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# Synthesis of ω-Oxo Amino Acids and *trans*-5-Substituted Proline Derivatives Using Cross-Metathesis of Unsaturated Amino Acids

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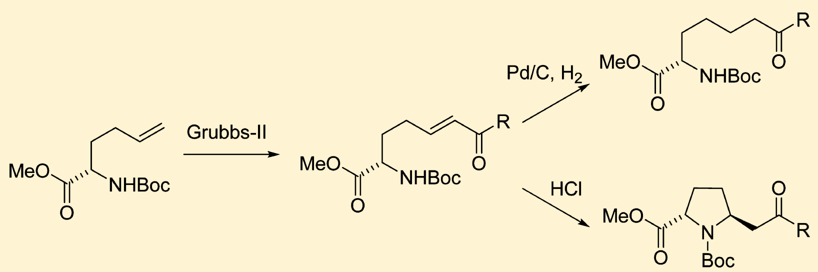
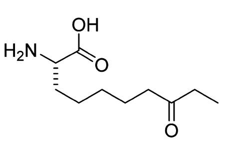
Supporting Information



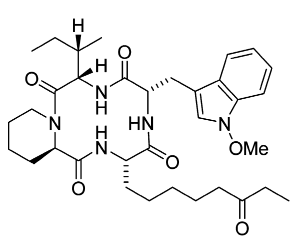

**ABSTRACT:** A range of 7-oxo, 8-oxo, and 9-oxo amino acids, analogues of 8-oxo-2-aminodecanoic acid, one of the key components of the cyclic tetrapeptide apicidin, have been prepared by a three-step process involving copper-catalyzed allylation of serine-, aspartic acid-, and glutamic acid-derived organozinc reagents, followed by cross-metathesis of the resulting terminal alkenes with unsaturated ketones and hydrogenation. The intermediate 7-oxo-5-enones underwent a highly diastereoselective (dr ≥96:4) acid-catalyzed aza-Michael reaction to give *trans*-2,5-disubstituted pyrrolidines, 5-substituted proline derivatives. The aza-Michael reaction was first observed when the starting enones were allowed to stand in solution in deuterochloroform but can be efficiently promoted by catalytic amounts of dry HCl.

## ■ INTRODUCTION

The synthesis of 8-oxo-2-aminodecanoic acid (Aoda) **1**, one of the key components of the cyclic tetrapeptide apicidin **2**,[1−3] has attracted considerable attention, as a result of the biological activity of apicidin[4,5] and its closely related analogues.[6−10] A number of approaches to the synthesis of Aoda **1** have been adopted, including the use of chiral pool starting materials[9,11−14] and the use of chiral auxiliary groups.[15−18] Of most direct relevance to the topic of this paper is the report on the use of radical addition of chiral nonracemic amino acid fragments to enones.[12] However, there is as yet no general approach to a range of simple analogues of 8-oxo-2-aminodecanoic acid in which the position of the ketone and the length of the side chain can be straightforwardly varied.

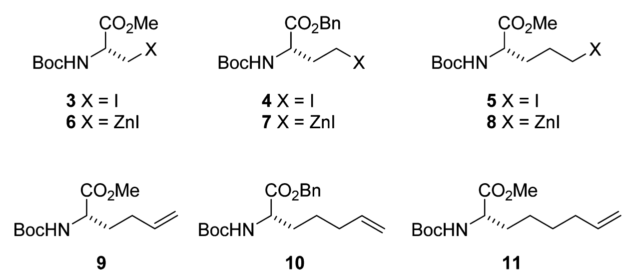



2-amino-8-oxo-decanoic acid (Aoda), **1**




Apicidin, **2**

We have developed a direct approach to the synthesis of enantiomerically pure α-amino acids using a family of organozinc reagents **6−8**, each prepared from the corresponding alkyl iodide **3−5**, respectively.[19] Zinc reagents **6−8** can undergo Negishi cross-coupling with a variety of coupling partners.[19] Copper-promoted reaction of zinc reagent **6** with a range of electrophiles, including allylic halides, is possible.[20] Specifically copper-catalyzed reaction of zinc reagent **3** with allyl chloride gave protected butenylglycine **9**,[21] and protected pentenylglycine **10** has also been prepared by related chemistry.[22] We considered that extension of this allylation reaction to zinc reagent **8** should allow access to homologous alkene **11**.




There is significant literature precedent that amino acids incorporating a terminal alkene in the side chain can undergo cross-metathesis reaction[23,24] with simple alkenes,[25,26] including reaction with electron-deficient alkenes.[27,28] A recent paper describes application of this approach to cyclic tetrapeptide derivatives.[29] It therefore appeared to be entirely reasonable that the terminal alkenes **9−11** might undergo cross-metathesis with simple enones. Subsequent hydrogenation would be

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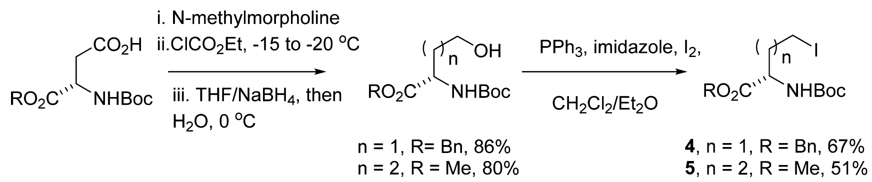
**Scheme 1**



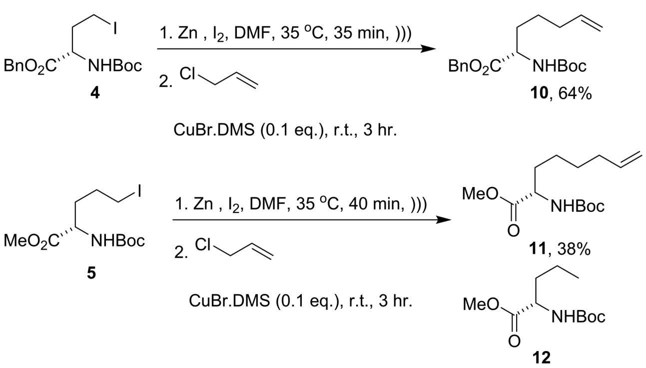

expected to give the desired analogues of 8-oxo-2-aminodecanoic acid in a straightforward and flexible manner.

## ■ RESULTS AND DISCUSSION

Synthesis of iodide **3** was conducted according to our previously reported methods from appropriately protected derivatives of serine.[30] Iodides **4** and **5** were prepared from protected aspartic and glutamic acids by reduction via the mixed anhydride,[31] an improvement on the method using *N*-hydroxysuccinimide activation,[32] followed by standard conversion of the primary alcohol to the iodide (Scheme 1).

Conversion of iodide **3** into corresponding zinc reagent **6** using iodine to activate the zinc metal prior to insertion, and copper-catalyzed allylation using allyl chloride, gave expected product **9** in a yield (75%) slightly higher than that achieved by our previously reported method.[21] Others have successfully prepared **9** using this general approach.[33] Conversion of each of the two iodides **4** and **5** into the corresponding zinc reagents using ultrasonication, followed by allylation using allyl chloride in the presence of CuBr·DMS (0.1 equiv), gave the corresponding allylated products in yields of 64% (**10**) and 38% (**11**), respectively (Scheme 2). While the yield of **10** is comparable to that of **9**, the yield of **11** was disappointing. In the latter case, the mass balance was protonated zinc reagent **12**, and attempts to improve this yield, including omitting the use of sonication, were not successful.

**Scheme 2**




Cross-metathesis reactions of each of the terminal alkenes **9–11** using the Grubbs second-generation catalyst with a range of unsaturated ketones gave excellent yields of expected products **13–15** (Scheme 3 and Table 1).

Homodimers of **9–11** were detected in all the crude reaction mixtures by MS analysis. This observation was not unexpected, because terminal alkenes are known to undergo rapid homodimerization under similar conditions.[34,35] When alkene **10** was subjected to a Grubbs second-generation catalyst in the absence of enone, homodimer **16** was isolated in excellent yield (98%). Subjecting **16** to the standard cross-metathesis conditions with 1-hexen-3-one gave expected product **14c**

**Scheme 3. Cross-Metathesis of Terminal Alkenes**

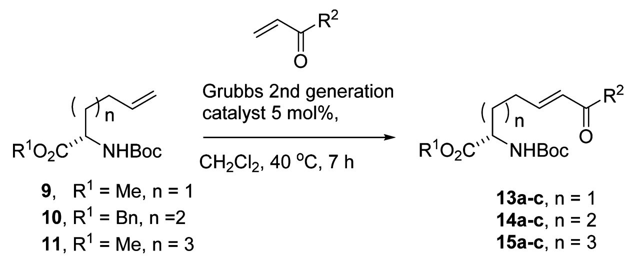


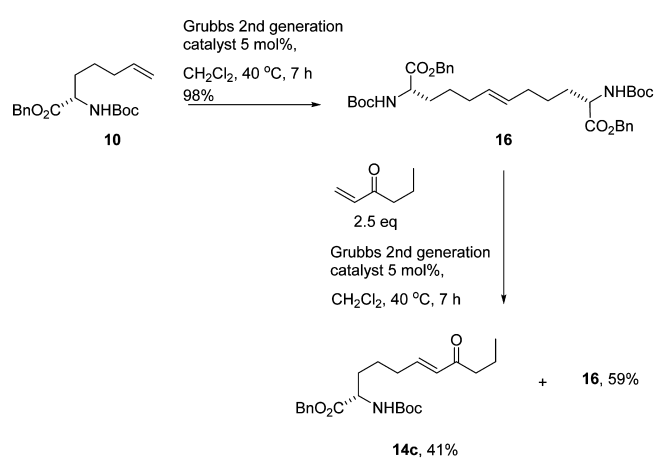

**Table 1. Cross-Metathesis of Terminal Alkenes**

| substrate | *n* | $R^1$ | $R^2$ | enone (equiv) | product | yield (%) |
|---|---|---|---|---|---|---|
| **9** | 1 | Me | $CH_3$ | 3.0 | **13a** | 91 |
| **9** | 1 | Me | $C_2H_5$ | 3.0 | **13b** | 92 |
| **9** | 1 | Me | $C_3H_7$ | 2.5 | **13c** | 90 |
| **10** | 2 | Bn | $CH_3$ | 3.0 | **14a** | 89 |
| **10** | 2 | Bn | $C_2H_5$ | 5.0 | **14b** | 90 |
| **10** | 2 | Bn | $C_3H_7$ | 2.5 | **14c** | 86 |
| **11** | 3 | Me | $CH_3$ | 2.5 | **15a** | 82 |
| **11** | 3 | Me | $C_2H_5$ | 2.5 | **15b** | 82 |
| **11** | 3 | Me | $C_3H_7$ | 2.5 | **15c** | 91 |

(41%), together with recovered homodimer **16** (59%) (Scheme 4). Because the homodimer was not completely consumed under the reaction conditions used for the initial cross-metathesis, we can conclude that it is probably not an intermediate in that process even though it is a substrate for the cross-metathesis reaction.

Hydrogenation of each of the enones **13–15** was conducted under standard conditions, leading to the desired protected amino acids **17–19**, respectively (Scheme 5 and Table 2). In the case of the three benzyl esters **14a–c**, the final isolated product was the corresponding free carboxylic acid **18a–c**, respectively, in principle ready for incorporation into a peptide.

**Scheme 4**





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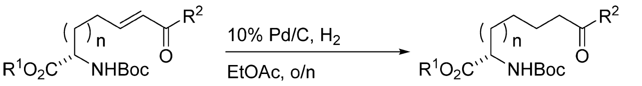
### Scheme 5




**13a-c**, n = 1, $R^1$ = Me
**14a-c**, n = 2, $R^1$ = Bn
**15a-c**, n = 3, $R^1$ = Me

**17a-c**, n = 1, $R^1$ = Me
**18a-c**, n = 2, $R^1$ = H
**19a-c**, n = 3, $R^1$ = Me

### Table 2. Hydrogenation of Cross-Metathesis Products

| substrate | *n* | $R^1$ | $R^2$ | product | $R^1$ | yield (%) |
|---|---|---|---|---|---|---|
| **13a** | 1 | Me | $CH_3$ | **17a** | Me | 94 |
| **13b** | 1 | Me | $C_2H_5$ | **17b** | Me | 99 |
| **13c** | 1 | Me | $C_3H_7$ | **17c** | Me | 98 |
| **14a** | 2 | Bn | $CH_3$ | **18a** | H | 90 |
| **14b** | 2 | Bn | $C_2H_5$ | **18b** | H | 89 |
| **14c** | 2 | Bn | $C_3H_7$ | **18c** | H | 98 |
| **15a** | 3 | Me | $CH_3$ | **19a** | Me | 94 |
| **15b** | 3 | Me | $C_2H_5$ | **19b** | Me | 99 |
| **15c** | 3 | Me | $C_3H_7$ | **19c** | Me | 99 |

These results demonstrate that it is possible to prepare a range of simple analogues of 8-oxo-2-aminodecanoic acid in which the position of the ketone and the length of the side chain can be straightforwardly varied simply by the choice of the starting amino acid (serine, aspartic acid, or glutamic acid) and the enone.

During the process of characterization of enones **13a−c**, and in particular when a solution of each of these enones was allowed to stand in $CDCl_3$, they were each converted in high yield into the corresponding pyrrolidines **20−22**, respectively, in an intramolecular aza-Michael reaction. Use of purified $CDCl_3$, in which any HCl present in the $CDCl_3$ was removed by passage through UG1 alumina, prevented the aza-Michael reaction from occurring, allowing characterization of enones **13a−c**. In separate experiments, each of the enones **13a−c** was separately treated with catalytic amounts of dry HCl in $CH_2Cl_2$, which resulted in efficient cyclization to give the same pyrrolidines **20−22**, respectively, already observed (Scheme 6 and Table 3). This established that the aza-Michael reaction was acid-catalyzed, something that has been observed previously.[36−38] What was striking about each of the three pyrrolidines **20−22** resulting from acid-catalyzed cyclization is that they appeared to be formed with very high diastereoselectivity, with dr values ranging from 96:4 to 98:2 (determined by GC analysis, and also corroborated by NMR in the case of **20a** and **20b**). X-ray diffraction analysis of the major product obtained by cyclization of **13b** provided a definitive answer, showing that the major isomer was of *trans* configuration, **21b**. To exclude the possibility that we had inadvertently selected a crystal of the minor isomer, $^1H$ NMR data of the specific crystal used for X-ray analysis were recorded. Although the concentration of the NMR sample was low, the spectrum matched closely that of the bulk material. The $^1H$ NMR spectra of the products formed from acid-catalyzed cyclization of **13a** and **13c** were essentially identical to the $^1H$ NMR spectrum of **21b** (apart from the signals due to the different side chains), which confirms that the products therefore have structures of **20b** and **22b**, respectively.

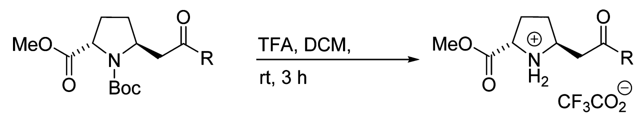
### Table 3. Acid-Catalyzed Cyclization of Amino Enones 13

| substrate | R | product | conversion | *dr (*cis*:*trans*) |
|---|---|---|---|---|
| **13a** | $CH_3$ | **20a/b** | complete | 0.04:0.96[a,b] |
| **13b** | $C_2H_5$ | **21a/b** | complete | 0.02:0.98[b] |
| **13c** | $C_3H_7$ | **22a/b** | 96 (4% SM) | 0.02:0.98[b] |

[a]Ratio determined by $^1H$ NMR. [b]Ratio determined with GC.

Boc deprotection of each of compounds **20b**, **21b**, and **22b** using trifluoroacetic acid (Scheme 7) gave the corresponding trifluoroacetate salt **23−25**, respectively, in essentially quantitative yield. Each of the trifluoroacetate salts **23−25** was determined to be of *trans* configuration by X-ray diffraction. Because the structure of **21b** had already been established as the *trans*-pyrrolidine, this demonstrated that the deprotection reaction had proceeded without influencing the stereochemistry (for example, by promoting a reversible aza-Michael process), which means that the assignments already made by comparison of the $^1H$ NMR spectra of **20b** and **22b** with those of **21b** are confirmed.

### Scheme 7

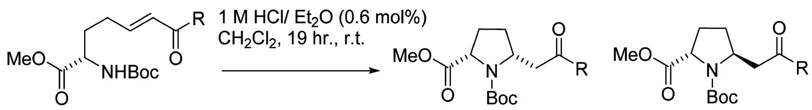



**20b**, R = Me
**21b**, R = Et
**22b**, R = Pr

**23**, R = Me (99%)
**24**, R = Et (99%)
**25**, R = Pr (99%)

A similar process has been reported previously, in which the cross-metathesis of Cbz-protected unsaturated amines with enones in the presence of a Lewis acid ($BF_3{\cdot}Et_2O$) leads to 2,5-disubstituted pyrrolidines with moderate levels of stereoselectivity (in the range from 2:1 to 6:1 in favor of the *trans* isomer).[39] Strong acid catalysis (TfOH) has also been used to promote the cyclization of a related Cbz-protected amino enone, again with moderate levels of stereoselectivity (39:61 in favor of the *trans* isomer).[38] The high levels of diastereoselectivity in the formation of *trans*-2,5-disubstituted pyrrolidines that we have observed were therefore not expected on the basis of this literature precedent. The two principal differences between our substrates and those previously reported are the nature of the nitrogen protecting group and the presence of a carbomethoxy group. In addition, the choice of the acid catalyst

### Scheme 6




**13a**, R Me
**13b**, R = Et
**13c**, R = Pr

**20a**, R = Me
**21a**, R = Et
**22a**, R = Pr

**20b**, R = Me
**21b**, R = Et
**22b**, R = Pr
**Major**



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may be important. Further studies of the influence of these features appear to be warranted.

## ■ EXPERIMENTAL SECTION

HRMS measurements were performed using electrospray ionization, with a TOF mass analyzer. IR spectra were recorded as thin films. Compound **3** was prepared by the literature method.[30] The preparation of compound **4** was performed by the literature method,[31] but on a scale substantially larger than that reported. In our hands, **4** was isolated as a yellow crystalline solid (mp 55−56 °C), as we had previously reported (mp 54−55 °C),[32] rather than as an oil.[31] All other data for **4** matched that reported previously.[31,32] Compound **5** (the methyl ester)[40] was prepared by the general method reported for the synthesis of the corresponding benzyl ester.[31] GC analysis of compounds **20**−**22** was performed using a Phenomenex ZB-5 column (0.25 mm inside diameter × 30 m, film thickness of 250 μm) with an oven temperature of 145 °C (isothermal), a carrier gas of $H_2$ at 1.4 mL/min, injection at 250 °C/split = 34.7:1, and detection via FID at 300 °C.

**General Procedure A: Allylation Reactions.** A two-neck round-bottom flask fitted with a magnetic stir bar was fitted with a rubber septum and three-way tap. The flask was flame-dried under vacuum and backfilled with nitrogen three times. Zinc dust (see each procedure for the amount) was added, and the flask was flame-dried, again evacuated, and backfilled with nitrogen three times, while its contents were being continuously stirred. The flask was allowed to cool; dry DMF (1 mL/1 mmol of alkyl iodide) was added via syringe, and the heterogeneous mixture was stirred vigorously. Iodine (see each procedure for the amount) was added by rapid removal and replacement of the three-way tap under a stream of nitrogen. The mixture was stirred for 1−2 min, until the solution was colorless. The alkyl iodide (1.0 mmol) was added by rapid removal and replacement of the three-way tap under a stream of nitrogen (in the case of compound **5**, the alkyl iodide was dissolved in DMF and added by syringe). The mixture was stirred, and an exotherm was observed while stirring continued for a further 50 min at rt or for 35−40 min at 35 °C with sonication; these details are specified with each example. The solid zinc dust was then allowed to settle, giving a clear supernatant. During the activation period, a separate two-neck round-bottom flask fitted with a magnetic stir bar, rubber septum, and three-way tap was flame-dried under vacuum and backfilled with nitrogen three times. The flask was allowed to cool; CuBr·DMS (0.1 equiv relative to alkyl iodide) was added, and the flask was gently heated, then evacuated, and backfilled with nitrogen until the CuBr·DMS changed appearance from a gray-brown to light green powder. The flask was allowed to cool, before the addition of dry DMF (0.6 mL/1 mmol of alkyl iodide) and allyl chloride (see each procedure for the amount) dropwise via syringe. The mixture was stirred at room temperature for ∼5 min, at which point the supernatant from the solution containing the organozinc reagent was added dropwise via syringe, and the reaction mixture was stirred at room temperature for 3 h. The crude reaction mixture was directly applied to the $SiO_2$ column, using a gradient of 20 to 30% EtOAc in petroleum ether.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}hex-5-enoate (**9**).* General procedure A using zinc dust (1.95 g, 30 mmol, 2.5 equiv), iodine (0.6 g, 2.4 mmol, 0.2 equiv), **3** (3.94 g, 12 mmol, 1 equiv), CuBr·DMS (0.246 g, 1.2 mmol, 0.1 equiv), and allyl chloride (1.36 mL, 16.8 mmol, 1.4 equiv) gave methyl (2*S*)-2-{[(*tert*-butoxy)-carbonyl]amino}hex-5-enoate **9** (2.2 g, 9 mmol, 75%) as a colorless oil. Zinc insertion took 50 min at rt: $[\alpha]_D$ −17.0 (*c* 1.0, MeOH) [lit.[33] $[\alpha]_D$ −20.7 (*c* 0.97, MeOH)]; $R_f$ = 0.57 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.80 (1 H, ddt, *J* = 16.9, 10.3, and 6.6 Hz), 4.98−5.08 (3 H, m), 4.28−4.37 (1 H, m), 3.74 (3 H, s), 2.06−2.17 (2 H, m), 1.85−1.96 (1 H, m), 1.65−1.77 (1 H, m), 1.44 (9 H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.3, 155.3, 136.9, 115.7, 79.8, 52.9, 52.3, 31.9, 29.5, 28.3; IR 3370, 1742, 1712, 1516, 1451, 1365, 1254, 1168 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 244.1549, $C_{12}H_{22}NO_4$ requires 244.1549.

*Benzyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}hept-6-enoate (**10**).*[22] General procedure A using zinc dust (1.17 g, 18 mmol, 3 equiv), iodine (0.335 g, 1.32 mmol, 0.22 equiv), **4** (2.5 g, 6 mmol, 1 equiv), CuBr·DMS (0.123 g, 0.6 mmol, 0.1 equiv), and allyl chloride (0.7 mL, 8.4 mmol, 1.4 equiv). Zinc insertion took 35 min with sonication at 35 °C. Purification by column chromatography (20% EtOAc in petroleum ether) followed by preparative HPLC [XBridge Prep OBD C18 5 μm 19 mm (inside diameter) × 250 mm, using 30:70 water/acetonitrile, at a flow rate of 17 mL $min^{-1}$ and UV detection at 210 nm] gave benzyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]-amino}hept-6-enoate **10** (1.28 g, 3.8 mmol, 64%) as a colorless oil ($t_R$ = 8−10 min): $[\alpha]_D$ −4.0 (*c* 1, $CHCl_3$) [lit.[22] $[\alpha]_D$ −5.5 (*c* 1.4, $CH_2Cl_2$)]; $R_f$ = 0.5 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31−7.40 (5 H, m), 5.72 (1 H, ddt, *J* = 16.9, 10.3, and 6.7 Hz), 5.22 (1 H, d, *J* = 12.4 Hz), 5.13 (1 H, d, *J* = 12.4 Hz), 5.05 (1 H, d, *J* = 8.3 Hz), 5.02−4.92 (2 H, m), 4.30−4.39 (1 H, m), 1.96−2.12 (2 H, m), 1.75−1.88 (1 H, m), 1.58−1.69 (1 H, m), 1.31−1.52 (11 H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.7, 155.4, 137.9, 135.5, 128.6, 128.4, 128.2, 115.1, 79.8, 66.9, 53.4, 33.1, 32.1, 28.3, 24.4; IR 3368, 1745, 1712, 1634, 1501, 1366, 1253, 1165, 1001, 912 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 334.2028, $C_{19}H_{28}NO_4$ requires 334.2018.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}oct-7-enoate (**11**).*[41] General procedure A using zinc dust (487.5 mg, 7.5 mmol, 2.5 equiv), iodine (152.3 mg, 0.6 mmol, 0.2 equiv), **5** (1.10 g, 3 mmol, 1 equiv), CuBr·DMS (61.5 mg, 0.3 mmol, 0.1 equiv), and allyl chloride (320 μL, 3.9 mmol, 1.3 equiv) gave methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]-amino}oct-7-enoate **11** (311 mg, 1.15 mmol, 38%) as a colorless oil. Zinc insertion took 40 min with sonication at 35 °C: $[\alpha]_D$ −17.6 (*c* 1.25, MeOH); $R_f$ = 0.52 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.77 (1 H, ddt, *J* = 16.9, 10.1, and 6.8 Hz), 4.9−5.05 (3 H, m), 4.25−4.33 (1 H, m), 3.73 (3 H, s), 1.99−2.1 (2 H, m), 1.69−1.86 (1 H, m), 1.53−1.68 (1 H, m), 1.24−1.51 (4 H, m), 1.44 (9 H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.4, 155.3, 138.5, 114.6, 79.8, 53.3, 52.2, 33.4, 32.6, 28.4, 28.3, 24.6; IR 3370, 1745, 1720, 1509, 1168 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 272.1850, $C_{14}H_{26}NO_4$ requires 272.1862.

**General Procedure B: Cross-Metathesis of Unsaturated Amino Acids.** A two-neck round-bottom flask with a magnetic stir bar was fitted with a condenser equipped with a three-way tap on top and a rubber septum. The flask was flame-dried under vacuum and backfilled with nitrogen three times. The flask was allowed to cool before the unsaturated amino acid **9**−**11** and enone in dry degassed $CH_2Cl_2$ (2 mL) were added via syringe. Grubbs second-generation catalyst (5 mol % relative to substrate) in dry $CH_2Cl_2$ (1 mL) was added by syringe, and the reaction mixture was heated at reflux for 7 h, allowed to cool to room temperature, and concentrated. The residue was purified by column chromatography using a gradient of 15 to 35% EtOAc in petroleum ether.

*Methyl (2S,5E)-2-{[(tert-Butoxy)carbonyl]amino}-7-oxooct-5-enoate (**13a**).* General procedure B using **9** (97 mg, 0.4 mmol, 1 equiv), 3-buten-2-one (100 μL, 1.2 mmol, 3 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ (3 mL) gave methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxooct-5-enoate **13a** (104 mg, 0.36 mmol, 91%) as an oil: $[\alpha]_D$ + 40.0 (*c* 0.4, $CHCl_3$); $R_f$ = 0.13 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.77 (1 H, dt, *J* = 16.0 and 6.7 Hz), 6.09 (1 H, br d, *J* = 16.0 Hz), 5.08 (1 H, d, *J* = 8.1 Hz), 4.30−4.42 (1 H, m), 3.76 (3 H, s), 2.19−2.39 (2 H, m), 2.25 (3 H, s), 1.92−2.11 (1 H, m), 1.74−1.86 (1 H, m), 1.45 (9 H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.3, 172.7, 155.3, 146.1, 131.9, 80.1, 52.8, 52.4, 31.3, 28.3, 28.2, 26.9; IR 3359, 1749, 1715, 1673, 1518, 1450, 1371, 1253, 1166 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 286.1648, $C_{14}H_{24}NO_5$ requires 286.1654.

*Methyl (2S,5E)-2-{[(tert-Butoxy)carbonyl]amino}-7-oxonon-5-enoate (**13b**).* General procedure B using **9** (97 mg, 0.4 mmol, 1 equiv), 1-penten-3-one (120 μL, 1.2 mmol, 3 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ (3 mL) gave methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxo-non-5-enoate **13b** (110 mg, 0.37 mmol, 92%) as an oil: $[\alpha]_D$ + 36.4 (*c* 0.55, $CHCl_3$); $R_f$ = 0.17 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.76 (1 H, dt, *J* = 15.8 and 6.8 Hz), 6.09 (1 H, d,



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$J$ = 15.8 Hz), 5.13 (1 H, d, $J$ = 7.6 Hz), 4.25−4.36 (1 H, m), 3.72 (3 H, s), 2.53 (2 H, q, $J$ = 7.3 Hz), 2.17−2.35 (2 H, m), 1.88−2.06 (1 H, m), 1.71−1.82 (1 H, m), 1.41 (9 H, s), 1.06 (3 H, t, $J$ = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.7, 172.8, 155.3, 144.6, 130.7, 80.0, 52.9, 52.4, 33.4, 31.3, 28.3, 28.2, 8.0; IR 3346, 1747, 1708, 1669, 1512, 1448, 1363, 1167 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 300.1800, $C_{15}H_{26}NO_5$ requires 300.1811.

***Methyl (2S,5E)-2-{[(tert-Butoxy)carbonyl]amino}-7-oxodec-5-enoate (13c).*** General procedure B using **9** (97 mg, 0.4 mmol, 1 equiv), 1-hexen-3-one (117 μL, 1 mmol, 2.5 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mmol %) in $CH_2Cl_2$ (3 mL) gave methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxodec-5-enoate **13c** (113 mg, 0.36 mmol, 90%) as an oil: $[\alpha]_D$ + 30.7 ($c$ 0.88, $CHCl_3$); $R_f$ = 0.17 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.78 (1 H, dt, $J$ = 15.8 and 6.8 Hz), 6.11 (1 H, d, $J$ = 15.8 Hz), 5.08 (1 H, d, $J$ = 7.6 Hz), 4.27−4.39 (1 H, m), 3.75 (3 H, s), 2.5 (2 H, t, $J$ = 7.3 Hz), 2.19−2.37 (2 H, m), 1.91−2.08 (1 H, m), 1.69−1.85 (1 H, m), 1.63 (2 H, sext., $J$ = 7.4 Hz), 1.44 (9 H, s), 0.93 (3 H, t, $J$ = 7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.4, 172.8, 155.3, 144.7, 130.9, 80.1, 52.9, 52.4, 42.2, 31.3, 28.3, 28.2, 17.6, 13.8; IR 3359, 1750, 1714, 1675, 1521, 1448, 1366, 1249, 1167 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 314.1972, $C_{16}H_{28}NO_5$ requires 314.1967.

***Benzyl (2S,6E)-2-{[(tert-Butoxy)carbonyl]amino}-8-oxonon-6-enoate (14a).*** General procedure B using **10** (133.4 mg, 0.4 mmol, 1 equiv), 3-buten-2-one (100 μL, 1.2 mmol, 3 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ (3 mL) gave benzyl (2*S*,6*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-8-oxonon-6-enoate **14a** (134 mg, 0.36 mmol, 89%) as an oil: $[\alpha]_D$ −22.0 ($c$ 0.91, MeOH); $R_f$ = 0.32 (30% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32−7.42 (5 H, m), 6.70 (1 H, dt, $J$ = 16.0 and 6.9 Hz), 6.04 (1 H, d, $J$ = 16.0 Hz), 5.22 (1 H, d, $J$ = 12.2 Hz), 5.14 (1 H, d, $J$ = 12.2 Hz), 5.05 (1 H, d, $J$ = 8.1 Hz), 4.33−4.41 (1 H, m), 2.13−2.31 (5 H, m), 1.77−1.91 (1 H, m), 1.59−1.72 (1 H, m), 1.37−1.57 (2 H, m), 1.44 (9 H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.5, 172.5, 155.4, 147.1, 135.3, 131.6, 128.6, 128.5, 128.3, 79.9, 67.1, 53.2, 32.3, 31.7, 28.3, 26.9, 23.7; IR 3342, 1715, 1694, 1673, 1625, 1499, 1364, 1250, 1157 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 376.2109, $C_{21}H_{30}NO_5$ requires 376.2124.

***Benzyl (2S,6E)-2-{[(tert-Butoxy)carbonyl]amino}-8-oxodec-6-enoate (14b).*** General procedure B using **10** (134 mg, 0.4 mmol, 1 equiv), 1-penten-3-one (200 μL, 2 mmol, 5 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ (3 mL) gave benzyl (2*S*,6*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-8-oxodec-6-enoate **14b** (141 mg, 0.36 mmol, 90%) as an oil: $[\alpha]_D$ −19.5 ($c$ 0.77, MeOH); $R_f$ = 0.18 in (15% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30−7.39 (5 H, m), 6.72 (1 H, dt, $J$ = 16.0 and 6.8 Hz), 6.05 (1 H, br d, $J$ = 16.0 Hz), 5.21 (1 H, d, $J$ = 12.2 Hz), 5.13 (1 H, d, $J$ = 12.2 Hz), 5.08 (1 H, d, $J$ = 8.3 Hz), 4.30−4.40 (1 H, m), 2.52 (2 H, q, $J$ = 7.3 Hz), 2.11−2.27 (2 H, m), 1.77−1.89 (1 H, m), 1.58−1.71 (1 H, m), 1.36−1.56 (11 H, m), 1.10 (3 H, t, $J$ = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.8, 172.4, 155.4, 145.6, 135.3, 130.4, 128.6, 128.4, 128.3, 79.8, 67.1, 53.2, 33.3, 32.2, 31.7, 28.3, 23.7, 8.1; IR 3362, 1741, 1696, 1673, 1629, 1499, 1248, 1159 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 390.2283, $C_{22}H_{32}NO_5$ requires 390.2280.

***Benzyl (2S,6E)-2-{[(tert-Butoxy)carbonyl]amino}-8-oxoundec-6-enoate (14c).*** General procedure B using **10** (133.4 mg, 0.4 mmol, 1 equiv), 1-hexen-3-one (117 μL, 1 mmol, 2.5 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ gave benzyl (2*S*,6*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-8-oxoundec-6-enoate **14c** (140 mg, 0.35 mmol, 86%) as an oil: $[\alpha]_D$ −30.0 ($c$ 0.1, MeOH); $R_f$ = 0.22 (15% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33−7.41 (5 H, m), 6.73 (1 H, dt, $J$ = 16.0 and 6.8 Hz), 6.06 (1 H, br d, $J$ = 16.0 Hz), 5.22 (1 H, d, $J$ = 12.2 Hz), 5.14 (1 H, d, $J$ = 12.2 Hz), 5.04 (1 H, br d, $J$ = 8.3 Hz), 4.32−4.42 (1 H, m), 2.48 (2 H, t, $J$ = 7.3 Hz), 2.13−2.27 (2 H, m), 1.78−1.91 (1 H, m), 1.57−1.71 (3 H, m), 1.37−1.56 (11 H, m), 0.93 (3 H, t, $J$ = 7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.6, 172.5, 155.5, 145.7, 135.3, 130.7, 128.6, 128.5, 128.3, 80.2, 67.1, 53.2, 42.1, 32.3, 31.7, 28.3, 23.7, 17.6, 13.8; IR 3357, 1747, 1712, 1675, 1629, 1499, 1457, 1365, 1256, 1162 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 404.2426, $C_{23}H_{34}NO_5$ requires 404.2437.

***Methyl (2S,7E)-2-{[(tert-Butoxy)carbonyl]amino}-9-oxodec-7-enoate (15a).*** General procedure B using **11** (108.5 mg, 0.4 mmol, 1 equiv), 3-buten-2-one (85 μL, 1 mmol, 2.5 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ (3 mL) gave methyl (2*S*,7*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-9-oxodec-7-enoate **15a** (103 mg, 0.33 mmol, 82%) as an oil: $[\alpha]_D$ + 20.0 ($c$ 0.95, $CHCl_3$); $R_f$ = 0.25 (30% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.76 (1 H, dt, $J$ = 16.0 and 6.9 Hz), 6.05 (1 H, d, $J$ = 16.0 Hz), 5.04 (1 H, br d, $J$ = 8.1 Hz), 4.24−4.34 (1 H, m), 3.73 (3 H, s), 2.17−2.26 (2 H, m), 2.23 (3 H, s), 1.75−1.87 (1 H, m), 1.56−1.68 (1 H, m), 1.29−1.55 (4 H, m), 1.43 (9 H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.6, 173.2, 155.3, 147.7, 131.5, 79.9, 53.2, 52.3, 32.5, 32.1, 28.3, 27.6, 26.9, 24.8; IR 3356, 1749, 1717, 1674, 1523, 1441, 1369, 1258, 1164 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 314.1956, $C_{16}H_{28}NO_5$ requires 314.1967.

***Methyl (2S,7E)-2-{[(tert-Butoxy)carbonyl]amino}-9-oxoundec-7-enoate (15b).*** General procedure B using **11** (108.5 mg, 0.4 mmol, 1 equiv), 1-penten-3-one (100 μL, 1 mmol, 2.5 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ (3 mL) gave methyl (2*S*,7*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-9-oxoundec-7-enoate **15b** (108 mg, 0.33 mmol, 82%) as an oil: $[\alpha]_D$ + 23.7 ($c$ 0.93, $CHCl_3$); $R_f$ = 0.22 (20% EtOAc in petroleum ether); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.79 (1 H, dt, $J$ = 16.0 and 6.9 Hz), 6.08 (1 H, br d, $J$ = 16.0 Hz), 5.02 (1 H, br d, $J$ = 7.5 Hz), 4.25−4.34 (1 H, m), 3.74 (3 H, s), 2.55 (2 H, q, $J$ = 7.3 Hz), 2.21 (2 H, dq, $J$ = 1.3 and 7.2 Hz), 1.73−1.87 (1 H, m), 1.58−1.68 (1 H, m), 1.28−1.55 (4 H, m), 1.44 (9 H, s), 1.09 (3 H, t, $J$ = 7.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 201.0, 173.2, 155.3, 146.2, 130.2, 79.9, 53.2, 52.2, 33.2, 32.5, 32.1, 28.3, 27.6, 24.8, 8.1; IR 3357, 1746, 1715, 1634, 1674, 1514, 1460, 1167 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 328.2111, $C_{17}H_{30}NO_5$ requires 328.2124.

***Methyl (2S,7E)-2-{[(tert-Butoxy)carbonyl]amino}-9-oxododec-7-enoate (15c).*** General procedure B using **11** (108.5 mg, 0.4 mmol, 1 equiv), 1-hexen-3-one (117 μL, 1 mmol, 2.5 equiv), and Grubbs second-generation catalyst (16 mg, 0.02 mmol, 5 mol %) in $CH_2Cl_2$ (3 mL) gave methyl (2*S*,7*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-9-oxododec-7-enoate **15c** (125.4 mg, 0.37 mmol, 91%) as an oil: $[\alpha]_D$ + 13.2 ($c$ 0.38, $CHCl_3$); $R_f$ = 0.29 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.77 (1 H, dt, $J$ = 16.0 and 6.9 Hz), 6.07 (1 H, br d, $J$ = 16.0 Hz), 5.04 (1 H, br d, $J$ = 8.3 Hz), 4.24−4.32 (1 H, m), 3.72 (3 H, s), 2.49 (2 H, t, $J$ = 7.3 Hz), 2.19 (2 H, dq, $J$ = 7.2 and 1.3 Hz), 1.74−1.85 (1 H, m), 1.56−1.67 (3 H, m), 1.27−1.54 (4 H, m), 1.42 (9 H, s), 0.92 (3 H, t, $J$ = 7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.7, 173.3, 155.3, 146.4, 130.5, 79.9, 53.2, 52.2, 42.1, 32.5, 32.1, 28.3, 27.6, 24.8, 17.7, 13.8; IR 3357, 1750, 1718, 1671, 1516, 1437, 1369, 1247, 1167 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 342.2269, $C_{18}H_{32}NO_5$ requires 342.2280.

***1,12-Dibenzyl (2S,6E/Z,11S)-2,11-Bis{[(tert-butoxy)carbonyl]-amino}dodec-6-enedioate (16).*** General procedure B, using benzyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}hept-6-enoate **10** (110 mg, 0.33 mmol, 1 equiv) as the starting material and Grubbs second-generation catalyst (14 mg, 0.016 mmol, 5 mmol %), gave compound **16** (104 mg, 0.163 mmol, 98%) as an oil: $[\alpha]_D$ −1.3 ($c$ 1.5, $CHCl_3$); $R_f$ = 0.3 (20% EtOAc in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29−7.40 (10 H, m), 5.25−5.36 (2 H, m), 5.21 (2 H, d, $J$ = 12.5 Hz), 5.12 (2 H, d, $J$ = 12.5 Hz), 4.99−5.01 (2 H, m), 4.27−4.43 (2 H, m), 1.87−2.08 (4 H, m), 1.72−1.86 (2 H, m), 1.54−1.71 (2 H, m), 1.19−1.52 (4 H, m), 1.44 (18 H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.8, 155.4, 135.5, 130.1, 128.6, 128.4, 128.3, 79.8, 66.9, 53.5, 32.5, 31.9, 28.3, 25.0; IR 3370, 1745, 1717, 1501, 1459, 1250, 1163 cm$^{-1}$; $m/z$ (ES+) found $MH^+$ 639.3638, $C_{36}H_{51}N_2O_8$ requires 639.3645.

**General Procedure C: Hydrogenation of the Cross-Metathesis Product.** A two-neck round-bottom flask with a magnetic stir bar was fitted with a rubber septum and three-way tap, flame-dried under vacuum, and backfilled with nitrogen three times. The flask was allowed to cool, and palladium on carbon [10% (w/w)] (amount specified in each experiment) was added to the flask, which was evacuated and backfilled with nitrogen three times. Then the nitrogen gas line was replaced with a balloon of hydrogen gas, and the cross-


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metathesis product (1 equiv) was added to the flask as a solution in EtOAc (7 mL) via syringe. The flask was evacuated until the reaction mixture began to boil and then backfilled with hydrogen gas. This procedure was repeated three more times, and the reaction mixture was stirred at room temperature for 1 day. To remove the catalyst, the mixture was filtered through Celite and then washed with EtOAc. The filtrate and washings were combined, and the solvent was removed under reduced pressure.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}-7-oxooctanoate (17a).* General procedure C using **13a** (105 mg, 0.368 mmol, 1 equiv) and 10% (w/w) palladium on carbon (20 mg) gave methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxooctanoate **17a** (100 mg, 0.348 mmol, 94%) as a colorless oil: $[\alpha]_D$ + 15.8 (*c* 0.95, $CHCl_3$); $R_f$ = 0.31 (40% EtOAc in petroleum ether); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.02 (1 H, d, *J* = 8.1 Hz), 4.23−4.34 (1 H, m), 3.74 (3 H, s), 2.43 (2 H, t, *J* = 7.2 Hz), 2.13 (3 H, s), 1.73−1.87 (1 H, m), 1.52−1.68 (3 H, m), 1.44 (9 H, s), 1.22−1.40 (2 H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 208.6, 173.3, 155.4, 79.8, 53.3, 52.3, 43.3, 32.5, 29.8, 28.3, 24.8, 23.2; IR 3370, 1749, 1715, 1516, 1439, 1364, 1250, 1169 $cm^{-1}$; *m*/*z* (ES+) found $MNa^+$ 310.1618, $C_{14}H_{25}NO_5Na$ requires 310.1630.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}-7-oxononanoate (17b).* General procedure C using **13b** (58 mg, 0.194 mmol, 1 equiv) and 10% (w/w) palladium on carbon (10 mg) gave methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxononanoate **17b** (58 mg, 0.193 mmol, 99%) as a colorless oil: $[\alpha]_D$ + 16.0 (*c* 1, $CHCl_3$); $R_f$ = 0.22 (20% EtOAc in petroleum ether); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.03 (1 H, d, *J* = 8.1 Hz), 4.21−4.31 (1 H, m), 3.70 (3 H, s), 2.34−2.43 (4 H, m), 1.69−1.84 (1 H, m), 1.50−1.66 (3 H, m), 1.42 (9 H, s), 1.22−1.37 (2 H, m), 1.02 (3 H, t, *J* = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 211.3, 173.3, 155.4, 79.8, 53.3, 52.2, 41.9, 35.9, 32.6, 28.3, 24.9, 23.3, 7.8; IR 3360, 1751, 1712, 1519, 1455, 1370, 1256, 1167 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 302.1955, $C_{15}H_{28}NO_5$ requires 302.1967.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}-7-oxodecanoate (17c).* General procedure C using **13c** (89 mg, 0.284 mmol, 1 equiv) and 10% (w/w) palladium on carbon (40 mg) gave methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxodecanoate **17c** (88 mg, 0.279 mmol, 98%) as a colorless oil: $[\alpha]_D$ + 15.0 (*c* 2, $CHCl_3$); $R_f$ = 0.46 (30% EtOAc in petroleum ether); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.01 (1 H, d, *J* = 8.1 Hz), 4.23−4.34 (1 H, m), 3.73 (3 H, s), 2.39 (2 H, t, *J* = 7.3 Hz), 2.36 (2 H, t, *J* = 7.3 Hz), 1.71−1.87 (1 H, m), 1.51−1.67 (5 H, m), 1.44 (9 H, s), 1.24−1.39 (2 H, m), 0.91 (3 H, t, *J* = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 210.8, 173.3, 155.4, 79.8, 53.3, 52.2, 44.7, 42.3, 32.6, 28.3, 24.9, 23.3, 17.3, 13.7; IR 3370, 1749, 1715, 1514, 1454, 1367, 1250, 1170 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 316.2134, $C_{16}H_{30}NO_5$ requires 316.2124.

*(2S)-2-{[(tert-Butoxy)carbonyl]amino}-8-oxononanoic Acid (18a).*[17] General procedure C using **14a** (50 mg, 0.133 mmol, 1 equiv) and 10% (w/w) palladium on carbon (25 mg) gave (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-8-oxononanoic acid **18a** (34 mg, 0.12 mmol 90%) as a colorless oil: $[\alpha]_D$ + 5.0 (*c* 1.0, $CHCl_3$); $R_f$ = 0.17 (5 mL of EtOAc/5 mL of petroleum ether/0.1 mL of acetic acid); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.02 (1 H, d, *J* = 7.8 Hz), 4.25−4.35 (1 H, m), 2.44 (2 H, t, *J* = 7.3 Hz), 2.14 (3 H, s), 1.79−1.93 (1 H, m), 1.63−1.74 (1 H, m), 1.58 (2 H, quint., *J* = 7.5 Hz), 1.27−1.48 (4 H, m), 1.45 (9 H, s); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 209.6, 176.9, 155.6, 80.1, 53.3, 43.5, 32.3, 29.8, 28.6, 28.3, 25.0, 23.4. IR 3340, 1730, 1700, 1658, 1520, 1390, 1368, 1252, 1167 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 288.1806, $C_{14}H_{26}NO_5$ requires 288.1811. In the $^1H$ NMR spectrum, the carboxylic acid proton was not observed, presumably, because of its broadness.

*(2S)-2-{[(tert-Butoxy)carbonyl]amino}-8-oxodecanoic Acid (18b).*[13,14,17,18] General procedure C using **14b** (52 mg, 0.134 mmol, 1 equiv) and 10% (w/w) palladium on carbon (23 mg) gave (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-8-oxodecanoic acid **18b** (35 mg, 0.12 mmol, 89%) as a colorless oil: $[\alpha]_D$ −37.2 (*c* 0.94, $CHCl_3$); $R_f$ = 0.28 (5 mL of EtOAc/5 mL of petroleum ether/0.1 mL of acetic acid); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.02 (1 H, d, *J* = 8.0 Hz), 4.24−4.35 (1 H, m), 2.42 (2 H, q, *J* = 7.3 Hz), 2.41 (2 H, t, *J* = 7.3 Hz), 1.79−1.92 (1 H, m), 1.63−1.74 (1 H, m), 1.58 (2 H, quint., *J* = 7.3 Hz), 1.27−1.48 (4 H, m), 1.45 (9 H, s), 1.05 (3 H, t, *J* = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 212.1, 176.9, 155.6, 80.2, 53.3, 42.1, 35.9, 32.2, 28.7, 28.3, 25.1, 23.5, 7.8; IR 3322, 1735, 1713, 1681, 1510, 1460, 1395, 1249, 1166 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 302.1953, $C_{15}H_{28}NO_5$ requires 302.1967.

*(2S)-2-{[(tert-Butoxy)carbonyl]amino}-8-oxoundecanoic Acid (18c).* General procedure C using **14c** (82 mg, 0.2 mmol, 1 equiv) and 10% (w/w) palladium on carbon (37 mg) gave (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-8-oxoundecanoic acid **18c** (62 mg, 0.196 mmol, 98%) as a colorless oil: $[\alpha]_D$ −16.0 (*c* 0.5, $CHCl_3$); $R_f$ = 0.25 (5 mL of EtOAc/5 mL of petroleum ether/0.1 mL of acetic acid); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.03 (1 H, d, *J* = 8.1 Hz), 4.24−4.35 (1 H, m), 2.40 (2 H, t, *J* = 7.8 Hz), 2.38 (2 H, t, *J* = 7.5 Hz), 1.77−1.93 (1 H, m), 1.52−1.74 (5 H, m), 1.24−1.51 (4 H, m), 1.45 (9 H, s), 0.91 (3 H, t, *J* = 7.4 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 211.6, 176.9, 155.6, 80.2, 53.3, 44.7, 42.5, 32.2, 28.7, 28.3, 25.1, 23.4, 17.3, 13.7; IR 3346, 1717, 1701, 1688, 1511, 1453, 1366, 1243, 1159 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 316.2119, $C_{16}H_{30}NO_5$ requires 316.2124. In the $^1H$ NMR spectrum, the carboxylic acid proton was not observed, presumably, because of its broadness.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}-9-oxodecanoate (19a).* General procedure C using **15a** (50 mg, 0.159 mmol, 1 equiv) and 10% (w/w) palladium on carbon (25 mg) gave methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-9-oxodecanoate **19a** (47.5 mg, 0.15 mmol, 94%) as a colorless oil: $[\alpha]_D$ + 10.9 (*c* 1.1, $CHCl_3$); $R_f$ = 0.17 (20% EtOAc in petroleum ether); $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.99 (1 H, br d, *J* = 7.7 Hz), 4.22−4.32 (1 H, m), 3.72 (3 H, s), 2.39 (2 H, t, *J* = 7.4 Hz), 2.12 (3 H, s), 1.69−1.82 (1 H, m), 1.51−1.65 (3 H, m), 1.43 (9 H, s), 1.22−1.37 (6 H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 209.1, 173.4, 155.3, 79.8, 53.3, 52.1, 43.6, 32.6, 29.8, 28.9, 28.8, 28.3, 25.0, 23.6; IR 3365, 1745, 1712, 1516, 1438, 1370, 1249, 1164 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 316.2137, $C_{16}H_{30}NO_5$ requires 316.2124. In the $^1H$ NMR spectrum, the carboxylic acid proton was not observed, presumably, because of its broadness.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}-9-oxoundecanoate (19b).* General procedure C using **15b** (49 mg, 0.15 mmol, 1 equiv) and 10% (w/w) palladium on carbon (17 mg) gave methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-9-oxoundecanoate **19b** (49 mg, 0.148 mmol, 99%) as a colorless oil: $[\alpha]_D$ + 19.3 (*c* 0.68, $CHCl_3$); $R_f$ = 0.27 (20% EtOAc in petroleum ether); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.00 (1 H, br d, *J* = 8.1 Hz), 4.22−4.31 (1 H, m), 3.72 (3 H, s, $OCH_3$), 2.34−2.44 (4 H, m), 1.69−1.82 (1 H, m), 1.49−1.65 (3 H, m), 1.43 (9 H, s), 1.20−1.37 (6 H, m), 1.03 (3 H, t, *J* = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 211.7, 173.4, 155.3, 79.8, 53.3, 52.2, 42.2, 35.8, 32.7, 28.9 (2 C), 28.3, 25.1, 23.7, 7.8; IR 3367, 1746, 1711, 1704, 1518, 1455, 1364, 1168 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 330.2290, $C_{17}H_{32}NO_5$ requires 330.2280.

*Methyl (2S)-2-{[(tert-Butoxy)carbonyl]amino}-9-oxododecanoate (19c).* General procedure C using **15c** (44 mg, 0.129 mmol, 1 equiv) and 10% (w/w) palladium on carbon (17 mg) gave methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-9-oxododecanoate **19c** (44 mg, 0.128 mmol, 99%) as a colorless oil: $[\alpha]_D$ + 14.1 (*c* 0.85, $CHCl_3$); $R_f$ = 0.57 (30% EtOAc in petroleum ether); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.00 (1 H, br d, *J* = 8.3 Hz), 4.23−4.33 (1 H, m), 3.73 (3 H, s), 2.37 (2 H, t, *J* = 7.3 Hz), 2.36 (2 H, t, *J* = 7.3 Hz), 1.69−1.85 (1 H, m), 1.49−1.67 (5 H, m), 1.44 (9 H, s), 1.21−1.37 (6 H, m), 0.90 (3 H, t, *J* = 7.5 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 211.4, 173.4, 155.4, 79.8, 53.4, 52.2, 44.7, 42.7, 32.7, 28.9 (2 C), 28.3, 25.1, 23.6, 17.3, 13.7; IR 3370, 1749, 1713, 1692, 1520, 1462, 1247, 1172 $cm^{-1}$; *m*/*z* (ES+) found $MH^+$ 344.2437, $C_{18}H_{34}NO_5$ requires 344.2437.

**General Procedure D: Intramolecular Aza-Michael Reactions.** Cross-metathesis product **13** (1 equiv) was dissolved in $CH_2Cl_2$ (2 mL), and a solution of HCl in $Et_2O$ (1 M, 0.6 mol %) was added. After the mixture had been stirred for 19 h, the resulting solution was concentrated under reduced pressure to give the product.

*1-tert-Butyl 2-Methyl (2S,5R)-5-(2-Oxopropyl)pyrrolidine-1,2-dicarboxylate (20a) and 1-tert-Butyl 2-Methyl (2S,5S)-5-(2-Oxopropyl)pyrrolidine-1,2-dicarboxylate (20b).* General procedure D using methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxooct-5-enoate **13a** (32 mg, 0.112 mmol, 1 equiv) and 1 M HCl/$Et_2O$ (6.6 ×


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$10^{-4}$ mmol, 0.66 μL, 0.6 mol %) in $CH_2Cl_2$ (2 mL), after the mixture had been stirred for 19 h at rt, gave the title compounds **20a** and **20b** (32 mg, 0.11 mmol, 100%) as an oil in a 0.04:0.96 *cis*-**20a**:*trans*-**20b** ratio (for *cis*-**20a**, $t_R$ = 11.82 min; for *trans*-**20b**, $t_R$ = 11.67 min) based on GC and $^1$H NMR: $[\alpha]_D$ −54.0 (*c* 1, $CHCl_3$); $R_f$ = 0.19 (20% EtOAc in petroleum ether); $^1$H NMR (500 MHz, DMSO, 100 °C) δ 4.14−4.23 (2 H, m), 3.65 (3 H, s), 2.85 (1 H, br d, *J* = 16.2 Hz), 2.53 (1 H, dd, *J* = 16.2 and 9.7 Hz), 2.17−2.29 (1 H, m), 2.09 (3 H, s), 1.95−2.06 (1 H, m), 1.78−1.85 (1 H, m), 1.55−1.64 (1 H, m), 1.36 (9 H, s); $^{13}$C NMR (125 MHz, DMSO) δ 207.5 (207.4), 173.5 (173.0), 153.1 (153.4), 79.5 (79.8), 59.4 (59.1), 54.1 (53.9), 52.3 (52.2), 47.2 (48.1), 30.6 (30.7), 28.6 (29.3), 28.3 (28.4), 27.9 (27.1); IR 1752, 1703, 1396, 1210, 1165, 1126 cm$^{-1}$; *m/z* (ES+) found MH$^+$ 286.1661, $C_{14}H_{24}NO_5$ requires 286.1654. For the $^{13}$C NMR data, the signals due to the minor rotamer are given in parentheses.

*1-tert-Butyl 2-Methyl (2S,5R)-5-(2-Oxobutyl)pyrrolidine-1,2-dicarboxylate (**21a**) and 1-tert-Butyl 2-Methyl (2S,5S)-5-(2-Oxobutyl)-pyrrolidine-1,2-dicarboxylate (**21b**).* General procedure D using methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxonon-5-enoate **13b** (30 mg, 0.1 mmol, 1 equiv) and 1 M HCl/$Et_2O$ (6 × $10^{-4}$ mmol, 0.6 μL, 0.6 mol %) in $CH_2Cl_2$ (2 mL), after the mixture had been stirred for 19 h at rt, gave the title compounds **21a** and **21b** (30 mg, 100%) as a solid in a 0.02:0.98 *cis*:*trans* ratio (for the *cis* form, $t_R$ = 17.69 min; for the *trans* form, $t_R$ = 17.40 min) based on GC of the crude product: mp 52−54 °C; $[\alpha]_D$ −50.5 (*c* 0.46, $CHCl_3$); $R_f$ = 0.22 (20% EtOAc in petroleum ether); $^1$H NMR (500 MHz, DMSO, 100 °C) δ 4.22−4.16 (2 H, m), 3.65 (3 H, s), 2.84 (1 H, br dd, *J* = 16.0 and 3 Hz), 2.52 (1 H, dd, *J* = 16.0 and 9.2 Hz), 2.41 (2 H, q, *J* = 7.4 Hz), 2.19−2.31 (1 H, m), 1.96−2.08 (1 H, m), 1.78−1.85 (1 H, m), 1.55−1.63 (1 H, m), 1.36 (9 H, s), 0.96 (3 H, t, *J* = 7.3); $^{13}$C NMR (125 MHz, DMSO) δ 209.9 (209.8), 173.5 (173.0), 153.1 (153.4), 79.5 (79.7), 59.4 (59.1), 54.2 (54.0), 52.3 (52.2), 46.0 (46.7), 35.8 (35.9), 28.6 (29.3), 28.3 (28.4), 27.9 (27.1), 7.94 (7.98); IR 1745, 1705, 1396, 1366, 1212, 1175, 1123 cm$^{-1}$; *m/z* (ES+) found MH$^+$ 300.1818, $C_{15}H_{26}NO_5$ requires 300.1811. For the $^{13}$C NMR data, signals due to the minor rotamer are given in parentheses.

*1-tert-Butyl 2-Methyl (2S,5R)-5-(2-Oxopentyl)pyrrolidine-1,2-dicarboxylate (**22a**) and 1-tert-Butyl 2-Methyl (2S,5S)-5-(2-Oxopentyl)pyrrolidine-1,2-dicarboxylate (**22b**).* General procedure D using methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-7-oxodec-5-enoate **13c** (49 mg, 0.16 mmol, 1 equiv) and 1 M HCl/$Et_2O$ (9 × $10^{-4}$ mmol, 0.9 μL, 0.6 mol %) in $CH_2Cl_2$ (2 mL), after the mixture had been stirred for 19 h at rt, gave the title compounds **22a** and **22b** (49 mg, 0.16 mmol, 100%) as an oil in a 0.02:0.98 *cis*:*trans* ratio (for the *cis* form, $t_R$ = 25.62 min; for the *trans* form, $t_R$ = 25.14 min) based on GC of the crude product: $[\alpha]_D$ −56.0 (*c* 1.25, $CHCl_3$); $R_f$ = 0.18 (15% EtOAc in petroleum ether); $^1$H NMR (500 MHz, DMSO, 100 °C) δ 4.15−4.22 (2 H, m), 3.65 (3 H, s), 2.84 (1 H, br d, *J* = 16.1 Hz), 2.52 (1 H, dd, *J* = 16.1 and 9.5 Hz), 2.38 (2 H, t, *J* = 7.3 Hz), 2.19−2.30 (1 H, m), 1.96−2.07 (1 H, m), 1.78−1.86 (1 H, m), 1.56−1.64 (1 H, m), 1.52 (2 H, sextet, *J* = 7.3 Hz), 1.36 (9 H, s), 0.87 (3 H, t, *J* = 7.4 Hz); $^{13}$C NMR (125 MHz, DMSO) δ 209.1 (209.0), 173.0 (172.6), 152.6 (152.9), 79.1 (79.3), 58.9 (58.7), 53.7 (53.5), 51.8 (51.7), 45.8 (46.6), 44.2 (44.3), 28.2 (28.8), 27.8 (27.9), 27.5 (26.6), 16.5 (16.6), 13.5 (13.4); IR 1751, 1699, 1392, 1258, 1085, 1020, 795 cm$^{-1}$; *m/z* (ES+) found MH$^+$ 314.1982, $C_{16}H_{28}NO_5$ requires 314.1967. In the $^{13}$C NMR data, signals due to the minor rotamer are given in parentheses.

**General Procedure E: Boc Deprotection of Pyrrolidines 20b, 21b, and 22b.** The *N*-Boc-protected compound was dissolved in $CH_2Cl_2$ (4 mL). Neat TFA (50 equiv) relative to the substrate was added and the reaction followed by TLC until the starting material had disappeared. The solvent and excess TFA were then removed under reduced pressure to give the TFA salts. The salts were not sufficiently thermally stable for melting points to be determined.

*(2S,5S)-2-(Methoxycarbonyl)-5-(2-oxopropyl)pyrrolidin-1-ium Trifluoroacetate (**23**).* General procedure E using **20b** (88 mg, 0.31 mmol, 1 equiv) and TFA (1.2 mL, 15.5 mmol, 50 equiv) gave (2*S*,5*S*)-2-(methoxycarbonyl)-5-(2-oxopropyl)pyrrolidin-1-ium trifluoroacetate **23** (94 mg, 0.31 mmol, 100%) as a solid: mp dec; $[\alpha]_D$ −10.0 (*c* 1, $CHCl_3$); $R_f$ = 0.075 (20% $CHCl_3$, 30% petroleum ether, and 50% acetonitrile); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.48−4.75 (1 H, m), 3.94−4.08 (1 H, m), 3.86 (3 H, s), 3.18−3.37 (1 H, m), 2.93−3.13 (1 H, m), 2.53−2.67 (1 H, m), 2.19−2.36 (1 H, m), 2.22 (3 H, s), 2.04−2.18 (1 H, m), 1.85−2.00 (1 H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.8, 169.7, 58.8, 57.1, 53.7, 44.1, 29.8, 29.5, 27.8; IR 3425, 1751, 1715, 1676, 1445, 1366, 1245, 1185 cm$^{-1}$; *m/z* (ES+) found M$^+$ 186.1125, $C_9H_{16}NO_3$ requires 186.1130. In the $^1$H NMR spectrum, there are additional signals in the low-field range due to the two acidic NH protons and trace residual $CF_3CO_2H$. The chemical shifts are quite variable depending on conditions.

*(2S,5S)-2-(Methoxycarbonyl)-5-(2-oxobutyl)pyrrolidin-1-ium Trifluoroacetate (**24**).* General procedure E using **21b** (43 mg, 0.144 mmol, 1 equiv) and TFA (0.55 mL, 7.2 mmol, 50 equiv) gave (2*S*,5*S*)-2-(methoxycarbonyl)-5-(2-oxobutyl)pyrrolidin-1-ium trifluoroacetate **24** (45 mg, 0.143 mmol, 99% yield) as a solid: mp dec; $[\alpha]_D$ −6.1 (*c* 1.15, $CHCl_3$); $R_f$ = 0.125 (20% $CHCl_3$, 30% petroleum ether, and 50% acetonitrile); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.55−4.80 (1 H, m), 3.92−4.04 (1 H, m), 3.88 (3 H, s), 3.22−3.38 (1 H, m), 2.93−3.08 (1 H, m), 2.60−2.72 (1 H, m), 2.41−2.59 (2 H, m), 2.21−2.35 (1 H, m), 2.05−2.18 (1 H, m), 1.91−2.05 (1 H, m), 1.08 (3 H, t, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 209.2, 169.7, 58.7, 56.9, 53.7, 43.1, 35.7, 30.1, 27.9, 7.3; IR 1752, 1715, 1674, 1446, 1246, 1203, 1176 cm$^{-1}$; *m/z* (ES+) found M$^+$ 200.1293, $C_{10}H_{18}NO_3$ requires 200.1287. In the $^1$H NMR spectrum, there are additional signals in the low-field range due to the two acidic NH protons and trace residual $CF_3CO_2H$. The chemical shifts are quite variable depending on conditions.

*(2S,5S)-2-(Methoxycarbonyl)-5-(2-oxopentyl)pyrrolidin-1-ium Trifluoroacetate (**25**).* General procedure E using **22b** (98 mg, 0.313 mmol, 1 equiv) and TFA (1.2 mL, 15.6 mmol, 50 equiv) gave (2*S*,5*S*)-2-(methoxycarbonyl)-5-(2-oxopentyl)pyrrolidin-1-ium trifluoroacetate **25** (100 mg, 0.31 mmol, 99% yield) as a solid: mp dec; $[\alpha]_D$ −2.0 (*c* 1, $CHCl_3$); $R_f$ = 0.15 (20% $CHCl_3$, 30% petroleum ether, and 50% acetonitrile); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.62 (1 H, t, *J* = 7.8 Hz), 3.89−4.04 (1 H, m), 3.87 (3 H, s), 3.29 (1 H, dd, *J* = 18.7 and 9.1 Hz), 2.97 (1 H, dd, *J* = 18.7 and 3.8 Hz), 2.56−2.67 (1 H, m), 2.35−2.55 (2 H, m), 2.20−2.34 (1 H, m), 2.03−2.16 (1 H, m), 1.87−2.02 (1 H, m), 1.62 (2 H, sextet, *J* = 7.3 Hz), 0.92 (3 H, t, *J* = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 208.9, 169.7, 58.8, 57.2, 53.8, 44.4, 43.2, 29.9, 27.8, 16.8, 13.4; IR 1749, 1715, 1674, 1446, 1246, 1203, 1176 cm$^{-1}$; *m/z* (ES+) found M$^+$ 214.1439, $C_{11}H_{20}NO_3$ requires 214.1443. In the $^1$H NMR spectrum, there are additional signals in the low-field range due to the two acidic NH protons and trace residual $CF_3CO_2H$. The chemical shifts are quite variable depending on conditions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01571.

Details of the X-ray structure determinations of compounds **21b** and **23**−**25**; $^1$H and $^{13}$C NMR spectra for **4**, **5**, **9**−**11**, **13a**−**c**, **14a**−**c**, **15a**−**c**, **16**, **17a**−**c**, **18a**−**c**, **19a**−**c**, **20b**, **21b**, **22b**, and **23**−**25**; and GC traces for **20a**/**20b**, **21a**/**21b**, and **22a**/**22b** (PDF)

Combined crystallographic file for **21b** and **23**−**25** (CIF)

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### Notes

The authors declare no competing financial interest.


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