$), 31.83 (C$CH_2$CH), 38.04 (NCH$_2$), 60.39 (C$_q$), 61.08 ($CH_2CH_3$), 121.71 (CH), 123.25 (CH), 126.25 (CH$_{arom.}$), 128.32 (CH$_{arom.}$), 129.16 (CH$_{arom.}$), 131.65 (C$_{q\ arom.}$), 153.99 (NC=ON), 172.42 (C=OO), 174.62 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1721 (br C=O), 1775 (C=O) cm^{-1}. MS: m/z (%) = 329.2 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (7:3)]: R_f = 0.21. C$_{18}$H$_{20}$N$_2$O$_4$ (328.36): calcd. C 65.84, H 6.14, N 8.53; found C 65.70, H 6.34, N 8.45.

Ethyl 3-[2-Benzyl-6-chloro-1,3-dioxo-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl]propanoate (15c): Instead of refluxing in CH$_2$Cl$_2$, the reaction is refluxed in dry benzene for 16 hours. Yield: 0.17 g (75%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.20 (t, J = 7.1 Hz, 3 H, CH$_3$), 2.00–2.33 (m, 4 H, COCH_2CH_2), 2.39–2.41 (m, 2 H, CH_2CH), 3.63 (dq, J = 17.9 Hz, J = 2.6 Hz, 1 H, NCH_AH$_B$CCl), 4.07 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.49 (dq, J = 17.9 Hz, J = 2.2 Hz, 1 H, NCH$_A$$H_B$CCl), 4.67 (s, 2 H, NC$H_2$Ph), 5.86 (dq, J = 1.6 Hz, J = 3.5 Hz, 1 H, CH), 7.27–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.19 (CH$_3$), 28.48 (COCH$_2$), 28.71 (COCH$_2$$CH_2$), 32.61 (C$CH_2$CH), 41.87 (NCH$_2$C), 42.64 (N$CH_2$Ph), 60.07 (C$_q$), 61.02 ($CH_2CH_3$), 119.28 (CH), 127.31 (CCl), 128.14 (CH$_{arom.}$), 128.52 (CH$_{arom.}$), 128.83 (CH$_{arom.}$), 135.91 (C$_{q\ arom.}$), 154.51 (NC=ON), 172.20 (C=OO), 174.49 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1660 (C=C), 1714 (br C=O), 1775 (C=O) cm^{-1}. MS: m/z (%) = 377.2/379.2 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (7:3)]: R_f = 0.29. C$_{19}$H$_{21}$ClN$_2$O$_4$ (376.83): calcd. C 60.56, H 5.62, N 7.43; found C 60.44, H 5.74, N 7.37.

Ethyl 3-[6-Methyl-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl]propanoate (15d): Yield: 0.16 g (79%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.23 (t, J = 7.2 Hz, 3 H, CH$_2$CH_3), 1.76 (s, 3 H, CCH_3), 2.19–2.52 (m, 6 H, COCH_2CH_2 and CCH_2), 3.50 (d, J = 18.0 Hz, 1 H, NCH_AH$_B$), 4.12 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 4.34 (d, J = 18.0 Hz, 1 H, NCH$_A$$H_B$), 5.51 (t, J = 1.9 Hz, 1 H, CH), 7.35–7.49 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.22 (CH$_2$$CH_3$), 20.21 (C$CH_3$), 28.79 (CO$CH_2$), 29.05 (COCH$_2$$CH_2$), 31.89 (C$CH_2$CH), 41.39 (NCH$_2$), 60.29 (C$_q$), 61.07 ($CH_2CH_3$), 116.05 (CH), 126.26 (CH$_{arom.}$), 128.31 (CH$_{arom.}$), 129.16 (CH$_{arom.}$), 130.57 (CCH$_3$), 131.68 (C$_{q\ arom.}$), 153.96 (NC=ON), 172.51 (C=OO), 174.74 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1721 (br C=O), 1775 (C=O) cm^{-1}. MS: m/z (%) = 343.2 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (7:3)]: R_f = 0.29. C$_{19}$H$_{22}$N$_2$O$_4$ (342.39): calcd. C 66.65, H 6.48, N 8.18; found C 66.25, H 6.39, N 8.17.

Ethyl 3-[2-Benzyl-6-(chloromethyl)-1,3-dioxo-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl]propanoate (15e): Yield: 0.20 g (85%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.20 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3), 2.05–2.21 (m, 4 H, COCH_2CH_2), 2.23–2.43 (m, 2 H, CCH$_2$), 3.59 (dq, J = 18.0 Hz, J = 2.4 Hz, 1 H, NCH_AH$_B$), 4.05 (s, 2 H, CH$_2$Cl), 4.07 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.54 (d, J = 18.0 Hz, 1 H, NCH$_A$$H_B$), 4.67 (d, J = 15.0 Hz, 1 H, NCH_AH$_B$Ph), 4.68 (d, J = 15.0 Hz, 1 H, NCH$_A$$H_B$Ph), 5.88 (q-like, J = 2.4 Hz, 1 H, CH), 7.28–7.41 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.21 (CH$_2$$CH_3$), 28.62 (CO$CH_2$), 28.73 (COCH$_2$$CH_2$), 31.58 (C$CH_2$CH), 38.38 (NCH$_2$), 42.56 (N$CH_2$Ph), 45.83 (CH$_2$Cl), 60.30 (C$_q$), 60.97 ($CH_2CH_3$), 121.85 (CH), 128.06 (CH$_{arom.}$), 128.55 (CH$_{arom.}$), 128.80 (CH$_{arom.}$), 131.45 (CCH$_2$Cl), 136.08 (C$_{q\ arom.}$), 154.77 (NC=ON), 172.33 (C=OO), 175.00 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1713 (br C=O), 1771 (C=O) cm^{-1}. MS:

m/*z* (%) = 391.2/393.2 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (7:3)]: R_f = 0.18. $C_{20}H_{23}ClN_2O_4$ (390.86): calcd. C 61.46, H 5.93, N 7.17; found C 61.19, H 5.85, N 7.13.

Ethyl 2-Benzyl-8a-(3-ethoxy-3-oxopropyl)1,3-dioxo-1,2,3,5,8,8a-hexahydroimidazo[1,5-*a*]pyridine-6-carboxylate (15f): Instead of the second generation Grubbs' catalyst, the second generation Hoveyda-Grubbs' catalyst is used for this reaction. Yield: 0.14 g (55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 2.04–2.17 (m, 4 H, $COCH_2CH_2$), 2.41 (dq, *J* = 18.4 Hz, *J* = 2.8 Hz, 1 H, CCH_AH_B), 2.54 (dd, *J* = 18.4 Hz, *J* = 5.5 Hz, 1 H, CCH_AH_B), 3.73 (ddt, *J* = 18.7 Hz, *J* = 3.7 Hz, *J* = 4.1 Hz, 1 H, NCH_AH_B), 4.07 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.21 (dq, *J* = 10.6 Hz, *J* = 7.0 Hz, 1 H, $CH_AH_BCH_3$), 4.25 (dq, *J* = 10.6 Hz, *J* = 7.1 Hz, 1 H, $CH_AH_BCH_3$), 4.68 (s, 2 H, NCH_2Ph), 4.70 (dt, *J* = 18.7 Hz, *J* = 1.9 Hz, 1 H, NCH_AH_B), 6.98 (dd, *J* = 5.8 Hz, *J* = 2.2 Hz, 1 H, CH), 7.29–7.59 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.19 (CH_2CH_3), 14.27 (CH_2CH_3), 28.61 ($COCH_2$), 28.76 ($COCH_2CH_2$), 32.09 (CCH_2CH), 36.91 (NCH_2), 42.58 (NCH_2Ph), 59.92 (C_q), 60.99 (CH_2CH_3), 61.16 (CH_2CH_3), 128.09 (CH), 128.35 (CH), 128.80 (CH), 133.42 (HC=C), 136.03 (HC=*C*), 137.67 ($C_{q,ar}$), 154.61 (NC=ON), 164.28 ($CCOOEt$), 172.13 (C=OO), 174.68 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1659 (C=C), 1716 (br C=O), 1774 (C=O) cm^{-1}. MS: *m*/*z* (%) = 415.3 (100) [M + H$^+$]. Chromatography: first Hex/EtOAc (3:1) until R_f = 0.26, then strip with EtOAc + 5% CH_2Cl_2. $C_{22}H_{26}N_2O_4$ (414.45): calcd. C 63.76, H 6.32, N 6.76; found C 63.54, H 6.51, N 6.72.

Ethyl 3-[7-Chloro-1,3-dioxo-2-propyl-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl]propanoate (15g): Instead of refluxing in CH_2Cl_2, the reaction is refluxed in dry benzene for 16 hours. Yield: 0.15 g (77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.24 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.66 (sext, *J* = 7.4 Hz, 2 H, NCH_2CH_2), 2.07–2.36 (m, 4 H, $COCH_2CH_2$), 2.51 (d, *J* = 17.4 Hz, 1 H, CCH_AH_BC), 2.64 (dq, *J* = 17.4 Hz, *J* = 3.1 Hz, 1 H, CCH_AH_BC), 3.49 (dt, *J* = 7.4 Hz, *J* = 2.2 Hz, 2 H, NCH_2CH_2), 3.61 (dq, *J* = 18.4 Hz, *J* = 3.2 Hz, 1 H, NCH_AH_B), 4.11 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.49 (dt, *J* = 18.4 Hz, *J* = 3.2 Hz, 1 H, NCH_AH_B), 5.90 (q, *J* = 3.2 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.26 (CH_3 pr), 14.21 (CH_2CH_3), 21.52 (CH_2 pr), 28.70 ($COCH_2CH_2$), 38.16 (NCH_2), 38.77 (CCH_2C), 40.64 (NCH_2 pr), 61.08 (CH_2CH_3), 61.55 (C_q), 120.17 (CH), 126.86 (CCl), 154.97 (NC=ON), 172.20 (C=OO), 174.29 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1663 (C=C), 1713 (br C=O), 1774 (C=O) cm^{-1}. MS: *m*/*z* (%) = 329.8/331.7 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (2:1)]: R_f = 0.43. $C_{15}H_{21}ClN_2O_4$ (328.79): calcd. C 54.79, H 6.44, N 8.52; found C 54.57, H 6.59, N 8.52.

Ethyl 3-[7-Methyl-1,3-dioxo-2-propyl-2,3,5,8-tetrahydroimidazo[1,5-*a*]pyridin-8a(1*H*)-yl]propanoate (15h): Yield: 0.16 g (86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.24 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.66 (sext, *J* = 7.4 Hz, 2 H, NCH_2CH_2), 1.74 (s, 3 H, CCH_3), 2.05–2.24 (m, 6 H, $COCH_2CH_2$ and CCH_2), 3.49 (dt, *J* = 7.4 Hz, *J* = 1.7 Hz, 2 H, NCH_2CH_2), 3.51 (dddd, *J* = 17.9 Hz, *J* = 12.5 Hz, *J* = 4.6 Hz, *J* = 2.2 Hz, 1 H, NCH_AH_B), 4.10 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.36 (d, *J* = 17.9 Hz, 1 H, NCH_AH_B), 5.44 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.29 (CH_3 pr), 14.22 (CH_2CH_3), 21.60 (CH_2 pr), 23.51 (CCH_3), 28.55 ($COCH_2$), 28.85 ($COCH_2CH_2$), 36.38 (CCH_2C), 37.72 (NCH_2), 40.42 (NCH_2 pr), 60.93 (C_q + CH_2CH_3), 116.78 (CH), 129.42 (C), 155.24 (NC=ON), 172.48 (HNC=O), 175.81 (C=OO) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 11.05 (CH_3 pr), 13.92 (CH_2CH_3), 21.60 (CH_2 pr), 22.93 (CCH_3), 28.73 ($COCH_2$), 28.85 ($COCH_2CH_2$), 35.95 (CCH_2C), 37.43 (NCH_2), 40.12 (NCH_2 pr), 60.41 (CH_2CH_3), 60.64 (C_q), 116.83 (CH), 128.83 (C), 154.98 (NC=ON), 171.90 (C=OO), 175.26 (NC=O) ppm. IR: $\tilde{\nu}_{max}$ = 1712 (br C=O), 1770 (C=O) cm^{-1}. MS: *m*/*z* (%) = 309.8 (100) [M + H$^+$]. Chromatography [Hex/EtOAc (7:3)]: R_f = 0.27. $C_{16}H_{24}N_2O_4$ (308.37): calcd. C 62.32, H 7.84, N 9.08; found C 62.38, H 8.00, N 9.10.

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