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A two-step synthesis of the bioprotective agent JP4-039 from *N*-Boc-L-leucinal

Barbara Bernardim, Antonio C.B. Burtoloso *

Instituto de Química de São Carlos, Universidade de São Paulo, São Carlos, SP CEP 13560-970, Brazil

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ABSTRACT

An expedited synthesis of the bioprotective agent JP4-039 is described from *N*-Boc-L-leucinal in 50% overall yield. The synthesis involves the use of an α,β-unsaturated diazoketone as the key intermediate, followed by a photochemical Wolff rearrangement in the presence of 4-amino-TEMPO (4-AT).

1. Introduction

X-rays have been used for a long time in the diagnosis of illness and as a treatment for it, especially in the case of cancer.[1] One of the utilities of radiation is the well-known radiotherapy, which works by damaging the DNA of cancerous cells, leading to their death. Although normal cells can also be damaged (to a lesser extent) after exposure to this ionizing irradiation, microenvironment is known to modulate repair of them under conditions that inhibit cell division. A major mechanism in cell death during radiotherapy involves the formation of reactive oxygen species (ROS) in mitochondria after ionizing irradiation.[2] Thus, molecules that are effective in scavenge these ROS and able to concentrate at the mitochondria, can be of extremely importance as radiation protectors and mitigators.[3,4] The lead compound JP4-039 (Fig. 1), inspired by the antibiotic gramicidin S, is a mitochondria-target nitroxide that has been proven to be of extremely effectiveness at scavenging reactive oxygen species, such as superoxide and nitric oxide.[5] For example, when compared to control irradiated cells, JP4-039 enhanced cell repair and increased clonogenic cell survival by an order of 5–13 times.[6,7]

JP4-039 is also considered an isostere of the leucine-glycine peptide.[8] Considering the well-known characteristic of peptides in being easily hydrolyzed in vivo by peptidases, *E*-alkene isosteres (containing an allylic amine fragment) come as interesting mimics to be used in chemical-biology.[8] Regarding the preparation of JP4-039, only one synthesis is described in the literature.[9] The research group of Peter Wipf has been involved for some years with the synthesis of many nitroxides of biological importance, including JP4-039 itself.[2,3,5–14] Their approach involves a beautiful one-pot hydrozirconation-transmetalation–addition to a chiral sulfinamide as the key reaction and furnishes JP4-039 in six steps from a chiral sulfinamide (Scheme 1).

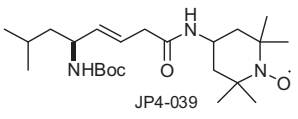
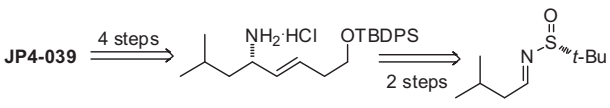


Fig. 1. Structure of JP4-039.



Scheme 1. Synthesis of JP4-039 by Wipf.

2. Results and discussion

In the last few years, our research group have been involved with the uncommon chemistry of α,β-unsaturated diazoketones.[15–18] Possessing a diazo group, a ketone function and

* Corresponding author. Tel.: +55 16 3373 8641; fax: +55 16 3373 9952; e-mail addresses: antonio@iqsc.usp.br, aburtoloso@gmail.com (A.C.B. Burtoloso).

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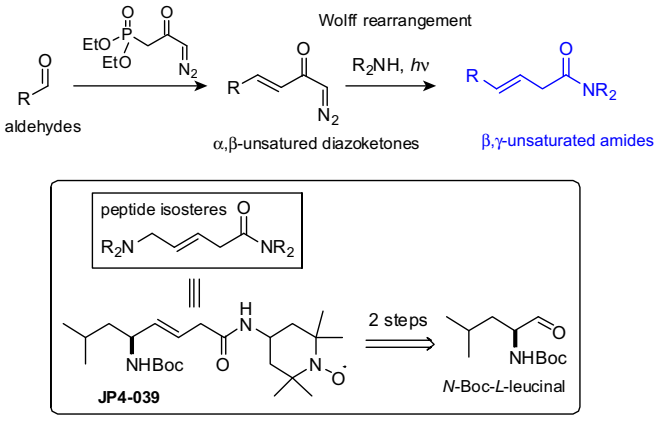
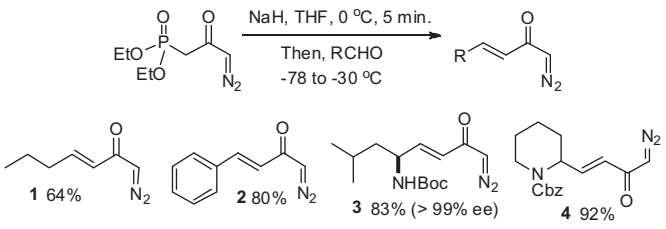
a double bond all together in a single molecule, α,β-unsaturated diazoketones constitute versatile building blocks in synthesis and could already be applied in the straightforward preparation of several nitrogen-heterocycles. One of their utilities is the ability of generating β,γ-unsaturated esters in the presence of alcohols, via the well-known Wolff rearrangement.[16] Considering that, we wondered if we could also apply these interesting platforms in the direct synthesis of β,γ-unsaturated amides. It is interesting to note that β,γ-unsaturated amides are generally prepared from the corresponding β,γ-unsaturated carboxylic acids, which are not readily available or easy to prepare when compared the α,β-unsaturated ones. Moreover, as mentioned above, the addition of an amino group in the δ position of these amides can led to alkene peptide isosteres, mimics that do not undergo the undesirable pharmacokinetic properties generally observed in real peptides. Herein, we would like to demonstrate how α,β-unsaturated diazoketones (easily prepared from aldehydes) are interesting platforms to prepare these important β,γ-unsaturated amides, as well as how a single-step synthesis of the bioprotective agent JP4-039 could be achieved from these building blocks (Scheme 2).



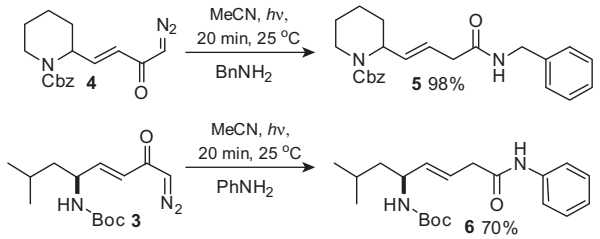
Scheme 2. Synthesis of β,γ-unsaturated amides from α,β-unsaturated diazoketones.

We started our work by preparing four structurally different unsaturated diazoketones, in order to evaluate the Wolff rearrangement in the presence of amines. Employing our recently described olefination methodology,[15] diazoketones **1**–**4** were prepared in 64–92%. These four examples represent unsaturated diazoketones containing aliphatic, aryl, acyclic-amino, and cyclic-amino groups, respectively (Scheme 3). Unlike butyraldehyde and benzaldehyde, the amino-aldehydes employed in this study are not commercially available and were easily prepared from the *N*-protected amino-acid after borane[19] reduction and Swern[20,21] or Parikh–Doering oxidation.[19,22] In the case of diazoketone **3**, chiral HPLC studies showed that no epimerization occurred during the Horner–Wadsworth–Emmons olefination.



Scheme 3. Synthesis of structurally different α,β-unsaturated diazoketones from aldehydes.

We next submitted these diazoketones to the photochemical Wolff rearrangement in the presence of different amines as nucleophiles, such as primary, secondary, and aromatic ones. Although there are plenty of examples of both the thermal and photochemical Wolff rearrangements from saturated diazoketones using amines as nucleophiles,[23–27] no example is found from the α,β-unsaturated ones. In fact, we were inquisitive about the behavior of such diazoketones, especially chiral diazoketone **3**, in the presence of these bases due to the presence of an acidic proton in their γ position. Positively, irradiation of an acetonitrile solution of diazoketone **4** and 1 equiv of benzylamine with an Osram 150 Xenon arc lamp for 20 min at 25 °C, furnished β,γ-unsaturated amide **5** in 98% yield with no need of purification (Scheme 4). A similar result was obtained when chiral diazoketone **3** was treated with aniline. For this specific case, as depicted in Fig. 2, no epimerization is observed during the formation of diazoketone **3** and the Wolff rearrangement.



Scheme 4. Synthesis of β,γ-unsaturated amides from α,β-unsaturated diazoketones **3** and **4**.

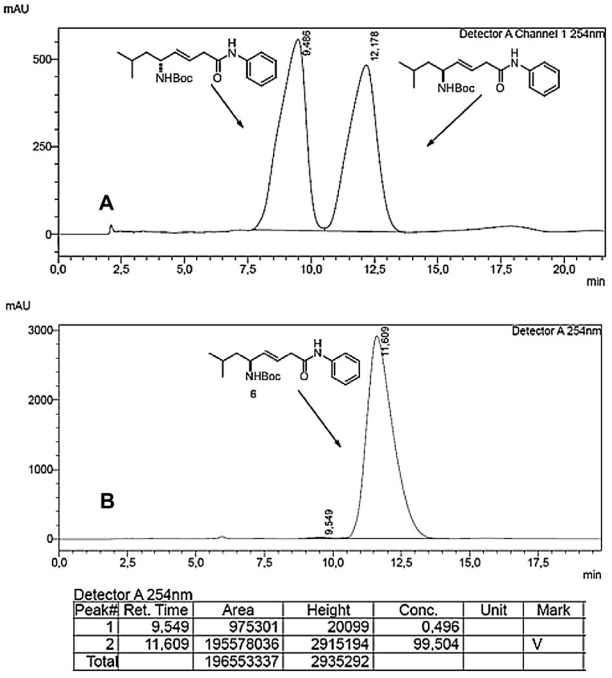


Fig. 2. Chiral HPLC studies. A: racemic compound; B: chiral compound derived from *N*-Boc-L-leucinal.

After this preliminary study, and to show the scope of this transformation, diazoketones **1**–**4** were irradiated in the presence of benzylamine, aniline, *p*-methoxy aniline, diallylamine, and cyclohexylamine to give β,γ-unsaturated amides **7**–**21** in yields varying from 50 to 98% (Fig. 3). Unlike the photochemical reactions involving diazoketones **1**, **3**, and **4**, reactions employing

unsaturated diazoketone **2** were accompanied by some isomerization of the double bond to the *Z* isomer.

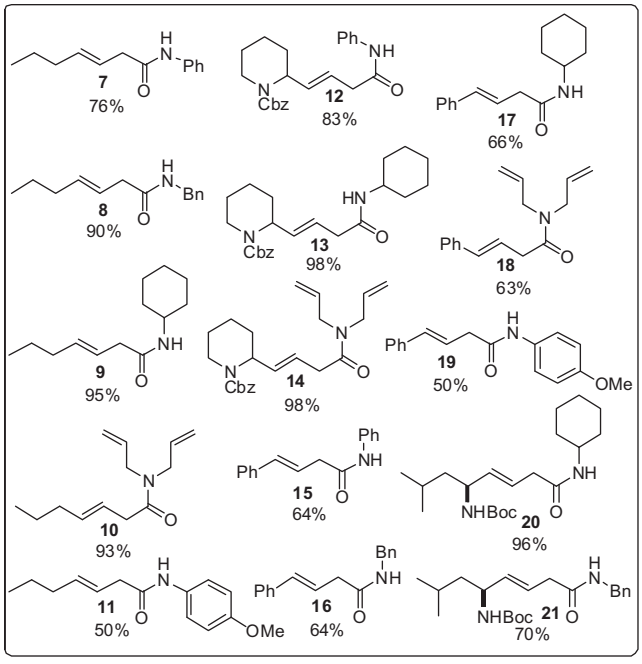
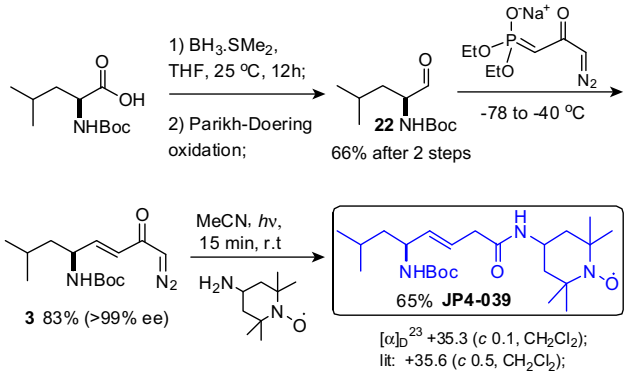


Fig. 3. Two-step synthesis of several β,γ-unsaturated amides from aldehydes.

Finally, to show the applicability of the present method, diazoketone **3** was converted to the bioprotective agent JP4-039 in 65% yield after irradiation in the presence of 4-amino-TEMPO. All the spectroscopic data are in complete accordance with those reported by Wipf.[9] To accomplish that, commercially available *N*-Boc-L-leucine was first reduced in the presence of borane dimethyl sulfide complex,[28] followed by oxidation with $SO_3 \cdot Py$.[19,22] Olefination of known leucinal **22** with the sodium anion of a diazophosphonate at −78 to −40 °C gave diazoketone **3** in 83% yield (>99% ee). Next, photochemical Wolff rearrangement with commercially available 4-amino-TEMPO furnished JP4-039 in 65% yield (Scheme 5).



Scheme 5. A two-step synthesis of JP4-039 from *N*-Boc-L-leucinal.

3. Conclusion

As a conclusion, we have demonstrated that α,β-unsaturated diazoketones are interesting building blocks for the direct synthesis of β,γ-unsaturated amides. When employed unsaturated diazoketones derived from amino-aldehydes, peptide isoesters are prepared as was illustrated during the short synthesis of the lead nitroxide JP4-039. This method overcomes a drawback in the synthesis of these types of amides, which are generally prepared after several steps.

4. Experimental

4.1. General methods

All solvents were dried and distilled prior to use by standard procedures. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC), carried out on 0.25 mm silica gel plates using UV light as visualizing agent and potassium permanganate in aqueous KOH for staining. Column chromatography was performed using silica gel 60 (particle size 0.063–0.210 mm). Unless stated otherwise, all of the yields refer to isolated products after flash column chromatography. The solvent mixtures employed in TLC analysis and in flash column chromatography purifications are reported as volume by volume and in percentages. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using 400 or 500 MHz equipment. For ^{1}H NMR spectra, chemical shifts (δ) are referenced from TMS (0.00 ppm). Coupling constants (J) are reported in hertz. For multiplicities the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; bs; broad singlet; dt, double triplet. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using an NMR spectrometer at 100 or 125 MHz. For ^{13}C NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm) or MeOH (49.0 ppm). Photochemical reactions were carried out using UV light generated by an Osram 150 Xenon lamp accommodated in an Oriel Model 8500 Universal arc lamp source with focusing quartz lens, a water-filled infrared filter, and a thermostated cell holder. Infrared spectra were obtained using FT-IR at 4.0 cm^{-1} resolution and are reported in wavenumbers. High resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) (hybrid linear ion trap–orbitrap FT-MS and QqTOF/MS–Microtof-QII model).

4.2. General procedure for Horner–Wadsworth–Emmons reaction

*4.2.1. (E)-1-Diazohept-3-en-2-one (**1**).* To a suspension of NaH (60% in mineral oil) (80.0 mg, 2.00 mmol, 2.2 equiv) in dry THF (6.0 mL), under argon atmosphere and at 0 °C, was added a 0.15 M solution of diethyl 3-diazo-2-oxopropylphosphonate (400 mg, 1.8 mmol, 2.0 equiv) in dry THF. After that, the mixture was stirred for 5 min at this temperature, the system was cooled to −78 °C and then a 0.1 M solution of butyraldehyde (65.5 mg, 0.91 mmol, 1.0 equiv) in dry THF was added dropwise. After 1 h, the temperature was allowed to rise naturally to −30 °C, when a saturated aqueous NH_4Cl solution (25 mL) was added to the reaction vessel. Next, the aqueous layer was extracted with dichloromethane (3×20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated in rotary evaporator. Purification by flash column chromatography (30% EtOAc/hexanes) afforded diazoketone **1** (82.0 mg, 0.59 mmol, 64%) as a stable yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (dt, J=15.4, 7.0 Hz, 1H), 5.98 (d, J=15.5 Hz, 1H), 5.29 (s, 1H), 2.17 (dq, J=7.2, 1.5 Hz, 2H), 1.48 (sxt, J=7.4 Hz, 2H), 0.93 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 145.3, 127.5, 55.1, 34.4, 21.5, 13.8; FT-IR (neat, cm^{-1}): 2962, 2933, 2100, 1656, 1606, 1367, 975; HRMS (ESI) calcd for $C_7H_{10}N_2NaO$ $[M+Na]^+$ 161.0685, found 161.0686; R_f 0.30 (20% EtOAc/hexanes).

*4.2.2. (E)-1-Diazo-4-phenylbut-3-en-2-one (**2**).* 80% yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J=15.8 Hz, 1H), 7.55–7.52 (m, 2H), 7.40–7.36 (m, 3H), 6.60 (d, J=15.8 Hz, 1H), 5.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 140.7, 134.4, 130.3, 128.9,

128.2, 123.6, 56.2; FT-IR (neat, cm^{-1}): 3070, 2098, 1636, 1584, 1450, 1373, 1149, 973, 759; HRMS (ESI) calcd for $C_{10}H_8N_2NaO$ $[M+Na]^+$ 195.05288, found 195.0628; mp 58–62 °C; R_f 0.30 (25% EtOAc/hexanes).

*4.2.3. (S,E)-tert-Butyl(8-diazo-2-methyl-7-oxooct-5-en-4-yl) carbamate (**3**).* 83% yield as a yellow solid. *N*-Boc-L-leucinal was freshly prepared from *N*-Boc-L-leucinol by Parikh–Doering oxidation. In this specific case, the HWE reaction was finished at −40 °C to avoid the epimerization. $[\alpha]_D^{23}$ −34.1 (*c* 0.66, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (dd, *J*=15.3, 5.8 Hz, 1H), 6.06 (d, *J*=15.3 Hz, 1H), 5.32 (s, 1H), 4.45 (s, 1H), 4.30 (s, 1H), 1.74–1.55 (m, 2H), 1.43 (s, 9H), 1.38 (t, *J*=7.1 Hz, 1H), 0.92 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4, 155.2, 144.7, 126.2, 79.9, 55.9, 50.1, 44.1, 31.1, 29.8, 28.5, 24.9, 22.8, 22.4; FT-IR (neat, cm^{-1}): 3365, 3105, 2968, 2929, 2914, 2100, 1680, 1660, 1614, 1521, 1367, 1330, 1284, 1238, 1172, 1157, 1105, 1004, 760; HRMS (ESI) calcd for $C_{14}H_{23}N_3NaO_3$ $[M+Na]^+$ 304.16316, found 304.1646; mp 94–96 °C; R_f 0.38 (30% EtOAc/hexanes); Chiral HPLC studies were performed in a CHIRALPAK® AD-H column (particle size: 5 μm; dimensions: 4.6 mm×250 mm), 98:2 (hexane/isopropanol), 1.5 mL/min, λ 254 nm.

*4.2.4. (E)-Benzyl-2-(4-diazo-3-oxobut-1-en-1-yl)piperidine-1-carboxylate (**4**).* 92% yield as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.30 (m, 5H), 6.78 (dd, *J*=15.6, 4.3 Hz, 1H), 5.91 (d, *J*=14.9 Hz, 1H), 5.25 (s, 1H), 5.16 (d, *J*=12.3 Hz, 1H), 5.12 (d, *J*=12.4 Hz, 1H), 5.03 (s, 1H), 4.07 (d, *J*=12.8 Hz, 1H), 2.88 (t, *J*=11.4 Hz, 1H), 1.89–1.60 (m, 4H), 1.52–1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 155.6, 142.8, 136.6, 128.5, 128.3, 128.0, 127.9, 67.3, 56.0, 52.0, 40.4, 29.1, 25.2, 19.7; FT-IR (neat, cm^{-1}) 3076, 3029, 2933, 2852, 2100, 1693, 1654, 1606, 1415, 1359, 1170; HRMS (ESI) calcd for $C_{17}H_{19}N_3NaO_3$ $[M+Na]^+$ 336.13186, found 336.13092; R_f 0.33 (50% EtOAc/hexanes).

4.3. General procedure for Wolff rearrangement

*4.3.1. (E)-N-Phenylhept-3-enamide (**7**).* To a solution of diazoketone **1** (29.7 mg, 0.215 mmol) in acetonitrile (10 mL) was added aniline (20 μL, 1.0 equiv) in a 1 cm optical path quartz cell. The solution was irradiated with an Osram 150 Xenon arc lamp for 20 min under magnetic stirring at room temperature (nitrogen gas evolution observed). Next, the solvent was evaporated in rotary evaporator. Purification by flash column chromatography (30% EtOAc/hexanes) afforded amide **7** as a white solid (33.2 mg, 0.163 mmol, 76%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J*=7.7 Hz, 2H), 7.39 (t, *J*=7.0 Hz, 3H), 7.10 (t, *J*=7.4 Hz, 1H), 5.78–5.70 (m, 1H), 5.67–5.58 (m, 1H), 3.11 (d, *J*=7.0 Hz, 2H), 2.10 (q, *J*=6.9 Hz, 2H), 1.46 (sxt, *J*=7.4 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H); FT-IR (neat, cm^{-1}): 3300, 3197, 3138, 3026, 2958, 2927, 1658, 1600, 1546, 1498, 1442, 1327, 1251, 1176, 1112, 1080, 1031, 970, 754, 692; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 137.8, 137.4, 129.0, 124.3, 122.5, 119.6, 41.7, 34.6, 22.3, 13.7; mp 33–35 °C; HRMS (ESI) calcd for $C_{13}H_{17}NNaO$ $[M+Na]^+$ 226.1202, found 226.1202; R_f 0.42 (30% EtOAc/hexanes).

*4.3.2. (E)-N-Benzylhept-3-enamide (**8**).* No purification was necessary, 90% yield as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 5.95 (s, 1H), 5.67–5.48 (m, 2H), 4.43 (d, *J*=5.8 Hz, 2H), 2.99 (d, *J*=7.4 Hz, 2H), 2.05 (q, *J*=7.4 Hz, 2H), 1.38 (sxt, *J*=7.4 Hz, 2H), 0.87 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 138.4, 136.7, 128.8, 127.8, 127.6, 122.7, 43.7, 40.7, 34.7, 22.4, 13.7; FT-IR (neat, cm^{-1}): 3294, 3084, 3064, 3032, 2956, 2926, 2872, 1639, 1546, 1454, 1415, 1369, 1238, 1080, 1028, 964, 694; mp 38–41 °C; HRMS (ESI) calcd for $C_{14}H_{20}NNaO$ $[M+Na]^+$ 240.1359, found 240.1360; R_f 0.13 (20% EtOAc/hexanes).

*4.3.3. (E)-N-Cyclohexylhept-3-enamide (**9**).* No purification was necessary, 95% yield as a pale yellow solid: ^1H NMR (500 MHz, $CDCl_3$) δ 5.64–5.56 (m, 1H), 5.54–5.45 (m, 1H), 3.79–3.69 (m, 1H), 2.90 (dd, *J*=7.0, 0.8 Hz, 2H), 2.03 (q, *J*=7.5 Hz, 2H), 1.92–1.84 (m, 2H), 1.71–1.63 (m, 2H), 1.59 (dq, *J*=7.4, 3.6 Hz, 1H), 1.45–1.30 (m, 4H), 1.20–1.05 (m, 3H), 0.90 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 136.3, 123.0, 48.0, 40.7, 34.6, 33.1, 25.5, 24.8, 22.3, 13.6; FT-IR (neat, cm^{-1}): 3296, 3070, 2956, 2929, 2854, 1637, 1546, 1446, 1409, 1247, 1078, 970, 891; mp 57–63 °C; HRMS (ESI) calcd for $C_{13}H_{24}NO$ $[M+H]^+$ 210.1852, found 210.1859; R_f 0.15 (20% EtOAc/hexanes).

*4.3.4. (E)-N,N-Diallylhept-3-enamide (**10**).* No purification was necessary, 93% yield as colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.80–5.70 (m, 2H), 5.61–5.48 (m, 2H), 5.23–5.08 (m, 4H), 3.97 (d, *J*=6.0 Hz, 2H), 3.87 (dt, *J*=4.8, 1.6 Hz, 2H), 3.07 (dd, *J*=6.1, 1.0 Hz, 2H), 2.04–1.98 (q, *J*=7.0 Hz, 2H), 1.38 (sxt, *J*=7.4 Hz, 2H), 0.88 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 133.8, 133.3, 133.0, 123.1, 117.2, 116.7, 49.2, 47.8, 37.5, 34.6, 22.3, 13.6; FT-IR (neat, cm^{-1}): 3082, 2958, 2927, 2872, 1653, 1463, 1411, 1284, 1249, 1217, 1193, 1136, 1116, 993, 968, 921; HRMS (ESI) calcd for $C_{13}H_{21}NNaO$ $[M+Na]^+$ 230.1515, found 230.1519; R_f 0.30 (20% EtOAc/hexanes).

*4.3.5. (E)-N-(4-Methoxyphenyl)hept-3-enamide (**11**).* Purification by flash column chromatography (30% EtOAc/hexanes), 50% yield as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J*=9.0 Hz, 2H), 7.27 (s, 1H), 6.85 (d, *J*=9.0 Hz, 2H), 5.77–5.58 (m, 2H), 3.78 (s, 3H), 3.09 (dd, *J*=7.0, 0.7 Hz, 2H), 2.09 (q, *J*=7.1 Hz, 2H), 1.45 (sxt, *J*=7.4 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 156.4, 137.3, 130.9, 122.6, 121.6, 114.1, 55.5, 41.4, 34.64, 22.3, 13.7; FT-IR (neat, cm^{-1}): 3311, 2954, 2926, 1654, 1600, 1541, 1514, 1465, 1409, 1247, 1172, 1029, 964, 825; HRMS (ESI) calcd for $C_{14}H_{19}NNaO_2$ $[M+Na]^+$, 256.13082 found 256.13080; mp 71–77 °C; R_f 0.45 (30% EtOAc/hexanes).

*4.3.6. (E)-Benzyl 2-(4-(benzylamino)-4-oxobut-1-en-1-yl)piperidine-1-carboxylate (**5**).* No purification was necessary, 98% yield as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.19 (m, 10H), 5.95 (s, 1H), 5.66–5.57 (m, 2H), 5.09–5.02 (m, 2H), 4.84 (s, 1H), 4.40 (d, *J*=5.7 Hz, 2H), 3.99 (d, *J*=13.1 Hz, 1H), 3.06–2.98 (m, 2H), 2.86 (t, *J*=12.0 Hz, 1H), 1.76–1.65 (m, 2H), 1.63–1.52 (m, 2H), 1.50–1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.7, 138.1, 136.8, 133.7, 128.7, 128.4, 127.9, 127.7, 127.7, 127.5, 124.4, 67.0, 52.2, 43.6, 40.3, 40.1, 29.0, 25.3, 19.4; FT-IR (neat, cm^{-1}): 3510, 3307, 3064, 3032, 2937, 2858, 1693, 1654, 1540, 1423, 1263, 1170, 1091, 1029, 972, 916, 744, 698; HRMS (ESI) calcd for $C_{24}H_{28}N_2NaO_3$ $[M+Na]^+$ 415.1992, found 415.1990; R_f 0.28 (50% EtOAc/hexanes).

*4.3.7. (E)-Benzyl 2-(4-oxo-4-(phenylamino)but-1-en-1-yl)piperidine-1-carboxylate (**12**).* No purification was necessary, 83% yield as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J*=7.9 Hz, 2H), 7.37–7.27 (m, 8H), 7.10 (t, *J*=7.9 Hz, 1H), 5.79–5.62 (m, 2H), 5.13 (d, *J*=4.3 Hz, 2H), 4.89–4.83 (m, 1H), 4.03 (d, *J*=11.8 Hz, 1H), 3.15 (d, *J*=6.5 Hz, 2H), 2.99 (t, *J*=11.8 Hz, 1H), 1.82–1.72 (m, 2H), 1.69–1.61 (m, 2H), 1.54–1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 155.9, 137.8, 136.7, 134.7, 128.9, 128.5, 128.0, 127.8, 124.3, 124.0, 119.7, 67.1, 52.7, 41.2, 29.7, 29.1, 25.2, 19.5; FT-IR (neat, cm^{-1}): 3506, 3311, 3062, 3034, 2926, 2854, 1693, 1674, 1600, 1544, 1498, 1442, 1425, 1344, 1261, 1172, 1091, 1029, 972, 906, 756, 696; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_3$ $[M+H]^+$ 379.2016, found 379.2022; R_f 0.38 (50% EtOAc/hexanes).

*4.3.8. (E)-Benzyl 2-(4-(cyclohexylamino)-4-oxobut-1-en-1-yl)piperidine-1-carboxylate (**13**).* No purification was necessary, 98% yield as a pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 5.65–5.54 (m, 2H), 5.48 (s, 1H), 5.13 (s, 2H), 4.88–4.83 (m, 1H), 4.03 (d, *J*=13.0 Hz, 1H), 3.78–3.68 (m, 1H), 2.94 (d, *J*=5.8 Hz, 2H), 1.91–1.82 (m, 2H), 1.79–1.55 (m, 8H), 1.55–1.29 (m, 4H), 1.20–1.01 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 155.7, 136.8, 133.5,

128.4, 127.9, 127.7, 124.8, 67.0, 52.2, 48.1, 40.3, 33.0, 32.9, 29.1, 25.5, 25.3, 24.8, 19.4; FT-IR (neat, cm^{-1}): 3305, 3064, 3034, 2933, 2854, 1699, 1651, 1543, 1448, 1423, 1352, 1336, 1261, 1170, 1091, 1041, 974, 734, 698; HRMS (ESI) calcd for $C_{23}H_{33}N_2O_3$ $[M+H]^+$ 385.2485, found 385.2483; R_f 0.28 (50% EtOAc/hexanes).

*4.3.9. (E)-Benzyl 2-(4-(diallylamino)-4-oxobut-1-en-1-yl)piperidine-1-carboxylate (**14**).* No purification was necessary, 98% yield as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.82–5.63 (m, 3H), 5.56–5.47 (m, 1H), 5.24–5.08 (m, 6H), 4.89 (s, 1H), 4.08–3.95 (m, 3H), 3.87–3.82 (m, 2H), 3.11 (d, J=6.5 Hz, 2H), 2.92 (td, J=13.0, 2.4 Hz, 1H), 1.82–1.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.8, 137.1, 133.3, 132.9, 131.5, 128.6, 128.0, 127.9, 125.3, 117.4, 116.9, 67.1, 52.2, 49.4, 48.0, 40.3, 37.3, 29.1, 25.7, 19.6; FT-IR (neat, cm^{-1}): 3032, 2937, 2860, 1697, 1651, 1498, 1419, 1352, 1261, 1170, 1091, 1041, 993, 972, 923, 765, 744, 698; HRMS (ESI) calcd for $C_{23}H_{31}N_2O_3$ $[M+H]^+$ 383.2329, found 383.2336; R_f 0.38 (50% EtOAc/hexanes).

*4.3.10. (E)-N,4-Diphenylbut-3-enamide (**15**).* 94% (E+Z); After purification by flash column chromatography (30% EtOAc/hexanes), pure **15** was obtained in 64% yield as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J=7.8 Hz, 2H), 7.41 (d, J=7.4 Hz, 3H), 7.38–7.27 (m, 5H), 7.12 (q, J=7.5 Hz, 1H), 6.63 (d, J=15.9 Hz, 1H), 6.38 (dt, J=15.7, 7.3 Hz, 1H), 3.33 (dd, J=7.3, 0.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 137.6, 136.4, 135.4, 129.0, 128.8, 128.0, 126.4, 124.5, 121.8, 119.9, 41.9; FT-IR (neat, cm^{-1}): 3290, 3261, 3197, 3140, 3082, 3057, 3026, 2953, 2922, 2850, 1660, 1647, 1598, 1550, 1496, 1442, 1330, 1307, 1249, 966, 754, 690; mp 87–91 °C; HRMS (ESI) calcd for $C_{16}H_{15}NNaO$ $[M+Na]^+$ 260.1046, found 260.1052; R_f 0.42 (30% EtOAc/hexanes).

*4.3.11. (E)-N-Benzyl-4-phenylbut-3-enamide (**16**).* 95% (E+Z); After purification by flash column chromatography (30% EtOAc/hexanes), pure **16** was obtained in 64% yield as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.22 (m, 10H), 6.54 (d, J=15.8 Hz, 1H), 6.31 (dt, J=15.8, 7.3 Hz, 1H), 5.96 (s, 1H), 4.46 (d, J=5.8 Hz, 2H), 3.21 (dd, J=7.3, 1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 138.1, 136.5, 134.8, 128.7, 128.6, 127.8, 127.8, 127.5, 126.3, 122.2, 43.7, 40.8; FT-IR (neat, cm^{-1}): 3238, 3055, 3035, 2954, 2922, 2875, 2850, 1633, 1548, 1411, 1238, 981, 968, 756, 698; mp 125–129 °C; HRMS (ESI) calcd for $C_{17}H_{18}NO$ $[M+H]^+$ 252.1383, found 252.1391; R_f 0.23 (30% EtOAc/hexanes).

*4.3.12. (E)-N-Cyclohexyl-4-phenylbut-3-enamide (**17**).* 94% (E+Z); After purification by flash column chromatography (30% EtOAc/hexanes), pure **17** was obtained in 66% yield as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2H), 7.35–7.30 (m, 2H), 7.28–7.22 (m, 1H), 6.53 (d, J=15.9 Hz, 1H), 6.29 (dt, J=15.8, 7.3 Hz, 1H), 5.47 (s, 1H), 3.83–3.73 (m, 1H), 3.13 (dd, J=7.3, 1.3 Hz, 2H), 1.95–1.86 (m, 2H), 1.73–1.64 (m, 2H), 1.61 (ddd, J=12.9, 6.2, 3.6 Hz, 1H), 1.43–1.30 (m, 2H), 1.19–1.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 136.7, 134.5, 128.6, 127.7, 126.3, 122.7, 77.3, 77.0, 76.7, 48.3, 41.1, 33.1, 25.5, 24.8; FT-IR (neat, cm^{-1}): 3286, 3062, 3030, 2931, 2852, 1635, 1546, 1446, 1346, 1247, 960, 891, 690; mp 89–96 °C; HRMS (ESI) calcd for $C_{16}H_{21}NNaO$ $[M+Na]^+$ 266.1515, found 266.1515; R_f 0.33 (30% EtOAc/hexanes).

*4.3.13. (E)-N,N-Diallyl-4-phenylbut-3-enamide (**18**).* 77% (E+Z); After purification by flash column chromatography (30% EtOAc/hexanes), pure **18** was obtained in 63% yield as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H), 7.33–7.27 (m, 2H), 7.24–7.19 (m, 1H), 6.46 (d, J=16.1 Hz, 1H), 6.38 (dt, J=16.0, 6.3 Hz, 1H), 5.85–5.73 (m, 2H), 5.27–5.11 (m, 4H), 4.01 (d, J=6.0 Hz, 2H), 3.93 (dt, J=4.7, 1.6 Hz, 2H), 3.30 (dd, J=6.3, 0.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 137.0, 133.2, 132.9, 132.6, 128.5, 127.4, 126.2, 123.4, 117.4, 116.8, 49.3, 48.0, 37.7; FT-IR (neat, cm^{-1}): 3082, 3059, 3024, 2980, 2954, 2926, 2854, 1654, 1463, 1448, 1413, 1217, 1193, 1132, 991, 966, 925, 742, 694; HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M+H]^+$ 242.1539, found 242.1551; R_f 0.38 (30% EtOAc/hexanes).

*4.3.14. (E)-N-(4-Methoxyphenyl)-4-phenylbut-3-enamide (**19**).* Purification by flash column chromatography (30% EtOAc/hexanes), 50% yield as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38 (m, 4H), 7.34 (t, J=7.5 Hz, 2H), 7.30–7.26 (m, 2H), 6.87–6.83 (m, 2H), 6.65–6.60 (m, 1H), 6.38 (dt, J=15.8, 7.3 Hz, 1H), 3.78 (s, 3H), 3.31 (dd, J=7.3, 1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 156.5, 136.4, 135.3, 130.7, 127.9, 126.4, 121.9, 121.9, 116.4, 114.0, 55.4, 41.7; FT-IR (neat, cm^{-1}): 3288, 3197, 3140, 3082, 2931, 1654, 1606, 1558, 1512, 1411, 1298, 1247, 1170, 1033, 964, 829; HRMS (ESI) calcd for $C_{17}H_{17}NNaO_2$ $[M+Na]^+$ 290.11515, found 290.11545; mp 128–131 °C; R_f 0.38 (30% EtOAc/hexanes).

*4.3.15. (S,E)-tert-Butyl (2-methyl-8-oxo-8-(phenylamino)oct-5-en-4-yl)carbamate (**6**).* Purification by flash column chromatography (30% EtOAc/hexanes), 70% yield as a colorless oil: $[\alpha]_D^{23}$ +18.8 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.67 (d, J=7.6 Hz, 2H), 7.35–7.27 (m, 2H), 7.08 (t, J=7.4 Hz, 1H), 5.79 (dt, J=15.0, 7.5 Hz, 1H), 5.56 (dd, J=15.4, 7.0 Hz, 1H), 4.56 (s, 1H), 4.15–4.01 (m, 1H), 3.15 (d, J=7.4 Hz, 2H), 1.69 (sep, J=6.7 Hz, 1H), 1.48–1.34 (m, 11H), 0.94 (dd, J=6.6, 1.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 155.6, 138.2, 129.0, 128.8, 124.1, 123.1, 120.1, 79.6, 51.7, 40.9, 28.41, 28.3, 24.6, 22.5; FT-IR (neat, cm^{-1}): 3319, 2956, 2929, 2870, 1670, 1697, 1600, 1541, 1498, 1442, 1367, 1311, 1249, 1249, 1172, 1026, 972, 750; HRMS (ESI) calcd for $C_{20}H_{31}N_2O_3$ $[M+H]^+$ 347.23292, found 347.23260; R_f 0.43 (30% EtOAc/hexanes); Chiral HPLC studies were performed in a CHIRALPAK® AD-H column (particle size: 5 μm; dimensions: 4.6 mm×250 mm), 95:5 (hexane/isopropanol), 1.5 mL/min, λ 254 nm.

*4.3.16. (S,E)-tert-Butyl (8-diazo-2-methyl-7-oxooct-5-en-4-yl) carbamate (**20**).* Purification by flash column chromatography (30% EtOAc/hexanes), 96% yield as a pale oil: $[\alpha]_D^{20}$ +11.4 (c 0.1, CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.72–5.59 (m, 1H), 5.44 (ddt, J=15.4, 6.8, 1.1 Hz, 1H), 4.47 (s, 1H), 4.07–3.98 (m, 1H), 3.73 (dddd, J=14.8, 11.0, 8.1, 4.0 Hz, 1H), 2.93 (d, J=7.4 Hz, 2H), 1.91–1.82 (m, 2H), 1.74–1.55 (m, 4H), 1.43 (s, 9H), 1.40–1.26 (m, 4H), 1.21–1.05 (m, 3H), 0.91 (dd, J=6.6, 2.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 155.3, 136.9, 123.5, 79.3, 51.7, 48.3, 44.0, 40.0, 33.0, 32.9, 29.7, 28.4, 25.5, 24.9, 24.9, 24.6, 22.5; FT-IR (neat, cm^{-1}): 3329, 3300, 2949, 2954, 2856, 1683, 1635, 1541, 1365, 1251, 1178, 972; HRMS (ESI) calcd for $C_{20}H_{37}N_2O_3$ $[M+H]^+$ 353.2798, found 353.2720; R_f 0.25 (30% EtOAc/hexanes).

*4.3.17. (S,E)-tert-Butyl (8-diazo-2-methyl-7-oxooct-5-en-4-yl) carbamate (**21**).* Purification by flash column chromatography (30% EtOAc/hexanes), 70% yield as a colorless oil: $[\alpha]_D^{20}$ +17.3 (c 0.1, CH_3Cl); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 6.66 (s, 1H), 5.74–5.67 (m, 1H), 5.45 (dd, J=15.4, 7.0 Hz, 1H), 4.52–4.34 (m, 3H), 4.01 (q, J=7.2 Hz, 1H), 3.02 (d, J=7.4 Hz, 2H), 1.62 (dq, J=13.5, 6.7 Hz, 1H), 1.35 (s, 9H), 1.34–1.28 (m, 2H), 0.89 (dd, J=6.6, 5.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 155.4, 138.5, 137.1, 128.5, 127.6, 127.2, 123.8, 79.4, 51.4, 43.8, 43.5, 39.9, 28.3, 24.6, 22.4; FT-IR (neat, cm^{-1}): 3342, 3032, 2981, 2954, 2929, 1678, 1637, 1525, 1367, 1294, 1170, 975; HRMS (ESI) calcd for $C_{21}H_{32}N_2NaO_3$ $[M+Na]^+$ 383.2305, found 383.2302; R_f 0.30 (30% EtOAc/hexanes).

4.3.18. (S,E)-N-(2,2,6,6-Tetramethyl-1-oxo-piperidin-4-yl)-5-(tert-butoxycarbonylamino)-7-methyloct-3-enamide. Purification by flash column chromatography (60% EtOAc/hexanes), 65% yield as a peach colored solid: mp 51–60 °C; $[\alpha]_D^{23}$ +35.3 (c 0.1, CH_2Cl_2); FT-IR (neat, cm^{-1}): 3321, 2972, 2956, 2931, 2870, 1685, 1670, 1645,

1525, 1458, 1390, 1317, 1300, 1244, 1175, 1043, 972; HRMS (ESI) calcd for $C_{23}H_{42}N_3NaO_4$ $[M+Na]^+$ 447.3068, found 447.3071; R_f 0.28 (60% EtOAc/hexanes). For NMR analysis, a sample of this nitroxide (20.0 mg, 0.047 mmol) was dissolved in dry MeOH (0.5 mL) and L-ascorbic acid (8.3 mg, 0.047 mmol) was added. Complete discoloration of the solution occurred within a few seconds. After stirring at room temperature for 10 min, the solvent was removed in vacuo. The resulting residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted twice with EtOAc, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to yield 16.1 mg (80%) of the corresponding hydroxylamine[9] as a white foam (**23**): ^{1}H NMR (500 MHz, CD_3OD) δ 6.60 (s, 1H), 5.69–5.61 (m, 1H), 5.50 (dd, J=15.3, 6.0 Hz, 1H), 4.16–3.95 (m, 2H), 2.88 (d, J=6.9 Hz, 2H), 1.72 (dt, J=15.9, 7.9 Hz, 2H), 1.66–1.54 (m, 1H), 1.43 (s, 9H), 1.43–1.26 (m, 4H), 1.17 (s, 6H), 1.15 (s, 6H), 0.91 (d, J=5.7 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.3, 157.9, 136.6, 124.3, 79.9, 59.9, 51.7, 45.9, 45.2, 42.2, 40.7, 32.7, 28.8, 25.9, 23.1, 22.6, 20.3.

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Supplementary data

NMR spectra of all new compounds and chiral HPLC studies. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.10.059.

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