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First Synthesis of α,β-Unsaturated Lactones with High Diversity through the Passerini Reaction and Ring-Closing Metathesis (RCM)[‡]

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A new class of α,β-unsaturated pyran-2-carboxamides was easily accessed by a multicomponent reaction (MCR), followed by a ring-closing metathesis (RCM) using a ruthenium catalyst. In the first step, α-acyloxy carboxamides with two terminal double bonds were formed from terminal unsaturated carboxylic acids, allyl ketones, and isocyanides (Passerini reaction, P-3CR).

Introduction

One-pot multicomponent reactions (MCRs) have emerged as powerful tools in organic synthesis because they offer significant advantages, such as the construction of complex molecules from readily available building blocks, the realization of higher yields than almost any sequential synthesis of the same target, the need for a single purification step, and the easy adaptation to combinatorial synthesis.[1] MCRs provide significant advantages over traditional stepwise strategies in terms of cost, waste, time, and atom economy, and these reactions constitute an extremely popular field of research within both academic and industrial domains.[2] Interest in the Passerini three-component reaction (P-3CR), which involves an isocyanide, a carbonyl compound, and a carboxylic acid, is growing because of its efficiency in the syntheses of diverse products.[3] As a result of the discovery of efficient catalysts,[4] ring-closing metathesis (RCM) is currently one of the best methods to create cyclic substructures from unsaturated substrates.[5,6]

The sequential combination of a MCR and a RCM provides even more complex structural types.[7,8] However, there are just a few examples found in the literature. For instance, the combination of an Ugi four-component reaction (U-4CR) and a RCM can produce a new class of bicyclic lactams.[9] The combination of the P-3CR and a RCM can successfully build macrocycles as well.[10]

In connection with our interest in the synthesis of new heterocyclic structures, we describe the formation of a new class of α,β-unsaturated-δ-oxacaprolactams from cyclic imines as starting materials.[11] α,β-Unsaturated lactams are present in many biologically active molecules.[12] However, the α,β-unsaturated-δ-oxacaprolactams are almost unknown in the literature.[11] The synthetic procedure is based on a sequence involving the Asinger four-component reaction (A-4CR),[13,14] followed by an acid chloride addition in the second step.[15,16] Finally a ring-closing metathesis is carried out using a ruthenium catalyst. The metathesis reactions proceed in moderate to very good yields using a Grubbs II catalyst.[6] The reported metathesis-based caprolactam synthesis is moderately optimized for solvent and temperature with respect to the catalysts. The described synthesis is of great value and it provides information about this potentially important class of molecules.

In this paper, we investigate the P-3CR of isocyanides **1**, allyl ketones **2**, and carboxylic acids **3**, which give α-acyloxy carboxamides **4** with two terminal double bonds. Furthermore, we report the preparation of a new family of α,β-unsaturated pyran-2-carboxamides **5** through a ruthenium-catalyzed ring-closing metathesis (Scheme 1).

Results and Discussion

The Passerini three-component reaction, first described in 1921,[2] is a reaction between carboxylic acids, oxo-compounds, and isocyanides that provides α-acyloxy carboxamides **4** in one step (Scheme 1).[17,18] This group of compounds is present in the structures of many natural products.[15,19] The Passerini reaction is an inexpensive and rapid way to generate compound libraries.

[‡] Sequential Multicomponent Reaction and Ring-Closing Metathesis in the Synthesis of New Heterocycles, 4. Part 1–3: Ref.[11]

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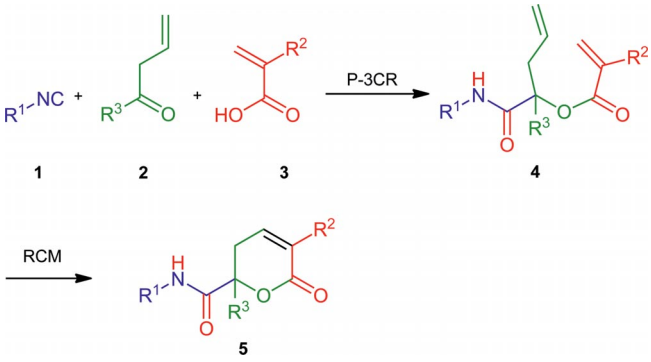
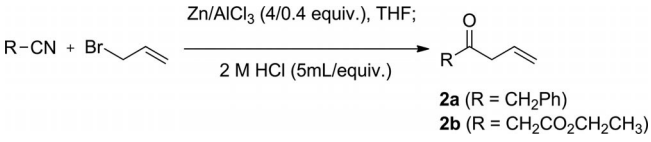


Scheme 1. Synthesis of α,β-unsaturated lactones **5**. R^1 = CH_2Ph, Cy, $CH_2CO_2CH_3$, $CH_2CO_2CH_2CH_3$; R^2 = H, CH_3; R^3 = CH_2Ph, $CH_2CO_2CH_2CH_3$.

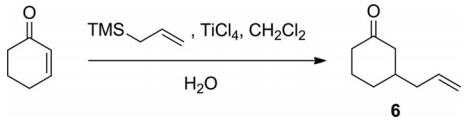
Passerini Reaction with Allyl Ketones

Rarely investigated is the use of allyl ketones in MCRs, as allyl ketones may isomerize easily to α,β-unsaturated ketones (Michael acceptor), which cannot be used in Ugi or Passerini reactions.[20] For the construction of new cyclic structures through a ring-closing metathesis, it is necessary to build a molecule with two terminal olefin groups. Produced in excellent yields, 1-phenylpent-4-en-2-one (**2a**) and ethyl 3-oxohex-5-enoate (**2b**) were synthesized from the mixture of zinc, nitrile, and allyl bromide in the presence of the Lewis acid $AlCl_3$ through a Barbier-type reaction (Scheme 2).[21]



Scheme 2. Synthesis of allyl ketones **2a** and **2b**.

The known compound 3-allylcyclohexanone (**6**) was synthesized from cyclohexenone and allyltrimethylsilane with titanium tetrachloride (1 equiv.) by a Sakurai reaction (Scheme 3).[22,23]



Scheme 3. Synthesis of 3-allyl ketone **6**.

To avoid the isomerization of the freshly prepared allyl ketones, they were used directly. Thus, the target molecules **4** were obtained in good to moderate yields. Acrylic acid or metacrylic acid were used to provide a second C=C bond in carboxamide **4**. Using this approach, various precursors (i.e., **4**) for ring-closing metathesis have been prepared. Furthermore, structure **4** bears elements of destruxin, which is an inducer of erythropoietin.[24] Details of the prepared carboxamides **4** and the reaction yields are summarized in Figure 1.

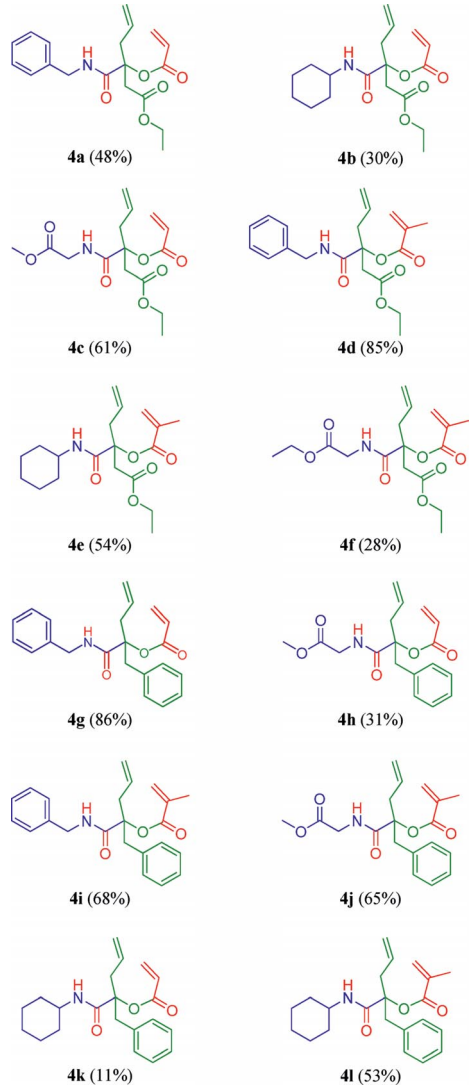


Figure 1. Products **4** obtained by the P-3CR (cf. Scheme 1). All yields are isolated yields.

We obtained single crystals of **4h** from a mixture of hexane and ethyl acetate, and its structure was further confirmed by X-ray crystallographic analysis (Figure 2).

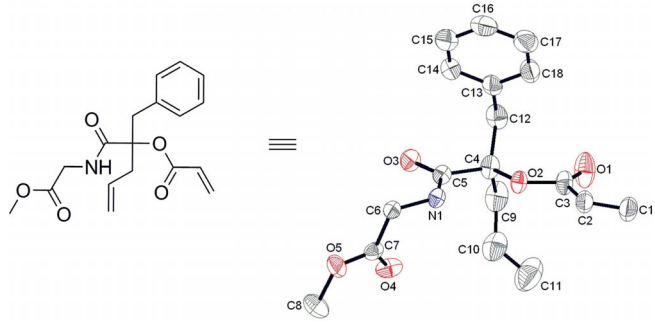
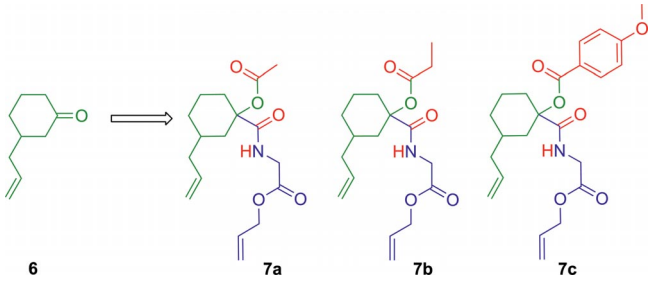


Figure 2. X-ray crystal structure of the racemic α-acyloxy carboxamide **4h**.

By using the 3-allylcyclohexanone (**6**), it was also possible to build the three structures **7a**–**c** in moderate yields from 27 to 41 % (Scheme 4).



Scheme 4. Synthesized structures by using 3-allylcyclohexanone (**6**).

Ring-Closing Metathesis (RCM)

The synthesis of new heterocycles through a ring-closing metathesis can be found in the literature.[25] As an extension of previous investigations,[6] we decided to employ the Evonik benzylidene ruthenium catalyst in the metathesis reaction (Figure 3).

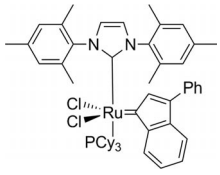


Figure 3. Metathesis catalyst used for RCM reactions.

With the expected ten dienes **4a**–**j** in hand, we next investigated the ring-closing metathesis. α-Acyloxy carboxamides **4** and the catalyst, in a ratio of 20:1, were dissolved in toluene and heated to approximately 70 °C. The reaction was monitored by TLC and stopped when the starting material (i.e., **4**) was no longer detected. With these reaction conditions, it was possible to obtain the desired α,β-unsaturated pyran-2-carboxamides **5** in good to excellent yields up to 97% (Figure 4). Furthermore, the ring-closing metathesis of α-acyloxy carboxamides **7a**–**c** was attempted under identical conditions, but the resultant 12-membered ring was not obtained. This could be due to the rigidity of the cyclohexane ring.

We obtained single crystals of **5g** from a mixture of hexane and ethyl acetate, and its structure was further confirmed by X-ray crystallographic analysis (Figure 5).

Finally the potential for the α,β-unsaturated pyran-2-carboxamides **5** as a Michael acceptor was demonstrated by an initial experiment adding thioacetic acid to give a sulfur atom attached to the β-C atom of the carbonyl compound.[26,27] Using the methods of Brown, Jones and Pinder,[26] a derivative of compound **5g** was synthesized by the addition of thioacetic acid in the presence of AIBN [azobis(isobutyronitrile), Scheme 5].

We obtained single crystals of new compound **8** from a mixture of hexane and ethyl acetate, and its structure was further confirmed by X-ray crystallographic analysis (Figure 6). The structure shows a *trans*-configuration between the proton attached to the C-1 position and the benzyl group connected to C-4.

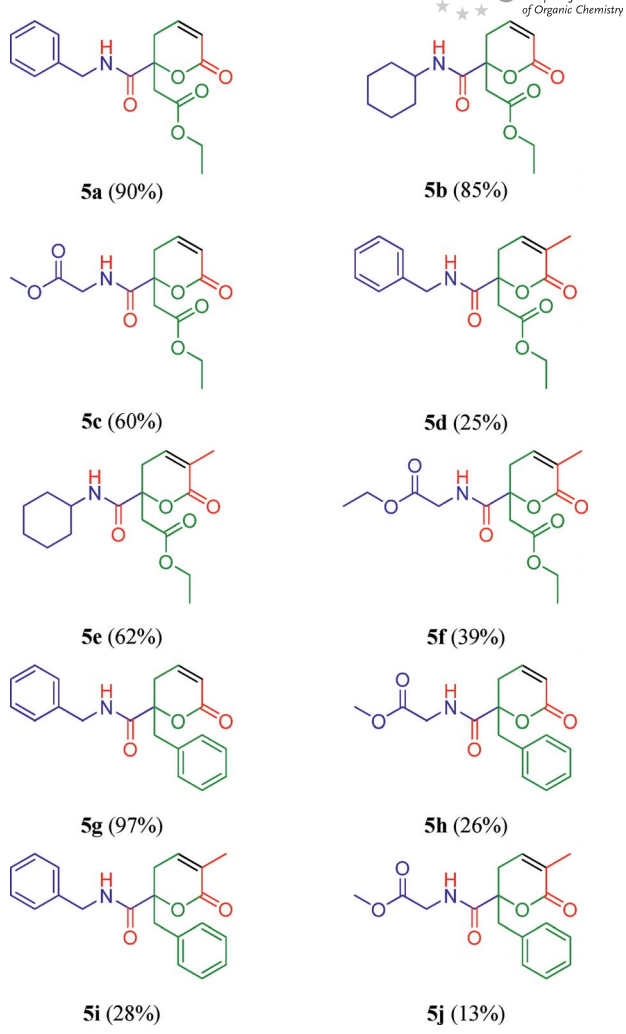


Figure 4. α,β-unsaturated pyran-2-carboxamides **5** obtained by RCM (cf. Scheme 1). All yields are isolated yields.

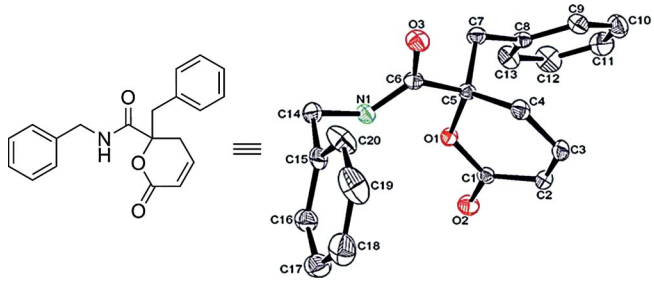
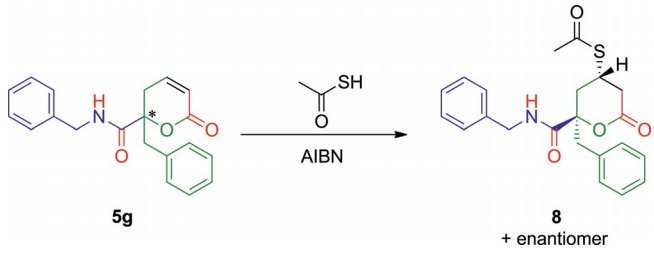


Figure 5. X-ray crystal structure of the racemic *N*,2-dibenzyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxamide (**5g**).



Scheme 5. Derivatization of the racemic α,β-unsaturated pyran-2-carboxamide **5g**.

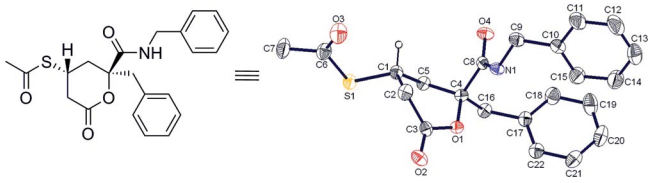


Figure 6. X-ray crystal structure of derivative **8** (only one enantiomer shown). The numbering of the atoms in the X-ray structure does not follow the IUPAC nomenclature.

Conclusions

We succeeded in the syntheses of a new class of α-acyloxy carboxamides **4** through a Passerini reaction involving allyl ketones. Furthermore, we created a new class of α,β-unsaturated pyran-2-carboxamides **5** in good to moderate yields through a ring-closing metathesis using a ruthenium catalyst in hot toluene. Because of the large number of known isocyanides, this reaction can be applied to build plenty of new α,β-unsaturated pyran-2-carboxamides **5**. In addition, the double bond in the α,β-unsaturated pyran-2-carboxamides **5** offers a great opportunity for further functionalizations.

Experimental Section

General Methods: All reagents and solvents were commercial grade and were purified prior to use when necessary. Preparative column chromatography was carried out using Grace SiO_2 (0.035–0.070 mm, type KG 60). TLC was performed on Merck SiO_2 F254 plates on aluminum sheets. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance DRX 500 and Avance DPX 300 spectrometers. Assignments of the signals in the ^{13}C NMR spectrum were supported by measurements applying DEPT and COSY techniques. EI-MS, CI-MS and HRMS spectra were obtained with a Finnigan MAT 95 spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR (attenuated total reflection) unit.

1-Phenylpent-4-en-2-one (2a): To a suspension of zinc powder (2.615 g, 40 mmol) in anhydrous THF (tetrahydrofuran, 10 mL), a solution of benzyl cyanide (1.171 g, 10 mmol) in anhydrous THF (10 mL) and allyl bromide (1.815 g, 15 mmol) were added under an argon atmosphere. The mixture was cooled to 0 °C. Aluminium trichloride (0.533 g, 4 mmol) was dissolved in cold anhydrous THF (exothermic reaction) and then slowly added to the reaction mixture. The suspension was warmed to room temperature and stirred for 30 min. After the reaction was completed (monitored by TLC), HCl (2 M aqueous solution, 50 mL) was added, and the reaction mixture was stirred at room temperature for 5 min. The mixture was passed through a short silica gel column. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was removed under reduced pressure using a rotary evaporator. The product was a colorless oil and was used without further purification (1.58 g, 9.9 mmol, 99%). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.21 (d, ^3J = 3.2 Hz, 2 H, $CH_2CH{=}CH_2$), 3.68 (s, 2 H, CH_2Ph), 5.08–5.21 (m, 2 H, $CH_2CH{=}CH_2$), 5.83–5.97 (m, 1 H, $CH_2CH{=}CH_2$), 7.31–7.34 (m, 5 H, ArCH) ppm.[15,28]

Ethyl 3-Oxohex-5-enoate (2b): To a suspension of zinc powder (2.615 g, 40 mmol) in anhydrous THF (10 mL), a solution of benzyl cyanide (1.130 g, 10 mmol) in anhydrous THF (30 mL) and allyl bromide (1.815 g, 15 mmol) were added under an argon atmosphere. The mixture was cooled to 0 °C. Aluminium trichloride (0.533 g, 4 mmol) was dissolved in cold anhydrous THF (exothermic reaction) and then slowly added to the reaction mixture. The suspension was warmed to room temperature and stirred for 18 h. After the reaction was completed (monitored by TLC), HCl (2 M aqueous solution, 50 mL) was added, and the reaction mixture was stirred at room temperature for 5 min. The mixture was passed through a short silica gel column. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was removed under reduced pressure using a rotary evaporator. The product was a yellow oil and was used without further purification (1.53 g, 9.8 mmol, 98%). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.28 (t, ^3J = 3.2 Hz, 3 H, CH_2CH_3), 3.31 (d, ^3J = 6.8 Hz, 2 H, $CH_2CH{=}CH_2$), 3.47 (s, 2 H, CH_2), 4.20 (q, ^3J = 7.2 Hz, 2 H, CH_2CH_3), 5.20 (dd, ^3J = 10.2 Hz, ^3J = 17.1 Hz, 2 H, $CH_2CH{=}CH_2$), 5.87–5.95 (m, 1 H, $CH_2CH{=}CH_2$) ppm.[19,20]

General Procedure (GP A): Under an argon atmosphere, the respective allyl ketone (1 equiv.) and the respective acid (1 equiv.) were dissolved in anhydrous dichloromethane. After stirring for 30 min at room temperature, the respective isocyanide (1 equiv.) was added dropwise to the mixture. The mixture was stirred at room temperature until the reaction was complete (detected by TLC). The solvent was removed under reduced pressure. Purification of the crude product is described in the experiments.

***rac*-3-Acroloxy-3-benzylaminocarbonyl-1-ethoxy-1-oxohex-5-ene (4a):** Following GP A, ethyl 3-oxohex-5-enoate (**2b**, 160 mg, 1.026 mmol), acrylic acid (73.90 mg, 1.026 mmol), benzyl isocyanide (120.19 mg, 1.026 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.35) and obtained as a colorless solid (170 mg, 0.490 mmol, 48%), m.p. 42–43 °C. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.18 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.81 (dd, ^2J = 14.0 Hz, ^3J = 6.7 Hz, 1 H, $CH_2CH{=}CH_2$), 3.11 (dd, ^2J = 14.1 Hz, ^3J = 8.0 Hz, 1 H, $CH_2CH{=}CH_2$), 3.28 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.54 (d, ^2J = 16.3 Hz, 1 H, CH_2CO), 4.06 (dq, ^2J = 2.1, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.48 (dd, ^2J = 14.8 Hz, ^3J = 5.5 Hz, 1 H, CH_2Ph), 4.57 (dd, ^2J = 14.8, ^3J = 6.6 Hz, 1 H, CH_2Ph), 5.10 (dd, ^2J = 14.3, ^3J = 8.6 Hz, 2 H, $CH_2CH{=}CH_2$), 5.62–5.64 (m, 1 H, $CH_2CH{=}CH_2$), 5.84 (d, ^3J = 10.4 Hz, 1 H, $CH{=}CH_2$), 6.09 (dd, ^3J = 10.4, ^3J = 17.6 Hz, 1 H, $CH{=}CH_2$), 6.37 (d, ^3J = 17.4 Hz, 1 H, $CH{=}CH_2$), 6.82 (br. s, 1 H, NH), 7.26–7.35 (m, 5 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.07 (CH_2CH_3), 39.55 (CH_2CO), 40.04 ($CH_2CH{=}CH_2$), 43.65 (CH_2Ph), 60.62 (CH_2CH_3), 84.13 (CCH_2CO), 120.10 ($CH_2CH{=}CH_2$), 127.53, 127.77 (ArCH), 128.26 ($CH{=}CH_2$), 128.67 (ArCH), 130.53 ($CH_2CH{=}CH_2$), 131.80 ($CH{=}CH_2$), 137.89 (ArC), 163.96, 169.33, 170.30 (CO) ppm. IR: $\tilde{\nu}$ = 3341, 2980, 1738, 1651, 1175, 698 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 368.1 (100) $[M + Na]^+$. TOF HRMS: calcd. for $C_{19}H_{23}NO_5Na$ $[M + Na]^+$ 368.1417; found 368.1483.

***rac*-3-Acryloxy-3-cyclohexylaminocarbonyl-1-ethoxy-1-oxohex-5-ene (4b):** Following GP A, ethyl 3-oxohex-5-enoate (**2b**, 216.5 mg, 1.390 mmol), acrylic acid (100.0 mg, 1.390 mmol), cyclohexyl isocyanide (151.7 mg, 1.390 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.20) and obtained as a colorless oil (170 mg, 0.504 mmol, 30%). ^1H

NMR (500.1 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.16–1.28, 1.35–1.42, 1.60–1.72, 1.90–1.96 (4m, 10 H, CyC*H*), 2.75 (dd, ^2J = 14.1 Hz, ^3J = 6.4 Hz, 1 H, $CH_2CH{=}CH_2$), 3.07 (dd, ^2J = 14.1 Hz, ^3J = 8.2 Hz, 1 H, $CH_2CH{=}CH_2$), 3.23 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.48 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.78–3.85 (m, 1 H, C*H*NH), 4.07 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 5.09 (dd, ^2J = 18.6 Hz, ^3J = 9.3 Hz, 2 H, $CH_2CH{=}CH_2$), 5.57–5.66 (m, 1 H, $CH_2CH{=}CH_2$), 5.87 (d, ^3J = 10.4 Hz, 1 H, $CH{=}CH_2$), 6.13 (dd, ^3J = 10.4 Hz, ^3J = 17.3 Hz, 1 H, $CH{=}CH_2$), 6.36 (br. s, 1 H, NH), 6.38 (d, ^3J = 17.1 Hz, 1 H, $CH{=}CH_2$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.10 (CH_2CH_3), 24.71, 24.73, 25.49, 32.72, 33.04 (CyCH), 39.48 (CH_2CO), 39.95 ($CH_2CH{=}CH_2$), 48.31 (CHNH), 60.50 (CH_2CH_3), 83.86 (CCH_2CO), 119.85 ($CH_2CH{=}CH_2$), 128.46 ($CH{=}CH_2$), 130.63 ($CH_2CH{=}CH_2$), 131.48 ($CH{=}CH_2$), 163.89, 169.33, 170.30 (CO) ppm. IR: $\tilde{\nu}$ = 3347, 2931, 1734, 1661, 1174 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 360.1 (100) [M + Na]$^+$. TOF HRMS: calcd. for $C_{18}H_{27}NO_5Na$ [M + Na]$^+$ 360.1787; found 360.1779.

***rac*-3-Acryloxy-1-ethoxy-3-(2-methoxy-2-oxoethylaminocarbonyl)-1-oxohex-5-ene (4c):** Following GP A, ethyl 3-oxohex-5-enoate (**2b**, 130.0 mg, 0.833 mmol), acrylic acid (60.0 mg, 0.833 mmol), methyl isocyanoacetate (71.7 mg, 0.833 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.10) and obtained as a colorless oil (160 mg, 0.511 mmol, 61%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.75–2.79 (m, 1 H, CH_2NH), 3.09–3.13 (m, 1 H, CH_2NH), 3.23 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.53 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.78 (s, 3 H, OCH_3), 4.03 (dd, ^2J = 18.6 Hz, ^3J = 4.6 Hz, 1 H, $CH_2CH{=}CH_2$), 4.08 (q, ^3J = 6.4 Hz, 2 H, CH_2CH_3), 4.18 (dd, ^2J = 18.4 Hz, ^3J = 5.5 Hz, 1 H, $CH_2CH{=}CH_2$), 5.10–5.12 (m, 2 H, $CH_2CH{=}CH_2$), 5.65–5.75 (m, 1 H, $CH_2CH{=}CH_2$), 5.90 (d, ^3J = 10.3 Hz, 1 H, $CH{=}CH_2$), 6.14 (dd, ^3J = 10.4 Hz, ^3J = 17.4 Hz, 1 H, $CH{=}CH_2$), 6.43 (d, ^3J = 17.4 Hz, 1 H, $CH{=}CH_2$), 7.10 (br. s, 1 H, NH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.72 (CH_2CH_3), 39.50 (CH_2CO), 40.06 (CH_2NH), 41.33 ($CH_2CH{=}CH_2$), 52.41 (OCH_3), 60.67 (CH_2CH_3), 83.96 (CCH_2CO), 120.10 ($CH_2CH{=}CH_2$), 128.29 ($CH{=}CH_2$), 130.41 ($CH_2CH{=}CH_2$), 131.79 ($CH{=}CH_2$), 163.85, 169.22, 170.03, 170.68 (CO) ppm. IR: $\tilde{\nu}$ = 3405, 2956, 1734, 1672, 1169 cm^{-1}. MS (ESI+): *m*/*z* (%) = 354.1 (100) [M + Na]$^+$. MS (CI, isobutane): *m*/*z* (%) = 332.1 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{18}H_{22}NO_5$ [M]$^+$ 332.1498; found 332.1500. TOF MS (ESI+): calcd. for $C_{21}H_{27}NO_3Na$ [M + Na]$^+$ 364.1472; found 364.1471. MS (CI, isobutane): *m*/*z* (%) = 328.2 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{15}H_{22}NO_7$ [M]$^+$ 328.1396; found 328.1406.

***rac*-3-Benzylaminocarbonyl-1-ethyloxy-3-methacryloxy-1-oxohex-5-ene (4d):** Following GP A, ethyl 3-oxohex-5-enoate (**2b**, 138.0 mg, 0.885 mmol), methacrylic acid (76.0 mg, 0.885 mmol), benzyl isocyanide (103.7 mg, 0.885 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.42) and obtained as a colorless oil (270 mg, 0.750 mmol, 85%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.18 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.89 (s, 3 H, CCH_3), 2.81 (dd, ^2J = 14.0 Hz, ^3J = 6.7 Hz, 1 H, $CH_2CH{=}CH_2$), 3.09 (dd, ^2J = 14.1 Hz, ^3J = 8.0 Hz, 1 H, $CH_2CH{=}CH_2$), 3.27 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.51 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 4.05 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.47–4.56 (m, 2 H, CH_2Ph), 5.08–5.12 (m, 2 H, $CH_2CH{=}CH_2$), 5.55 (s, 1 H, $C{=}CH_2$), 5.59–5.67 (m, 1 H, $CH_2CH{=}CH_2$), 6.00 (s, 1 H, $C{=}CH_2$), 6.74 (br. s, 1 H, N*H*), 7.26–7.35 (m, 5 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.05 (CH_2CH_3), 18.29 (CCH_3), 39.49 (CH_2CO), 40.03 ($CH_2CH{=}CH_2$), 43.72 (CH_2Ph), 60.59 (CH_2CH_3), 83.96 (CCH_2CO), 120.00 ($CH_2CH{=}CH_2$), 126.12 ($C{=}CH_2$), 127.46, 127.52, 127.61, 128.68 (ArCH), 130.53 ($CH_2CH{=}CH_2$), 136.33 ($C{=}CH_2$), 137.90 (ArC), 165.28, 169.35, 170.50 (CO) ppm. IR: $\tilde{\nu}$ = 3447, 2982, 1725, 1670, 1164, 699 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 382.2 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{20}H_{25}NO_5Na$ [M + Na]$^+$ 382.1630; found 382.1629.

***rac*-3-Cyclohexylaminocarbonyl-1-ethyloxy-3-methacryloxy-1-oxohex-5-ene (4e):** Following GP A, ethyl 3-oxohex-5-enoate (**2b**, 72.5 mg, 0.465 mmol), methacrylic acid (40.0 mg, 0.465 mmol), cyclohexyl isocyanide (50.7 mg, 0.465 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.36) and obtained as a colorless solid (88.0 mg, 0.250 mmol, 54%), m.p. 58–63 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.35–1.43, 1.58–1.61, 1.67–1.70, 1.89–1.92 (4m, 10 H, CyC*H*), 1.95 (s, 3 H, CCH_3), 2.75 (dd, ^2J = 14.1 Hz, ^3J = 6.5 Hz, 1 H, $CH_2CH{=}CH_2$), 3.07 (dd, ^2J = 14.1 Hz, ^3J = 8.2 Hz, 1 H, $CH_2CH{=}CH_2$), 3.22 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.48 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.78–3.85 (m, 1 H, C*H*NH), 4.06 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 5.09 (dd, ^2J = 17.8 Hz, ^3J = 8.1 Hz, 2 H, $CH_2CH{=}CH_2$), 5.57–5.65 (m, 1 H, $CH_2CH{=}CH_2$), 5.59 (s, 1 H, $C{=}CH_2$), 6.05 (s, 1 H, $C{=}CH_2$), 6.38 (d, ^3J = 7.7 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.12 (CH_2CH_3), 18.39 (CCH_3), 24.57, 25.51, 32.71, 33.02 (Cy*C*H), 39.48 (CH_2CO), 39.89 ($CH_2CH{=}CH_2$), 48.10 (CHNH), 60.53 (CH_2CH_3), 83.80 (CCH_2CO), 119.81 ($CH_2CH{=}CH_2$), 126.06 ($C{=}CH_2$), 130.72 ($CH_2CH{=}CH_2$), 136.42 ($C{=}CH_2$), 165.17, 169.22, 169.33 (CO) ppm. IR: $\tilde{\nu}$ = 3334, 2936, 1718, 1650, 1145 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 374.2 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{19}H_{29}NO_5Na$ [M + Na]$^+$ 374.1943; found 374.1942.

***rac*-1-Ethyloxy-3-(2-ethoxy-2-oxoethylaminocarbonyl)-3-methacryloxy-1-oxohex-5-ene (4f):** Following GP A, ethyl 3-oxohex-5-enoate (**2b**, 110.0 mg, 0.710 mmol), methacrylic acid (61.0 mg, 0.710 mmol), ethyl isocyanoacetate (80.7 mg, 0.710 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.10) and obtained as a colorless oil (70.0 mg, 0.197 mmol, 28%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.30 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.99 (s, 3 H, CCH_3), 2.76 (dd, ^3J = 14.1 Hz, ^3J = 6.4 Hz, 1 H, CH_2NH), 3.12 (dd, ^3J = 14.1 Hz, ^3J = 8.3 Hz, 1 H, CH_2NH), 3.23 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 3.53 (d, ^2J = 16.2 Hz, 1 H, CH_2CO), 4.03–4.16 (m, 4 H, $CH_2CH{=}CH_2$, CH_2CH_3), 4.24 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 5.09–5.12 (m, 2 H, $CH_2CH{=}CH_2$), 5.63 (s, 1 H, $C{=}CH_2$), 5.65–5.72 (m, 1 H, $CH_2CH{=}CH_2$), 6.13 (s, 1 H, $C{=}CH_2$), 7.11 (br. s, 1 H, NH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.01 (CH_2CH_3), 14.10 (CH_2CH_3), 18.36 (CH_3), 39.52 (CH_2CO), 39.95 (CH_2NH), 41.59 ($CH_2CH{=}CH_2$), 60.63 (CH_2CH_3), 61.63 (CH_2CH_3), 83.88 (CCH_2CO), 119.97 ($CH_2CH{=}CH_2$), 126.39 ($C{=}CH_2$), 130.50 ($CH_2CH{=}CH_2$), 136.23 ($C{=}CH_2$), 165.19, 169.54, 170.72 (CO) ppm. IR: $\tilde{\nu}$ = 3441, 2983, 1733, 1677, 1148 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 356.2 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{17}H_{26}NO_7$ [M]$^+$ 356.1709; found 356.1716.

***rac*-2-Acryloxy-2-benzyl-1-benzylamino-1-oxopent-4-ene (4g):** Following GP A, 1-phenylpent-4-en-2-one (**2a**, 250.0 mg, 1.560 mmol), acrylic acid (112.0 mg, 1.560 mmol), benzyl isocyanide (182.0 mg, 1.560 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.34) and obtained as a colorless oil (470.0 mg, 1.346 mmol, 86%). ^{1}H NMR (500.1 MHz,

$CDCl_3$): δ = 2.97 (dd, ^2J = 14.1 Hz, ^3J = 6.4 Hz, 1 H, $CH_2CH=CH_2$), 3.25 (dd, ^2J = 14.1 Hz, ^3J = 8.3 Hz, 1 H, $CH_2CH=CH_2$), 3.32 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 3.65 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 4.29 (m, 2 H, CH_2NH), 4.99, 5.06 (2d, ^2J = 17.0 Hz, ^3J = 10.9 Hz, 2 H, $CH_2CH=CH_2$), 5.52–5.60 (m, 1 H, $CH_2CH=CH_2$), 5.70 (dd, ^3J = 10.4 Hz, ^3J = 1.1 Hz, 1 H, $CH=CH_2$), 5.92 (dd, ^3J = 10.4 Hz, ^3J = 17.3 Hz, 1 H, $CH=CH_2$), 6.23 (dd, ^3J = 17.3 Hz, ^3J = 1.1 Hz, 1 H, $CH=CH_2$), 6.26 (br. s, 1 H, NH), 6.95–7.18 (m, 10 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 39.70 ($CH_2CH=CH_2$), 40.65 (CH_2Ph), 43.35 (CH_2NH), 88.75 (CCH_2Ph), 119.46 ($CH_2CH=CH_2$), 126.81, 127.41, 127.61, 128.18, 128.56 (ArCH), 129.98, 130.05 (ArCH), 131.33 ($CH=CH_2$), 131.38 ($CH_2CH=CH_2$), 135.49, 137.67 (ArC), 164.05, 170.36 (CO) ppm. IR: $\tilde{\nu}$ = 3355, 3029, 2934, 1730, 1655, 1175, 698 cm^{-1}. MS (ESI+): *m*/*z* (%) = 372.2 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{22}H_{23}NO_3Na$ [M + Na]$^+$ 372.1576; found 372.1577.

***rac*-2-Acryloxy-2-benzyl-1-(2-methoxy-2-oxoethylamino)-1-oxopent-4-ene (4h):** Following GP A, 1-phenyl-pent-4-en-2-one (**2a**, 280.0 mg, 1.750 mmol), acrylic acid (126.0 mg, 1.750 mmol), methyl isocyanoacetate (551.0 mg, 1.750 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.13) and obtained as a colorless oil (180.0 mg, 0.543 mmol, 31%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 3.01 (dd, ^2J = 14.2 Hz, ^3J = 6.2 Hz, 1 H, $CH_2CH=CH_2$), 3.32 (dd, ^2J = 14.2 Hz, ^3J = 8.5 Hz, 1 H, $CH_2CH=CH_2$), 3.39 (d, ^2J = 13.9 Hz, 1 H, CH_2Ph), 3.75 (s, 3 H, OCH_3), 3.82 (dd, ^2J = 18.3 Hz, ^3J = 4.4 Hz, 1 H, CH_2NH), 4.12 (dd, ^2J = 18.7 Hz, ^3J = 5.6 Hz, 1 H, CH_2NH), 5.13 (dd, ^2J = 18.3 Hz, ^3J = 5.6 Hz, 2 H, $CH_2CH=CH_2$), 5.60–5.68 (m, 1 H, $CH_2CH=CH_2$), 5.85 (d, ^3J = 11.4 Hz, 1 H, $CH=CH_2$), 6.07 (dd, ^3J = 10.4 Hz, ^3J = 17.2 Hz, 1 H, $CH=CH_2$), 6.37 (d, ^3J = 17.2 Hz, 1 H, $CH=CH_2$), 6.63 (br. s, 1 H, NH), 7.04–7.06 (m, 2 H, ArC*H*), 7.17–7.19 (m, 3 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 39.72 ($CH_2CH=CH_2$), 40.58 (CH_2Ph), 41.08 (CH_2NH), 52.30 (OCH_3), 88.45 (CCH_2Ph), 119.44 ($CH_2CH=CH_2$), 126.84, 128.05 (ArCH), 128.11 ($CH=CH_2$), 128.63, 129.79 (ArCH), 129.86 (ArC), 131.21 ($CH=CH_2$), 131.31 ($CH_2CH=CH_2$), 135.29 (ArC), 163.98, 169.76, 170.85 (CO) ppm. IR: $\tilde{\nu}$ = 3424, 3085, 2947, 1725, 1671, 1176, 700 cm^{-1}. MS (ESI+): *m*/*z* (%) = 354.1 (100) [M + Na]$^+$. MS (CI, isobutane): *m*/*z* (%) = 332.1 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{18}H_{22}NO_5$ [M]$^+$ 332.1498; found 332.1500. TOF MS (ESI+): calcd. for $C_{21}H_{27}NO_3Na$ [M + Na]$^+$ 364.1472; found 364.1471.

***rac*-2-Benzyl-1-benzylamino-2-methacryloxy-1-oxopent-4-ene (4i):** Following GP A, 1-phenylpent-4-en-2-one (**2a**, 260.0 mg, 1.620 mmol), methacrylic acid (139.0 mg, 1.620 mmol), benzyl isocyanide (189.0 mg, 1.620 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.42) and obtained as a colorless solid (400.0 mg, 1.100 mmol, 68%), m.p. 42–45 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.70 (s, 3 H, CH_3), 2.97 (dd, ^2J = 14.2 Hz, ^3J = 6.4 Hz, 1 H, $CH_2CH=CH_2$), 3.24 (dd, ^2J = 14.1 Hz, ^3J = 8.3 Hz, 1 H, $CH_2CH=CH_2$), 3.31 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 3.63 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 4.29 (d, ^3J = 5.7 Hz, 2 H, CH_2NH), 5.00, 5.06 (2d, ^2J = 17.0 Hz, ^3J = 10.2 Hz, 2 H, $CH_2CH=CH_2$), 5.39 (s, 1 H, $CH=CH_2$), 5.52–5.60 (m, 1 H, $CH_2CH=CH_2$), 5.76 (s, 1 H, $CH=CH_2$), 6.19 (br. s, 1 H, NH), 6.92–7.18 (m, 10 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 18.33 (CH_3), 39.57 ($CH_2CH=CH_2$), 40.55 (CH_2Ph), 43.34 (CH_2NH), 88.52 (CCH_2Ph), 119.44 ($CH_2CH=CH_2$), 125.73 ($CH=CH_2$), 126.81, 127.36, 128.15, 128.56, 129.98 (ArCH), 131.38 ($CH_2CH=CH_2$), 135.49 (ArC), 136.52 ($C=CH_2$), 137.57 (ArC), 165.41, 170.58 (CO) ppm. IR: $\tilde{\nu}$ = 3433, 3085, 2926, 1720, 1672, 1153, 699 cm^{-1}. MS (ESI+): *m*/*z* (%) = 386.2 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{23}H_{25}NO_3Na$ [M + Na]$^+$ 386.1732; found 386.1738.

***rac*-2-Benzyl-2-methacryloxy-1-(2-methoxy-2-oxoethylamino)-1-oxopent-4-ene (4j):** Following GP A, 1-phenylpent-4-en-2-one (**2a**, 1.090 g, 7.500 mmol), methacrylic acid (0.645 g, 7.500 mmol), methyl isocyanoacetate (0.743 g, 7.500 mmol), and anhydrous dichloromethane (15.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.21) and obtained as a colorless solid (1.440 g, 4.056 mmol, 65%), m.p. 48–54 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.86 (s, 3 H, CH_3), 2.97 (dd, ^2J = 14.2 Hz, ^3J = 6.2 Hz, 1 H, $CH_2CH=CH_2$), 3.30 (dd, ^2J = 14.4 Hz, ^3J = 8.4 Hz, 1 H, $CH_2CH=CH_2$), 3.34 (d, ^3J = 13.9 Hz, 1 H, CH_2Ph), 3.69 (d, ^3J = 14.2 Hz, 1 H, CH_2Ph), 3.71 (s, 3 H, OCH_3), 3.80 (dd, ^2J = 18.6 Hz, ^3J = 4.3 Hz, 1 H, CH_2NH), 4.07 (dd, ^2J = 18.7 Hz, ^3J = 5.5 Hz, 1 H, CH_2NH), 5.09 (dd, ^2J = 20.5 Hz, ^3J = 10.1 Hz, 2 H, $CH_2CH=CH_2$), 5.52 (s, 1 H, $C=CH_2$), 5.60–5.68 (m, 1 H, $CH_2CH=CH_2$), 5.96 (s, 1 H, $C=CH_2$), 6.63 (br. s, 1 H, NH), 7.04–7.06 (m, 2 H, ArC*H*), 7.17–7.19 (m, 3 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 18.31 (CH_3), 39.57 ($CH_2CH=CH_2$), 40.48 (CH_2Ph), 41.13 (CH_2NH), 52.35 (OCH_3), 88.34 (CCH_2Ph), 119.38 ($CH_2CH=CH_2$), 125.89 ($C=CH_2$), 126.84, 128.07, 129.76 (ArCH), 131.25 ($CH_2CH=CH_2$), 135.32 (ArC), 136.51 ($C=CH2$), 165.39, 169.77, 170.95 (CO) ppm. IR: $\tilde{\nu}$ = 3395, 3038, 1717, 1657, 1153, 706 cm^{-1}. MS (ESI+): *m*/*z* (%) = 368.1 (100) [M + Na]$^+$. MS (CI, isobutane): *m*/*z* (%) = 346.2 (10) [M + H]$^+$, 327.2 (100). HRMS (CI, isobutane): calcd. for $C_{19}H_{24}NO_5$ [M]$^+$ 346.1654; found 346.1663.

***rac*-2-Acryloxy-2-benzyl-1-cyclohexylamino-1-oxopent-4-ene (4k):** Following GP A, 1-phenylpent-4-en-2-one (**2a**, 810.0 mg, 5.050 mmol), acrylic acid (364.0 mg, 5.050 mmol), cyclohexyl isocyanide (551.0 mg, 5.050 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 8:2; R_f = 0.29) and obtained as a colorless oil (190.0 mg, 0.556 mmol, 11%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.86–0.89, 1.06–1.16, 1.33–1.43, 1.59–1.68, 1.82–1.86 (5m, 10 H, CyH_2), 3.01 (dd, ^2J = 14.2 Hz, ^3J = 6.0 Hz, 1 H, $CH_2CH=CH_2$), 3.26 (dd, ^2J = 14.2 Hz, ^3J = 8.7 Hz, 1 H, $CH_2CH=CH_2$), 3.40 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 3.64 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 3.73–3.80 (m, 1 H, Cy*H*), 5.07, 5.13 (2d, ^2J = 17.0 Hz, ^3J = 10.9 Hz, 2 H, $CH_2CH=CH_2$), 5.57–5.63 (m, 1 H, $CH_2CH=CH_2$), 5.88 (dd, ^2J = 1.4 Hz, ^3J = 10.4 Hz, 1 H, $CH=CH_2$), 6.01 (br. s, 1 H, NH), 6.10 (dd, ^3J = 10.4 Hz, ^3J = 17.3 Hz, 1 H, $CH=CH_2$), 6.42 (dd, ^3J = 10.4 Hz, ^3J = 1.4 Hz, 1 H, $CH=CH_2$), 7.11–7.13, 7.20–7.26 (2m, 5 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.74, 25.44, 32.51, 32.99, 34.91 (CyCH_2), 39.69 ($CH_2CH=CH_2$), 40.59 (CH_2Ph), 48.16 (Cy*C*), 88.76 (CCH_2Ph), 119.10 ($CH_2CH=CH_2$), 126.84, 127.95, 128.09, 129.89 (ArCH), 131.39 ($CH=CH_2$), 131.60 ($CH_2CH=CH_2$), 135.56 (ArC), 165.75, 168.25 (CO) ppm. IR: $\tilde{\nu}$ = 3445, 3065, 2931, 1726, 1670, 1168, 702 cm^{-1}. MS (ESI+): *m*/*z* (%) = 364.2 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{21}H_{27}NO_3Na$ [M + Na]$^+$ 364.1472; found 364.1471.

***rac*-2-Benzyl-1-cyclohexylamino-2-methacryloxy-1-oxopent-4-ene (4l):** Following GP A, 1-phenylpent-4-en-2-one (**2a**, 170.0 mg, 1.060 mmol), methacrylic acid (91.35 mg, 1.060 mmol), cyclohexyl isocyanide (115.72 mg, 1.060 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 9:1; R_f = 0.36) and obtained as a colorless oil (200.0 mg, 0.563 mmol, 53%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.75–0.83, 0.95–1.32, 1.40–1.56

(m, 1H, CyCH_2), 1.75 (s, 3 H, CH_3), 2.93 (dd, ^2J = 14.1 Hz, ^3J = 6.2 Hz, 1 H, CH_2CH=CH$_2$), 3.20 (dd, ^2J = 14.1 Hz, ^3J = 8.4 Hz, 1 H, CH_2CH=CH$_2$), 3.28 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 3.58 (d, ^3J = 13.8 Hz, 1 H, CH_2Ph), 3.63–3.70 (m, 1 H, C*H*NH), 4.97, 5.03 (2d, ^2J = 16.8 Hz, ^3J = 10.1 Hz, 2 H, CH$_2$CH=CH_2), 5.42 (s, 1 H, C=CH_2), 5.49–5.57 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.81 (s, 1 H, C=CH_2), 5.87 (br. s, 1 H, CHN*H*), 7.01–7.13 (m, 5 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 18.31 (CH$_3$), 24.34, 24.38, 25.42, 32.40, 32.91 (Cy*C*H), 39.49 (*C*H$_2$CH=CH$_2$), 40.52 (*C*H$_2$Ph), 47.56 (CHNH), 88.28 (*C*CH$_2$Ph), 119.09 (CH$_2$CH=*C*H$_2$), 125.45 (C=*C*H$_2$), 126.71, 127.97, 128.64, 129.39, 129.93 (ArCH), 131.54 (CH$_2$*C*H=CH$_2$), 135.59 (ArC), 136.76 (*C*=CH2), 165.29, 169.35 (CO) ppm. IR: $\tilde{\nu}$ = 3445, 3031, 2930, 1723, 1675, 1153, 701 cm^{-1}. MS (ESI+): *m*/*z* (%) = 378.2 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{22}H_{29}NO_3Na$ [M + Na]$^+$ 378.2045; found 378.2051.

General Procedure (GP B): The α-acyloxy carboxamides **4** (1 equiv.), synthesized according to GP A, and the ruthenium catalyst (0.05 equiv., Figure 3) in toluene (10 mL) were slowly heated to 70 °C until the reaction was complete (monitored by TLC). The solvent was removed under reduced pressure. Purification of the crude product is described in the experiments.

***rac*-Ethyl 2-[2-(Benzylcarbamoyl)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-acetate (5a):** Following GP B, α-acyloxy carboxamide **4a** (72 mg, 0.208 mmol) and the ruthenium catalyst (9.88 mg, 10 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1; R_f = 0.30) and obtained as a colorless solid (60 mg, 0.189 mmol, 90%), m.p. 77–79 °C. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.22 (t, ^3J = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 2.88–3.07 (m, 4 H, C*H*$_2$CH=CH$_2$, C*H*$_2$CO), 4.12 (q, ^3J = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 4.46 (d, ^3J = 5.8 Hz, 2 H, C*H*$_2$Ph), 6.04 (d, ^3J = 9.8 Hz, 1 H, CH$_2$CH=C*H*), 6.48–6.88 (m, 1 H, CH$_2$C*H*=CH), 6.90 (br. s, 1 H, NH), 7.25–7.34 (m, 5 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 14.04 (*C*H$_3$), 30.51 (*C*H$_2$CH=CH), 41.96 (*C*H$_2$CO), 43.84 (*C*H$_2$Ph), 61.15 (*C*H$_2$CH$_3$), 82.44 (*C*CH$_2$CH=CH), 120.34 (CH$_2$CH=*C*H), 127.69, 127.74, 128.74, (Ar*C*H), 137.31 (ArC), 144.51 (CH$_2$*C*H=CH), 161.13, 167.93, 170.26 (CO) ppm. IR: $\tilde{\nu}$ = 3356, 2982, 1730, 1671, 1188 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 340.1 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{17}H_{19}NO_5Na$ [M + Na]$^+$ 340.1161; found 340.1164.

***rac*-Ethyl 2-[2-(Cyclohexylcarbamoyl)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]acetate (5b):** Following GP B, α-acyloxy carboxamide **4b** (135 mg, 0.400 mmol) and the ruthenium catalyst (18.9 mg, 20 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:4; R_f = 0.16) and obtained as a colorless oil (106 mg, 0.343 mmol, 85%). ^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.16–1.21 (m, 3 H, CyC*H*$_2$), 1.25 (t, ^3J = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.30–1.39, 1.59–1.95 (2m, 7 H, CyC*H*$_2$), 2.85–3.03 (m, 4 H, C*H*$_2$CH=CH, C*H*$_2$CO), 3.71–3.77 (m, 1 H, C*H*NH), 4.14 (q, ^3J = 6.9 Hz, 2 H, C*H*$_2$CH$_3$), 6.04 (d, ^3J = 9.9 Hz, 1 H, CH$_2$CH=C*H*), 6.41 (d, ^3J = 7.7 Hz, 1 H, CHN*H*), 6.84–6.87 (m, 1 H, CH$_2$C*H*=CH) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 14.07 (CH$_2$*C*H$_3$), 24.72, 25.34 (Cy*C*H$_2$), 30.44 (*C*H$_2$CH=CH), 32.51, 32.81 (Cy*C*H$_2$), 41.86 (*C*H$_2$CO), 48.73 (*C*HNH), 61.09 (*C*H$_2$CH$_3$), 82.27 (*C*CH$_2$CH=CH), 120.20 (CH$_2$CH=*C*H), 144.69 (CH$_2$*C*H=CH), 161.43, 167.98, 169.16 (CO) ppm. IR: $\tilde{\nu}$ = 3345, 2931, 1731, 1666, 1187, 1053 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 310.2 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{16}H_{24}NO_5$ [M]$^+$ 310.1654; found 310.1648.

***rac*-Ethyl 2-[2-(2-Methoxy-2-oxoethylcarbamoyl)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]acetate (5c):** Following GP B, α-acyloxy carboxamide **4c** (54 mg, 0.172 mmol) and the ruthenium catalyst (8.2 mg, 8.6 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1; R_f = 0.16) and obtained as a colorless oil (31 mg, 0.103 mmol, 60%). ^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.23 (t, ^3J = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 2.88–2.93 (m, 1 H, C*H*$_2$CH=CH), 2.89 (d, ^3J = 15.2 Hz, 1 H, C*H*$_2$CO), 3.00 (d, ^3J = 15.2 Hz, 1 H, C*H*$_2$CO), 3.01–3.06 (m, 1 H, C*H*$_2$CH=CH), 3.74 (s, 3 H, OC*H*$_3$), 3.99 (dd, ^2J = 15.2 Hz, ^3J = 5.4 Hz, 1 H, C*H*$_2$NH), 4.10 (dd, ^2J = 15.6 Hz, ^3J = 5.9 Hz, 1 H, C*H*$_2$NH), 4.13 (q, ^3J = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 6.04–6.06 (m, 1 H, CH$_2$CH=C*H*), 6.83–6.87 (m, 1 H, CH$_2$C*H*=CH), 7.11 (br. t, 1 H, NH) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 13.98 (CH$_2$*C*H$_3$), 30.12 (*C*H$_2$CH=CH), 41.22 (*C*H$_2$NH), 41.63 (*C*H$_2$CO), 52.37 (O*C*H$_3$), 61.16 (*C*H$_2$CH$_3$), 82.31 (*C*CH$_2$CH=CH), 120.32 (CH$_2$CH=*C*H), 144.35 (CH$_2$*C*H=CH), 161.04, 167.96, 169.33, 170.88 (CO) ppm. IR: $\tilde{\nu}$ = 3366, 2924, 1720, 1674, 1043 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 300.1 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{13}H_{18}NO_7$ [M]$^+$ 300.1083; found 300.1076.

***rac*-Ethyl 2-[2-(Benzylcarbamoyl)-5-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]acetate (5d):** Following GP B, α-acyloxy carboxamide **4d** (85 mg, 0.237 mmol) and the ruthenium catalyst (11.2 mg, 11 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1; R_f = 0.35) and obtained as a colorless oil (20 mg, 0.060 mmol, 25%). ^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.22 (t, ^3J = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.88 (s, 3 H, C*H*$_3$), 2.82–3.10 (m, 4 H, CH$_2$CH=C, C*H*$_2$CO), 4.11 (q, ^3J = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 4.39 (dd, ^2J = 14.7 Hz, ^3J = 5.5 Hz, 1 H, C*H*$_2$Ph), 4.52 (dd, ^2J = 14.7 Hz, ^3J = 6.2 Hz, 1 H, C*H*$_2$Ph), 6.52–6.56 (m, 1 H, CH$_2$C*H*=C), 6.91 (br. s, 1 H, NH), 7.23–7.33 (m, 5 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 14.03 (CH$_2$*C*H$_3$), 16.82 (*C*H$_3$), 30.87 (*C*H$_2$CH=C), 41.96 (*C*H$_2$CO), 43.70 (*C*H$_2$Ph), 61.07 (*C*H$_2$CH$_3$), 82.45 (*C*CH$_2$CH=C), 127.62, 127.64, 128.69 (Ar*C*H), 137.47 (ArC), 138.13 (CH$_2$*C*H=C), 162.95, 168.03, 170.50 (CO) ppm. IR: $\tilde{\nu}$ = 3362, 2982, 1723, 1673, 1091 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 354.2 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{18}H_{21}NO_5Na$ [M + Na]$^+$ 354.1317; found 354.1322.

***rac*-Ethyl 2-[2-(Cyclohexylcarbamoyl)-5-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]acetate (5e):** Following GP B, α-acyloxy carboxamide **4e** (88 mg, 0.251 mmol) and the ruthenium catalyst (11.9 mg, 13 μmol) were used. The crude product was purified by column chromatography on silica gel (dichloromethane/ethyl acetate, 8:2; R_f = 0.52) and obtained as a colorless solid (50 mg, 0.155 mmol, 62%), m.p. 88–89 °C. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.12–1.20 (m, 3 H, CyC*H*$_2$), 1.25 (t, ^3J = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 1.29–1.40, 1.59–1.81 (2m, 7 H, CyC*H*$_2$), 1.91 (s, 3 H, C*H*$_3$), 2.79–2.96 (m, 4 H, C*H*$_2$CH=C, C*H*$_2$CO), 3.70–3.78 (m, 1 H, C*H*NH), 4.13 (q, ^3J = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 6.39–6.41 (m, 1 H, CH$_2$C*H*=C), 6.54 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 14.02 (CH$_2$*C*H$_3$), 16.81 (*C*H$_3$), 24.67, 25.28, 32.46, 32.80 (Cy*C*H$_2$), 30.79 (*C*H$_2$CH=C), 41.73 (*C*H$_2$CO), 48.53 (*C*HNH), 60.96 (*C*H$_2$CH$_3$), 82.25 (*C*CH$_2$CH=C), 127.52 (CH$_2$CH=*C*), 138.20 (CH$_2$*C*H=C), 163.18, 168.04, 169.39 (CO) ppm. IR: $\tilde{\nu}$ = 3346, 2938, 1717, 1651, 1051 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 324.5 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{17}H_{26}NO_5$ [M]$^+$ 324.1811; found 324.1816.

***rac*-Ethyl 2-[2-(2-Ethoxy-2-oxoethyl)-5-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxamido]acetate (5f):** Following GP B, α-acyloxy carboxamide **4f** (56 mg, 0.157 mmol) and the ruthenium catalyst (7.5 mg, 79 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.22) and obtained as a colorless oil (20 mg, 0.061 mmol, 39%). ^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.23–1.30 (m, 8 H, 2 CH$_2$C*H*$_3$, C*H*$_2$CH=C), 1.93 (s, 3 H, CH$_3$), 2.99 (d, ^3J = 15.1 Hz, 2

H, CH_2CO), 3.95 (dd, ^2J = 18.1 Hz, ^3J = 5.2 Hz, 1 H, CH_2NH), 4.12 (dd, ^2J = 18.1 Hz, ^3J = 6.1 Hz, 1 H, CH_2NH), 4.14 (q, ^3J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.21 (q, ^3J = 7.1 Hz, 2 H, CH_2CH$_3$), 6.52 (m, 1 H, CHN*H*), 7.02 (m, 1 H, C*H*=C) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.03, 14.11 (2 CH$_2$*C*H$_3$), 16.96 (CH$_3$), 29.94 (*C*H$_2$CH=C), 30.53 (*C*H$_2$CO), 41.37 (*C*H$_2$NH), 61.16, 61.57 (2 *C*H$_2$CH$_3$), 82.35 (*C*CH$_2$NH), 127.81 (CH$_2$CH=*C*), 137.90 (CH$_2$*C*H=C), 162. 87, 168.11, 168.87, 171.13 (CO) ppm. IR: $\tilde{\nu}$ = 3441, 2983, 1733, 1677, 1148 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 328.1 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{15}H_{22}NO_7$ [M]$^+$ 328.1396; found 328.1400.

***rac*-*N*,2-Dibenzyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxamide (5g):** Following GP B, α-acyloxy carboxamide **4g** (81 mg, 0.232 mmol) and the ruthenium catalyst (11.0 mg, 11 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:4; R_f = 0.24) and obtained as a colorless solid (19 mg, 0.059 mmol, 97%), m.p. 100–101 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.51–2.56 (dm, 1 H, CH_2CH=CH), 3.06–3.10 (dm, 1 H, CH_2CH=CH), 3.11 (s, 2 H, CH_2Ph), 4.14–4.22 (m, 2 H, CH_2NH), 5.90–5.94 (m, 1 H, CH$_2$CH=C*H*), 6.38 (br. s, 1 H, NH), 6.77–6.81 (m, 1 H, CH$_2$C*H*=CH), 6.87–6.89, 7.12–7.19 (m, 10 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 30.60 (*C*H$_2$CH=CH), 43.53 (*C*H$_2$NH), 43.86 (*C*H$_2$Ph), 85.48 (*C*CH$_2$Ph), 120.27 (CH=*C*H), 127.27, 127.48, 127.53, 128.36, 128.56, 130.49 (Ar*C*H), 133.97, 136.95 (ArC), 145.32 (*C*H=CH), 162.08, 170.55 (CO) ppm. IR: $\tilde{\nu}$ = 3379, 3030, 2942, 1714, 1661, 1241, 1055, 699 cm^{-1}. MS (ESI+): *m*/*z* (%) = 344.1 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{19}H_{29}NO_5Na$ [M + Na]$^+$ 374.1943; found 374.1942.

***rac*-Methyl 2-(2-Benzyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxamido)acetate (5h):** Following GP B, α-acyloxy carboxamide **4h** (81 mg, 0.244 mmol) and the ruthenium catalyst (14.0 mg, 12 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:4; R_f = 0.10) and obtained as colorless oil (20 mg, 0.065 mmol, 26%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.45–2.50 (dm, 1 H, CH_2CH=CH), 3.01–3.05 (dm, 1 H, CH_2CH=CH), 3.11 (dd, ^2J = 37.4 Hz, ^3J = 14.1 Hz, 2 H, CH_2Ph), 3.63 (s, 3 H, OCH_3), 3.74 (dd, ^2J = 17.9 Hz, ^3J = 5.4 Hz, 1 H, CH_2NH), 3.91 (dd, ^2J = 18.0 Hz, ^3J = 5.8 Hz, 1 H, CH_2NH), 5.90–5.92 (m, 1 H, C*H*=CH), 6.63 (br. s, 1 H, NH), 6.73–6.77 (m, 1 H, C*H*=CH), 7.14–7.23 (m, 5 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 30.29 (*C*H$_2$CH=CH), 41.51 (*C*H$_2$NH), 44.32 (*C*H$_2$Ph), 52.81 (OCH$_3$), 85.94 (*C*CH$_2$Ph), 120.76 (CH=*C*H), 127.81, 128.80, 130.99 (ArCH), 134.38 (ArC), 145.60 (*C*H=CH), 162.49, 169.58, 171.89 (CO) ppm. IR: $\tilde{\nu}$ = 3366, 3031, 2952, 1731, 1673, 1205, 1046, 603 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 304.1 (100) [M + H]$^+$. HRMS (CI, isobutane): calcd. for $C_{16}H_{18}NO_5$ [M]$^+$ 304.1185; found 304.1189.

***rac*-*N*,2-Dibenzyl-5-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxamide (5i):** Following GP B, α-acyloxy carboxamide **4i** (94 mg, 0.258 mmol) and the ruthenium catalyst (13.3 mg, 12 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:4; R_f = 0.32) and obtained as a colorless solid (25 mg, 0.075 mmol, 28%), m.p. 114–120 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.77 (s, 3 H, CH_3), 2.48–2.52 (dm, 1 H, CH_2CH=C), 3.00–3.06 (dm, 1 H, CH_2CH=C), 3.09 (s, 2 H, CH_2Ph), 4.12 (dd, ^2J = 14.6 Hz, ^3J = 5.8 Hz, 1 H, CH_2NH), 4.25 (dd, ^2J = 14.8 Hz, ^3J = 5.9 Hz, 1 H, CH_2NH), 6.40 (br. s, 1 H, NH), 6.47 (s, 1 H, CH$_2$C*H*=C), 6.88–6.90, 7.12–7.18 (2m, 10 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.82 (CH$_3$), 30.79 (*C*H$_2$CH=C), 43.39 (*C*H$_2$NH), 43.82 (*C*H$_2$Ph), 85.55 (C*C*H$_2$Ph), 127.20, 127.44 (Ar*C*H), 127.52 (CH=*C*), 128.32, 128.45, 128.54, 130.48, 134.19, 137.16 (Ar*C*H), 139.05 (*C*H=C), 163.88, 170.88 (CO) ppm. IR: $\tilde{\nu}$ = 3389, 3006, 2927, 1712, 1670, 1127, 1047, 700 cm^{-1}. MS (ESI+): *m*/*z* (%) = 692.7 (100) [2M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{21}H_{21}NO_6Na$ [M + Na]$^+$ 358.1419; found 358.1413.

***rac*-Methyl *2*-(2-Benzyl-5-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxamido)acetate (5j):** Following GP B, α-acyloxy carboxamide **4j** (82 mg, 0.237 mmol) and the ruthenium catalyst (23.75 mg, 22 μmol) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.07) and obtained as a colorless oil (10 mg, 0.032 mmol, 13%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.79 (d, ^4J = 1.7 Hz, 3 H, CH$_3$), 2.42–2.48 (dm, 1 H, CH_2CH=C), 2.94–2.99 (dm, 1 H, CH_2CH=C), 3.08 (dd, ^2J = 33.6 Hz, ^3J = 14.1 Hz, 2 H, CH_2Ph), 3.62 (s, 3 H, OCH_3), 3.69 (dd, ^2J = 17.9 Hz, ^3J = 5.3 Hz, 1 H, CH$_2$NH), 3.94 (dd, ^2J = 17.9 Hz, ^3J = 6.1 Hz, 1 H, CH$_2$NH), 6.40–6.42 (m, 1 H, CH$_2$C*H*=C), 6.58 (br. s, 1 H, NH), 7.13–7.21 (m, 5 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.84 (CH$_3$), 30.17 (*C*H$_2$CH=C), 41.02 (*C*H$_2$NH), 43.93 (*C*H$_2$Ph), 52.29 (O*C*H$_3$), 85.53 (*C*CH$_2$Ph), 127.29 (ArCH), 127.73 (CH=*C*), 128.32, 130.54 (ArCH), 134.21 (ArC), 138.64 (*C*H=C), 163.78, 169.13, 171.78 (CO) ppm. IR: $\tilde{\nu}$ = 3366, 2924, 1720, 1674, 1202, 1043, 701 cm^{-1}. MS (ESI+): *m*/*z* (%) = 324.2 (100) [M + Li]$^+$. HRMS (CI, isobutane): calcd. for $C_{17}H_{20}NO_5$ [M]$^+$ 318.1341; found 318.1337.

3-Allylcyclohexanone (6): Under an argon atmosphere, to a solution of cyclohexenone (0.97 mL, 10 mmol) in anhydrous dichloromethane (15 mL) was added titanium tetrachloride (1.09 mL, 10 mmol) at –78 °C. At this point, the mixture had a dark red color. A solution of allyltrimethylsilane (1.75 mL, 11 mmol) in anhydrous dichloromethane was added dropwise with a syringe. The mixture was stirred at –30 °C for 3 h. After that time, water (20 mL) was added very carefully. The organic layer was separated, and the inorganic layer was extracted with diethyl ether (3 × 40 mL). The combined layers were dried with magnesium sulfate. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.72). The product was obtained as a colorless oil (550 mg, 3.98 mmol, 40%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.31–1.38, 1.59–1.67, 1.84–1.91, 2.02–2.08, 2.21–2.27, 2.33–2.42 (6m, 11 H, CyCH_2, Cy*H*, CH_2CH=CH$_2$), 5.00–5.03 (m, 2 H, CH$_2$CH=CH_2), 5.69–5.77 (m, 1 H, CH$_2$C*H*=CH$_2$) ppm.[29]

***rac*-Allyl *N*-{[1-(Acetyloxy)-3-allylcyclohexyl]carbonyl}glycinate (7a):** Following GP A, 3-allylcyclohexanone **6** (110.0 mg, 0.80 mmol), acetic acid (48.0 mg, 0.80 mmol), allyl isocyanoacetate (100.0 mg, 0.80 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.19) and obtained as a colorless oil (95.0 mg, 0.290 mmol, 37%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.26–1.31, 2.42–2.48 (5 m, 11 H, CyCH_2, CH_2CH=CH$_2$), 2.05 (s, 3 H, CH_3), 4.06–4.08 (m, 2 H, CH_2NH), 4.65 (d, ^3J = 5.9 Hz, 2 H, OCH_2CH=CH$_2$), 4.99 (dd, ^3J = 7.7 Hz, ^3J = 10.3 Hz, 2 H, CH$_2$CH=CH_2), 5.31 (dd, ^3J = 10.3 Hz, ^3J = 17.3 Hz, 2 H, CH$_2$CH=CH_2), 5.71–5.79 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.87–5.95 (m, 1 H, OCH$_2$C*H*=CH$_2$), 6.33 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.36 (Cy*C*H$_2$), 21.94 (CH$_3$), 31.18 (Cy*C*H$_2$), 33.45 (Cy*C*H), 34.00 (*C*H$_2$CH=CH$_2$), 39.63 (*C*H$_2$NH), 41.04, 41.18 (Cy*C*H$_2$), 66.08 (O*C*H$_2$CH=CH$_2$), 82.48 (Cy*C*), 116.51 (CH$_2$CH=*C*H$_2$), 119.09 (OCH$_2$CH=*C*H$_2$), 131.02 (OCH$_2$*C*H=CH$_2$), 136.92 (CH$_2$*C*H=CH$_2$), 169.67, 171.15, 172.13 (CO) ppm. IR: $\tilde{\nu}$ = 3354, 2935, 1740, 1668, 1181 cm^{-1}. MS (ESI+): *m*/*z* (%) = 346.1 (100) [M + Na]$^+$. TOF MS (ESI+): calcd. for $C_{17}H_{25}NO_5Na$ [M + Na]$^+$ 346.1630; found 346.1627.

***rac*-3-Allyl-1-[2-(allyloxy)-2-oxoethylcarbamoyl]cyclohexyl Propionate (7b):** Following GP A, 3-allylcyclohexanone **6** (70.0 mg, 0.51 mmol), propionic acid (38.0 mg, 0.51 mmol), allyl isocyanoacetate (64.0 mg, 0.51 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.26) and obtained as a colorless oil (46.0 mg, 0.126 mmol, 27%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.09 (t, ^3J = 7.5 Hz, 3 H, CH_2CH_3), 1.23–2.03, 2.32–2.45 (5m, 11 H, CyCH_2, $CH_2CH{=}CH_2$), 2.30 (q, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 4.03–4.05 (m, 2 H, CH_2NH), 4.62 (d, ^3J = 5.9 Hz, 2 H, $OCH_2CH{=}CH_2$), 4.97 (dd, ^3J = 7.0 Hz, ^3J = 10.1 Hz, 2 H, $CH_2CH{=}CH_2$), 5.27 (dd, ^3J = 10.4 Hz, ^3J = 17.1 Hz, 2 H, $OCH_2CH{=}CH_2$), 5.69–5.77 (m, 1 H, $CH_2CH{=}CH_2$), 5.84–5.92 (1 H, $OCH_2CH{=}CH_2$), 6.35 (br. s, 1 H, NH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 8.93 (CH_2CH_3), 21.87 (CyCH_2), 28.05 (CH_2CH_3), 31.21 (CyCH_2), 33.70 (CyCH), 33.39 ($CH_2CH{=}CH_2$), 39.74 (CH_2NH), 41.04, 41.17 (CyCH_2), 66.01 ($OCH_2CH{=}CH_2$), 82.22 (CyC), 116.04 ($CH_2CH{=}CH_2$), 119.02 ($OCH_2CH{=}CH_2$), 131.36 ($OCH_2CH{=}CH_2$), 136.60 ($CH_2CH{=}CH_2$), 169.63, 172.19, 173.06 (CO) ppm. IR: $\tilde{\nu}$ = 3352, 2937, 1740, 1668, 1177 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 398.3 (100) $[M + Na]^+$. TOF MS (ESI+): calcd. for $C_{18}H_{27}NO_5Na$ $[M + Na]^+$ 360.1787; found 360.1783.

***rac*-3-Allyl-1-[2-(allyloxy)-2-oxoethylcarbamoyl]cyclohexyl 4-Methoxybenzoate (7c):** Following GP A, 3-allylcyclohexanone **6** (104.0 mg, 0.76 mmol), 4-methoxybenzoic acid (115.0 mg, 0.76 mmol), allyl isocyanoacetate (95.0 mg, 0.76 mmol), and anhydrous dichloromethane (5.0 mL) were used. The crude product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 7:3; R_f = 0.37) and obtained as a colorless oil (130.0 mg, 0.313 mmol, 41%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.35–1.56 (5m, 11 H, CyCH_2, $CH_2CH{=}CH_2$), 3.80 (s, 3 H, OCH_3), 3.96–4.06 (m, 2 H, CH_2NH), 4.53 (d, ^3J = 5.7 Hz, 2 H, $OCH_2CH{=}CH_2$), 4.92 (dd, ^3J = 6.0 Hz, ^3J = 10.6 Hz, 2 H, $CH_2CH{=}CH_2$), 5.19 (dd, ^3J = 10.3 Hz, ^3J = 17.2 Hz, 2 H, $OCH_2CH{=}CH_2$), 5.64–5.88 (m, 2 H, $CH_2CH{=}CH_2$, $OCH_2CH{=}CH_2$), 6.36 (br. s, 1 H, N*H*), 6.87 (d, ^3J = 8.8 Hz, 2 H, ArC*H*), 7.98 (d, ^3J = 8.8 Hz, 2 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.96, 31.31 (CyCH_2), 33.85 (CyCH), 34.33 ($CH_2CH{=}CH_2$), 39.90 (CH_2NH), 41.11, 41.26 (CyCH_2), 55.46 (OCH_3), 67.13 ($OCH_2CH{=}CH_2$), 82.70 (Cy*C*), 113.69 (ArCH), 116.05 ($CH_2CH{=}CH_2$), 119.90 ($OCH_2CH{=}CH_2$), 122.55 (Ar*C*), 130.69 ($OCH_2CH{=}CH_2$), 131.85 (ArCH), 136.72 ($CH_2CH{=}CH_2$), 163.67 (ArC), 164.81, 169.59, 172.34 (CO) ppm. IR: $\tilde{\nu}$ = 3345, 2923, 1715, 1606, 1254 cm^{-1}. TOF MS (ESI+): *m*/*z* (%) = 438.3 (100) $[M + Na]^+$. TOF MS (ESI+): calcd. for $C_{23}H_{29}NO_6Na$ $[M + Na]^+$ 438.1893; found 438.1902.

(2*S,4*R**)- and (2*S**,4*S**)-*S*-2-Benzyl-2-(benzylcarbamoyl)-6-oxotetrahydro-2*H*-pyran-4-yl Ethanethioate (8):** For the derivatization, racemic α,β-unsaturated pyran-2-carboxamide **5g** (80 mg, 0.249 mmol) was dissolved in 0.9 mL thioacetic acid. A pinch of AIBN was added, and the mixture was heated to 100 °C for 6 h. Then the thioacetic acid was removed under reduced pressure. The diastereomers were separated by column chromatography on silica gel (dichloromethane/ethyl acetate, 7:3), with a diastereomeric ratio (*dr*) = 56:44. The major diastereoisomer (2*S**,4*R**)-**8** (R_f = 0.26) was obtained as a colorless solid (35 mg, 0.088 mmol, 35%), m.p. 109–110 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.74 (t, ^3J = 13.3 Hz, 1 H, CyCH_2), 2.31 (s, 3 H, CH_3), 2.31–2.37 (m, 1 H, CyCH_2), 2.90–2.94 (m, 1 H, CyCH_2), 3.00 (ddd, ^2J = 17.9 Hz, ^3J = 5.5 Hz, ^4J = 2.0 Hz, 1 H, CyCH_2), 3.05 (d, ^2J = 14.0 Hz, 1 H, CH_2Ph), 3.21 (d, ^2J = 14.0 Hz, 1 H, CH_2Ph), 3.59–3.66 (m, 1 H, CyCH), 4.28 (dd, ^2J = 14.7 Hz, ^3J = 5.2 Hz, 1 H, CH_2NH), 4.39 (dd, ^2J = 14.7 Hz, ^3J = 6.3 Hz, 1 H, CH_2NH), 6.50 (t, ^3J = 5.5 Hz, 1 H, NH), 7.01–7.02, 7.19–7.28 (2m, 10 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 30.53 (CH_3), 32.66 (CyCH), 34.31, 36.83 (CyCH_2), 43.76 (CH_2Ph), 45.27 (CH_2NH), 87.46 (Cy*C*), 127.35, 127.57, 127.62, 128.38, 128.68, 130.62, 133.67, 136.99 (ArC), 167.41, 170.12 (CO), 193.58 (SCO) ppm. IR: $\tilde{\nu}$ = 3316, 2933, 1738, 1651, 1083, 694 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 398.2 (100) $[M + H]^+$. HRMS (CI, isobutane): calcd. for $C_{22}H_{24}NO_4S$ $[M]^+$ 398.1426; found 398.1437. The minor diastereoisomer (2*S**,4*S**)-**8** (R_f = 0.17) was obtained as a colorless oil (33 mg, 0.083 mmol, 33%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.39 (dd, ^2J = 14.4 Hz, ^3J = 9.5 Hz, 1 H, CyCH_2), 2.50 (dd, ^2J = 17.8 Hz, ^3J = 8.9 Hz, 1 H, CyCH_2), 2.53 (dd, ^2J = 14.8 Hz, ^3J = 4.9 Hz, 1 H, CyCH_2), 2.82 (dd, ^2J = 17.7 Hz, ^3J = 5.5 Hz, 1 H, CyCH_2), 3.15 (d, ^2J = 13.9 Hz, 1 H, CH_2Ph), 3.25 (d, ^2J = 13.9 Hz, 1 H, CH_2Ph), 3.91–3.96 (m, 1 H, CyCH), 4.22 (dd, ^2J = 14.7 Hz, ^3J = 5.3 Hz, 1 H, CH_2NH), 4.32 (dd, ^2J = 14.6 Hz, ^3J = 6.3 Hz, 1 H, CH_2NH), 6.59 (t, ^3J = 5.4 Hz, 1 H, NH), 6.96–6.98, 7.18–7.27 (2m, 10 H, ArCH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 30.61 (CH_3), 33.05 (CyCH), 34.63, 35.94 (CyCH_2), 43.41 (CH_2Ph), 44.80 (CH_2NH), 86.31 (Cy*C*), 127.35, 127.49, 127.79, 128.42, 128.62, 130.60, 133.73, 136.98 (ArC), 166.99, 170.07 (CO), 193.84 (SCO) ppm. IR: $\tilde{\nu}$ = 3316, 2933, 1738, 1651, 1083, 694 cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 398.5 (100) $[M + H]^+$. HRMS (CI, isobutane): calcd. for $C_{22}H_{24}NO_4S$ $[M]^+$ 398.1426; found 398.1435.

X-ray Crystallographic Study

Crystal Data for 4c: $C_{18}H_{21}NO_5$, M = 331.36, T = 153(2) K, orthorhombic, space group $P2_12_12_1$, a = 8.4092(3) Å, b = 16.8186(5) Å, c = 25.1187(8) Å, β = 90°, V = 3552.6(2) Å^3, $\rho_{calcd.}$ = 1.239 Mg/m^3, Z = 8, R(int) = 0.0326 [for 4414 reflections with $I > 2.0\sigma(I)$], wR_2 = 0.0902 (all data), GOF = 1.019.

Crystal Data for 5g: $C_{20}H_{19}NO_3$, M = 321.36, T = 153(2) K, triclinic, space group $P\bar{1}$, a = 6.1078(3) Å, b = 10.1201(6) Å, c = 13.7540(8) Å, β = 82.531(3)°, V = 838.00(8) Å^3, $\rho_{calcd.}$ = 1.274 Mg/m^3, Z = 2, R(int) = 0.0343 [for 4954 reflections with $I > 2.0\sigma(I)$], wR_2 = 0.1433 (all data), GOF = 0.923.

Crystal Data for 8: $C_{22}H_{23}NO_4S$, M = 397.47, T = 153(2) K, monoclinic, space group $P2_1/n$, a = 17.6264(7) Å, b = 13.6851(6) Å, c = 25.3138(10) Å, β = 100.641(2)°, V = 6001.2(4) Å^3, $\rho_{calcd.}$ = 1.320 Mg/m^3, Z = 12, R(int) = 0.0731[for 8170 reflections with $I > 2.0\sigma(I)$], wR_2 = 0.1557 (all data), GOF = 1.003.

CCDC-827416, -827417, and -827418 contain 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.

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