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FULL PAPER

Rapid synthesis of bicyclic *N*-heterocyclic cores from *N*-terminal *α,β*-unsaturated diazoketones

João Victor Santiago [a] and Antonio C. B. Burtoloso*[a]

Dedication ((optional))

Abstract: The synthesis of bicyclic *N*-heterocycles cores from *N*-terminal *α,β*-unsaturated diazoketones is described. The transformation consists in just three sequential steps and involves a one-pot *N*-deprotection/intramolecular aza-Michael reaction, followed by a photochemical Wolff rearrangement. By this strategy, a series of substituted bicyclic *N*-heterocycles (especially indolizidines and pyrrolizidines) were synthesize in good yields.

Introduction

The synthesis of *N*-heterocycles is a field in organic synthesis that has been calling attention for many years. The pursuit in the synthesis of these *N*-heterocyclic systems has grown mainly due to the variety of compounds found in nature containing these cores, as well as the broad biological activities that they possess (Figure 1).[1-7] Therefore, many contributions for the isolation and synthesis of different types of *N*-heterocycles can be found in the literature, starting with the pioneering work of Sertüner,[8] Pelletier-Caventou,[9] Parker-Wilkinson[10] and Woodward[11]. Considering this perspective, the importance of new methods to synthesize different kinds of *N*-heterocyclic systems has been described over the years. Usually, these methodologies are based on well-established reactions, such as the Mannich reaction, aza-Michael addition, cycloadditions, reductive amination and metal-catalyzed reactions.[12]

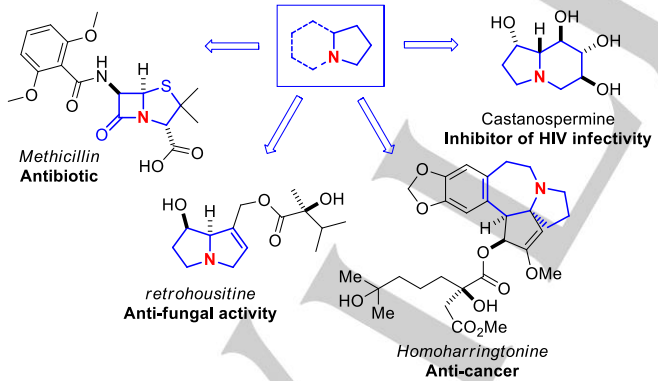
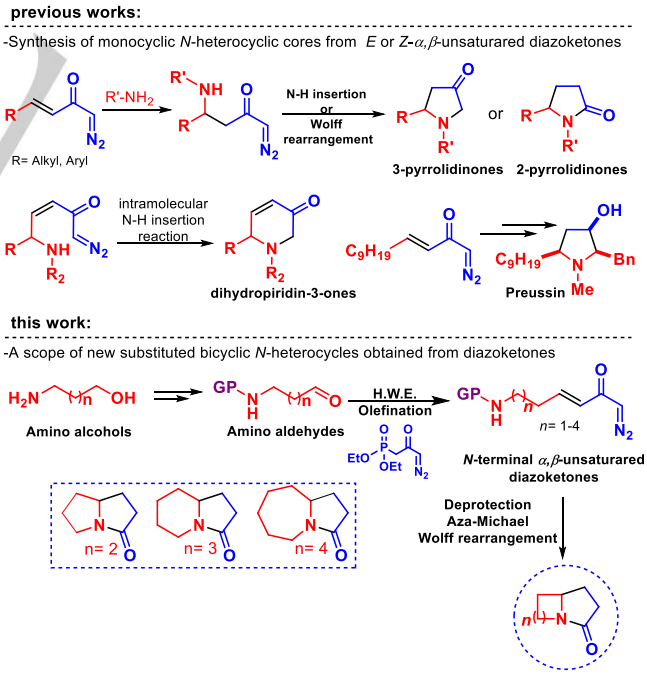


Figure 1. Examples of *N*-heterocycles with biological activity.

Considering the importance of *N*-heterocycles, especially for the pharmaceutical industry, the development of new synthetic methodologies to access these cores in different ways and with different substitution patterns is highly desired. Since 2010, our research group has been involved with the chemistry of *α,β*-unsaturated diazoketones, aiming the direct preparation of *O*- and *N*-heterocycles.[13] For example, the synthesis of the popular pyrrolidine alkaloid preussin could be accomplished in just three steps from decanal, employing an unsaturated diazoketone as the key intermediate.[14] Most of our focus has been directed to the construction of monocyclic rings, being intermolecular Michael additions and metal-catalyzed insertion reactions, the main transformations involved (Scheme 1A).[13b,13c] Considering these achievements so far, we wondered if by constructing new types of *α,β*-unsaturated diazoketones, containing an appropriate *N*-terminal chain, the sequential construction of two fused rings would be feasible (after an intramolecular Michael addition, followed by cyclization) (Scheme 1B). These *N*-terminal *α,β*-unsaturated diazoketones could be synthesized from different amino-alcohols by the appropriate protection of the amino group, oxidation of hydroxyl group to the aldehyde and, finally, by an Horner-Wadsworth-Emmons olefination in the presence of a diazophosphonate.



Scheme 1. Synthetic strategy for the construction of bicyclic *N*-heterocycles.

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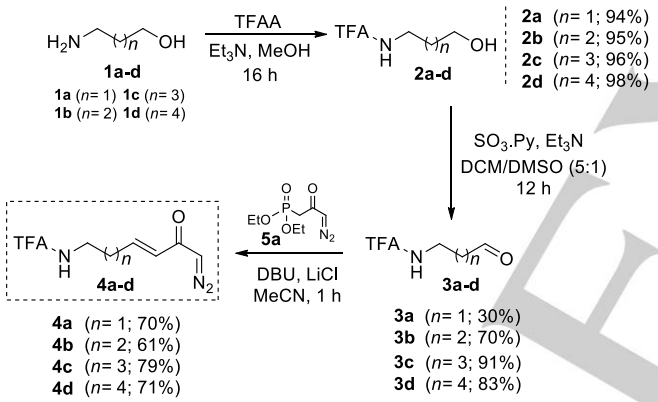
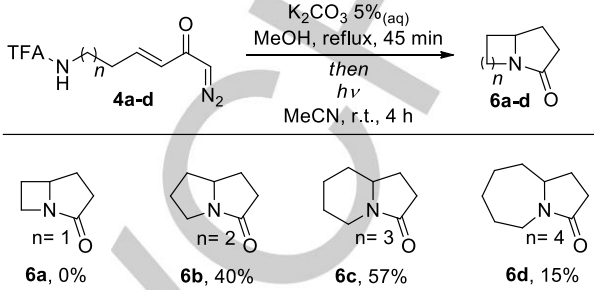
Results and Discussion

We started the synthesis of the desired *α,β*-unsaturated diazoketones by first performing the *N*-protection and oxidation of the commercially available amino alcohols **1a-d**, containing 3 to 6 carbons in the chain, respectively (Scheme 2). We first decided to protect the amino group as a trifluoroacetamide (TFA). This is due to the need of a protecting group that could be easily removed in basic conditions after the synthesis of the diazoketones (deprotection in acid conditions would decompose the diazoketones). Protection of the amino alcohols **1a-d** with trifluoroacetic anhydride (TFAA) proved to be efficient,[15] furnishing the *N*-protected amino alcohols **2a-d** in 94-96% yield. Next, the classic Parik-Doering oxidation[16] afforded the *N*-protected amino aldehydes **3a-d** in 83-91% yield. Once the amino aldehydes were prepared, we were able to investigate the Horner-Wadsworth-Emmons olefination (HWE) in the presence of **5a** and NaH as the base, following our previously described protocol.[17] Unfortunately, these conditions only led to low yields of the desired *N*-terminal *α,β*-unsaturated diazoketones. This problem was easily circumvented by using the classical condition for HWE reactions, described by Masamune-Roush, which employs 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base and Lithium Chloride (LiCl) as additive.[18] Using these conditions, the *N*-terminal *α,β*-unsaturated diazoketones **4a-d** were prepared in 61-79% yield with the exclusive formation of the *E*-isomer (Scheme 2).



Scheme 2. Synthetic route for the synthesis of *N*-terminal *α,β*-unsaturated diazoketones

After the secure synthesis of diazoketones **4a-d**, we then turned our attention to evaluate the key sequential transformation that would led to the bicyclic *N*-heterocycles depicted in Scheme 1. For this study, the amino deprotection, the intramolecular aza-Michael addition and the photochemical Wolff rearrangement were carried out in a consecutive way, without any work-up or purification (Scheme 3). For example, exposure of diazoketones **4a-d** to an aqueous solution of potassium carbonate in methanol, over reflux for approximately 45 minutes,[19] led to the one-pot deprotection/Michael reaction. Then, concentration of the solvent, addition of acetonitrile and irradiation in the presence of an Osram 150 Xenon lamp,[20] furnished the desired bicyclic *N*-heterocycles in 0-57% yields after these three transformations. For the bicyclic **6a** (n= 1; four-membered ring) none of the desired product was observed. Furthermore, bicyclic **6d** (n= 4; seven-membered ring) was formed only in 15% yield. This is in accordance with the difficulty in the formation of four and seven membered-rings, respectively. In the case of the indolizidine **6c** (n= 3) and pyrrolizidine **6b** (n= 2), both could be prepared in 57% and 40% yields, respectively (good overall yields for a reaction with three transformations).

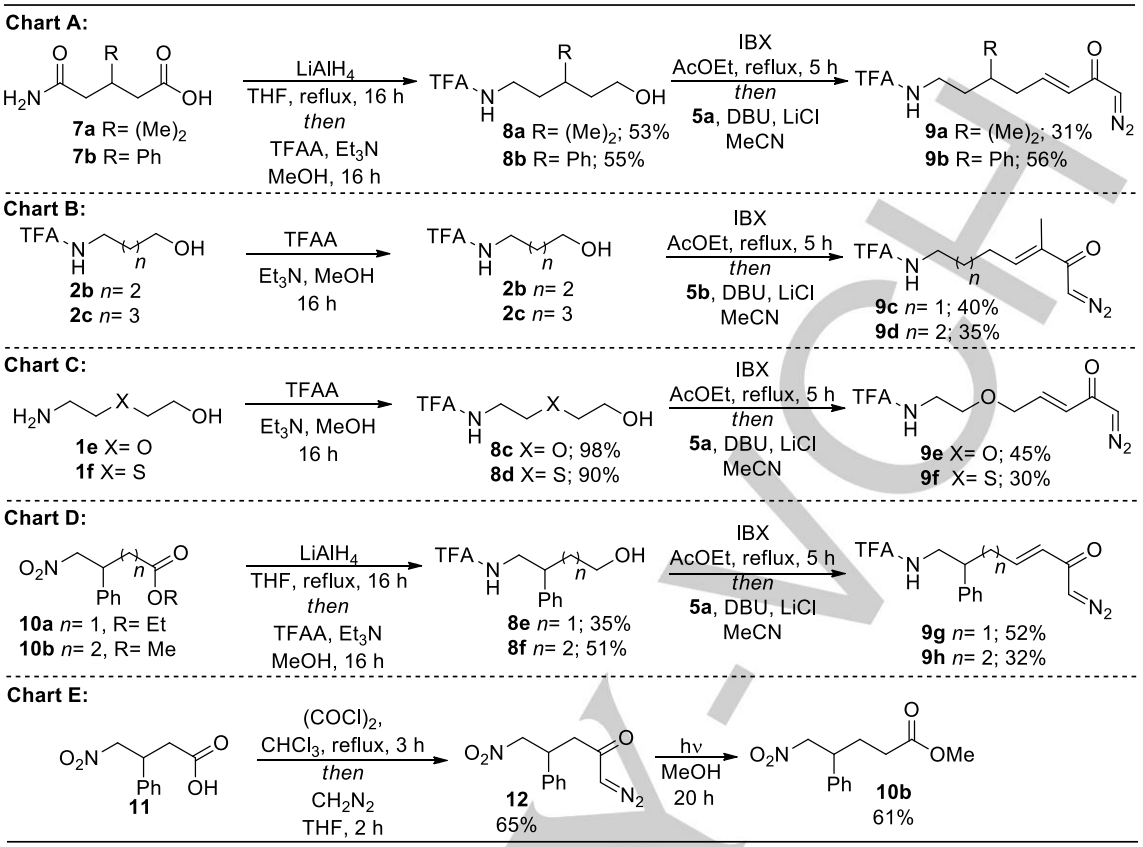


Scheme 3. Synthesis of bicyclic *N*-heterocyclic cores from *N*-terminal *α,β*-unsaturated diazoketones

As the best results were achieved for the indolizidine and pyrrolizidine cores, we next decided to improve the substrate scope of these heterocycles. First, several substituted *N*-terminal *α,β*-unsaturated diazoketones (**9a-h**) were synthesized, aiming the preparation of more complex indolizidines and pyrrolizidines (Scheme 4).

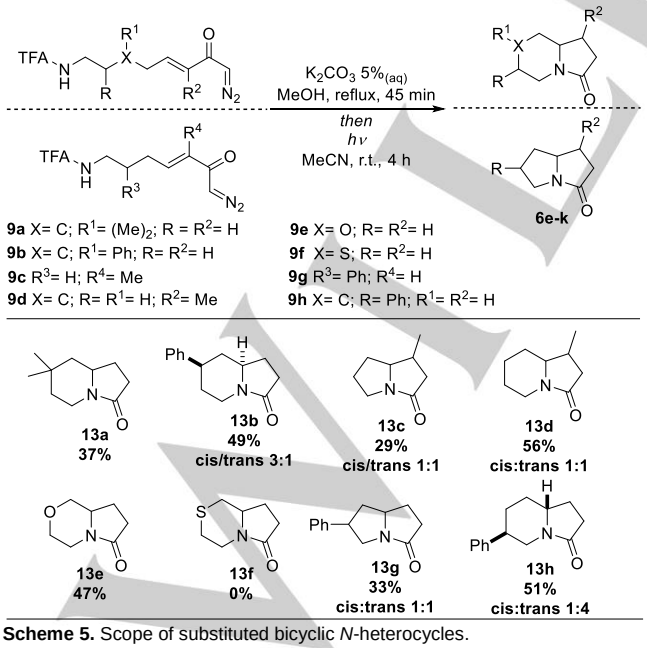
The *N*-terminal amino alcohols **8a** and **8b** were prepared from the reduction of 5-amino-3,3-dimethyl-5-oxopentanoic acid **7a**[21] and 5-amino-5-oxo-3-phenylpentanoic acid **7b**[21], respectively (Scheme 4, Chart A). The *N*-protected amino alcohols **8a** and **8b** were prepared in 53% and 55% yield, respectively, after the reaction with lithium aluminum hydride ($LiAlH_4$),[22] followed by amino group protection with trifluoroacetic anhydride (TFAA), in a single step. *N*-terminal amino alcohols **8c** and **8d** (Scheme 4, Chart C) were synthesized from the commercially available amino alcohols **1e** and **1f**. The Compounds **8c** and **8d** were obtained in 98% and 90% yield, following the reduction/protection protocol previously described. On the other hand, alcohols **8e** and **8f** were synthesized from the ethyl 4-nitro-3-phenylbutanoate **10a**[23] by the employment of a divergent strategic synthesis approach (Scheme 4, Chart D). The amino alcohol **8e** was prepared in 35% yield from the reduction reaction with $LiAlH_4$ and the consecutive protection with TFAA of the ethyl nitro ester **10a**. For the synthesis of the amino alcohol **8f** (Scheme 4, Chart E), we performed an Arndt-Eistert homologation reaction from the nitro acid **11** to furnish the methyl 5-nitro-4-phenylpentanoate **10b** (diazomethane acylation and a photochemical Wolff rearrangement).[17,20] Applying the same reduction/protection protocol, we could afford the amino alcohol **8f** in 51% yield.

Once the substituted *N*-protected amino alcohols **8a-f** were prepared, we performed the oxidation of these amino alcohols in the presence of 2-Iodoxybenzoic acid (IBX) in reflux with ethyl acetate.[24] Horner-Wadsworth-Emmons olefination using diazophosphonate **5a** and the substituted diazophosphonate **5b**, under the same conditions described in Scheme 2, was carried-out directly on the clean crude aldehydes. Hence, a series of *N*-terminal *α,β*-unsaturated diazoketones (**9a-h**) were synthesized in 31-56% yield after two steps.



Scheme 4. Synthesis of substituted *N*-terminal *α,β*-unsaturated diazoketones as key intermediates.

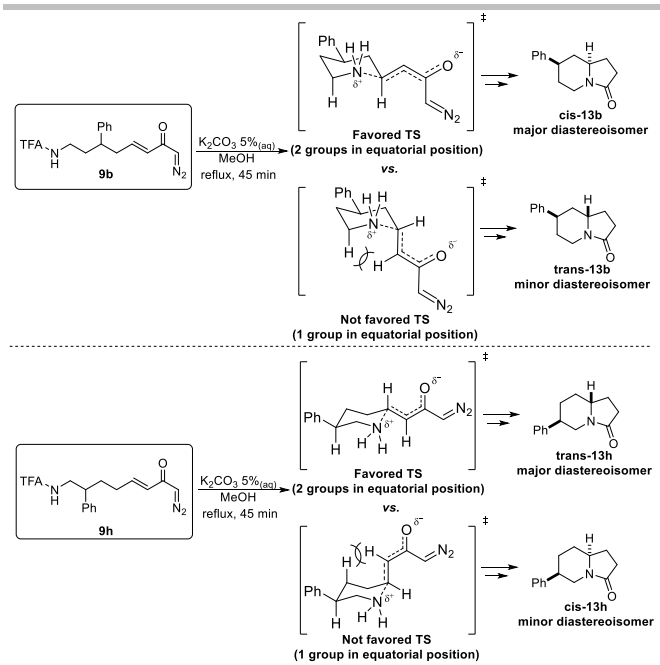
From the new synthesized *N*-terminal substituted *α,β*-unsaturated diazoketones, we applied the same protocol described for the construction of the simple bicyclic *N*-heterocyclic cores, depicted in Scheme 3 above. Hence, a series of substituted indolizidines and pyrrolizidines (**13a-h**) could be prepared in 30-57% overall yield for the three key transformations (Scheme 5).



Scheme 5. Scope of substituted bicyclic *N*-heterocycles.

It is worth mentioning that the bicyclic *N*-heterocycle derived from **9f** was not achieved by the developed methodology. Despite the other substrates, the reaction with **9f** formed a complex mixture and the desired indolizidine **13f** was not observed. We suppose that this complex mixture may has been formed by competition reactions between the sulfur and nitrogen atoms in the Wolff rearrangement and/or Michael addition.

Due to the presence of a chiral center or a prochiral carbon on some of these *N*-terminal substituted *α,β*-unsaturated diazoketones, *cis* or *trans* diastereoisomers could be formed. The stereochemical outcome for the reaction with these diazoketones were evaluated by proton NMR and GC as well as by comparison with already described data.[25] For the *N*-heterocycles **13c**, **13d** and **13g** equal proportion of the *cis* and *trans* diastereoisomers was observed, showing that the substituent in that specific position did not have some influence in the aza-Michael cyclization step. On the other hand, the indolizidines **13b** and **13h** showed good diastereoselectivity for the formation of a specific diastereoisomer. Indolizidine **13b** has shown diastereoselectivity in 3:1 ratio for the *cis* diastereoisomer. On the other hand, the indolizidine **13h** has shown the opposite diastereoselectivity, favoring the *trans* diastereoisomer, in a 4:1 ratio. This shows that by just changing the position of the substituent in the *N*-terminal substituted *α,β*-unsaturated diazoketones is enough to invert the diastereoselectivity in the aza-Michael cyclization step. The stereochemical outcome for these two examples can be explained considering a transition state which the two hindered groups (phenyl and diazoketone portion) are in the equatorial position as depict in the Scheme 6.



Scheme 6. Proposed transition states for the diastereoselective achievement of the indolizidines **13b** and **13h**.

Conclusions

In summary, we have described a new method for the construction of bicyclic *N*-heterocycles cores in a single step from *N*-terminal *α,β*-unsaturated diazoketones. The key transformations involved a cascade deprotection and Michael addition, followed by a photochemical Wolff rearrangement. Ten structurally different bicyclic nitrogen heterocycles, the majority being indolizidines and pyrrolizidines could be synthesized in a direct fashion from these diazoketones in 15-57% overall yield.

Experimental Section

GENERAL INFORMATION

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 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 ratios. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using 400 and 500 MHz equipment. For ^{1}H NMR spectra, chemical shifts (δ) are referenced from TMS (0.00 ppm). Coupling constants (J) are reported in Hz. For multiplicities the following abbreviations were used: bs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets; dt, doublet of triplets; dtd, doublet of triplet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; td, triplet of doubles; dddt; doublet of doublet of doublet of triplets; tt, triplet of triples; tq, triplet of quartets; qd, quartet of doublets; m, multiplet. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a NMR spectrometer at 101 and 126 MHz. For ^{13}C NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm) or CD_3OD (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. Melting points were determined using a digital melting point apparatus and were not corrected. High resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) (Hybrid linear ion trap-orbitrap FT-MS and QqTOF/MS-Microtof-QII models).

GENERAL PROCEDURES

Protection of commercial amino alcohols as Trifluoroacetamide.[15]

2,2,2-trifluoro-*N*-(3-hydroxypropyl)acetamide 2a.

Colorless oil; 98% yield (4.45 g, 23.03 mmol); R_f = 0.40 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3300, 3101, 2954, 2891, 1701, 1558, 1148, 1061 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (bs, 1H), 3.80 (dd, *J* = 5.6, 5.5 Hz, 2H), 3.56-3.50 (m, 2H), 2.35 (bs, 1H), 1.87-1.79 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (q, *J*= 36.7, 1C), 115.8 (q, *J*= 287.5, 1C), 61.1, 38.3, 30.4 ppm; HRMS (ESI-TOF) calcd for $C_5H_8F_3NNaO_2$ [M+Na] 194.0399 found 194.0403.

2,2,2-trifluoro-*N*-(4-hydroxybutyl)acetamide 2b.

Colorless oil; 95% yield (2.0 g, 10.80 mmol); R_f = 0.44 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3299, 3096, 2944, 2881, 1702, 1561, 1448, 1376, 1149, 1055,cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (bs, 1H), 3.71-3.69 (m, 2H), 3.39 (q, *J* = 6.4 Hz, 2H), 2.61-2.41 (m, 1H), 1.75-1.67 (m, 2H), 1.67-1.59 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5 (q, *J*= 36.8, 1C), 115.9 (q, *J*= 287.5, 1C), 62.1, 39.7, 29.4, 25.6 ppm. HRMS (ESI-Orbitrap) calcd for $C_6H_{10}F_3NNaO_2$ $[M+Na]^+$ 208.05558 found 208.05528.

2,2,2-trifluoro-*N*-(5-hydroxypentyl)acetamide 2c.

Colorless oil; 96% yield (3.68 g, 18.48 mmol), R_f = 0.41 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3446, 3301, 3096, 2941, 2868, 1701, 1560, 1149, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (bs, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 3.38 (q, *J* = 6.8 Hz, 2H), 2.33 (s, 1H), 1.71-1.51 (m, 4H), 1.51-1.35 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (q, *J*= 36.8, 1C), 115.9 (q, *J*= 287.7 Hz, 1C), 62.4, 39.8, 31.8, 28.5, 22.9 ppm; HRMS (ESI-Orbitrap) calcd for $C_7H_{12}F_3NNaO_2$ $[M+Na]^+$ 222.07123 found 222.07103.

2,2,2-trifluoro-*N*-(6-hydroxyhexyl)acetamide 2d.

White solid; 98% yield (1.68 g, 7.88 mmol)*;* m.p. 54–56°C*;*R_f = 0.64 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3446, 3298, 3095, 2937, 2863, 1702, 1562, 1150, 1055 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (bs, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 3.37 (q, *J* = 6.8 Hz, 2H), 1.51-1.66 (m, 4H), 1.49-1.27 (m, 4H) ppm, [OH absent]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (q, *J* = 36.7 Hz, 1C), 116.0 (q, *J* = 287.14 Hz, 1C), 62.6, 39.8, 32.3, 28.8, 26.3, 25.2 ppm. HRMS (ESI-TOF) calcd for $C_8H_{14}F_3NNaO_2$ $[M+Na]^+$ 236.0869 found 236.0880.

2,2,2-trifluoro-N-(2-(2-hydroxyethoxy)ethyl)acetamide 8c.

Colorless oil; 98% yield (1.90 g, 9.44 mmol); R_f = 0.47 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3297, 3094, 2938, 2881, 1708, 1561, 1447, 1357, 1130, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (bs, 1H), 3.79-3.74 (m, 2H), 3.66- 3.62 (m, 2H), 3.62- 3.59 (m, 2H), 3.57 (q, *J* = 5.1 Hz, 2H), 2.71 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5 (q, *J* = 37.1 Hz, 1C), 115.9 (q, *J* = 287.5 Hz, 1C), 72.2, 68.8, 61.6, 39.8 ppm.

2,2,2-trifluoro-N-(2-((2-hydroxyethyl)thio)ethyl)acetamide 8d.

Colorless oil; 90% yield (1.60 g, 7.37 mmol); R_f = 0.21 (Hexanes/AcOEt 1:1); IR ν_{max} = 3304, 3095, 2927, 2884, 1703, 1557, 1148, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (bs, 1H), 3.87-3.73 (m, 2H), 3.58 (q, *J* = 6.1 Hz, 2H), 2.84-2.68 (m, 4H), 2.44 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (q, *J* = 37.2 Hz), 115.8 (q, *J* = 287.6 Hz), 61.3, 39.2, 34.9, 31.1 ppm. HRMS (ESI-Orbitrap) calcd for $C_6H_{10}F_3KNO_2S$ $[M+K]^+$ 256.00159 found 256.02212

General procedure for the synthesis of *N*-terminal amino alcohols 8a and 8b.[21]

In a previously flamed 125 mL two-neck round-bottom flask with a connected condenser were added 1.43 g (37.69 mmol, 3.0 equiv.) of $LiAlH_4$ and 83.8 mL of anhydrous THF. The system was cooled to -10 ºC with a NaCl/ice bath, then 2.0 g (12.56 mmol, 1.0 equiv.) of 5-amino-3,3-dimethyl-5-oxopentanoic acid **7a** was added in portions (CAUTION: Gas extrusion). After the addition, the reaction was allowed to stir at room temperature for 15 min, then allowed to reflux for 16 hours. After this period, the reaction was cooled with an ice bath and quenched with cold water. The solution was filtered and the aqueous phase was extracted with Ethyl Ether (10 x 20.0 mL), followed by another extraction with AcOEt (5 x 20.0 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. To a 50.0 mL round-bottom flask with the crude reaction mixture of the first step was added 10.5 mL of anhydrous methanol and the system was cooled to -10 °C with a NaCl/ice bath. Then 4.2 mL of Et_3N (30.2 mmol, 2.4 equiv.) and 4.5 mL of TFAA (31.4 mmol, 2.5 equiv.) were added and the reaction was allowed to stir at room temperature for 16 hours. After this period the reaction was concentrated and the crude reaction mixture was purified by flash column chromatography (Silica Gel, Hexanes/AcOEt 7:3→1:1) to afford the *N*-terminal amino alcohol **8a** in 53% yield (1.52 g, 6.70 mmol) as a colorless oil.

2,2,2-trifluoro-*N*-(5-hydroxy-3,3-dimethylpentyl)acetamide 8a.

Colorless oil; 53% yield (1.52 g, 6.70 mmol); R_f = 0.46 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3447, 3301, 3099, 2960, 2876, 1702, 1560, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (bs, 1H), 3.76 (t, *J* = 6.8 Hz, 2H), 3.48-3.28 (m, 2H), 2.36 (s, 1H), 1.62-1.52 (m, 4H), 0.96 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (q, *J*= 36.8, 1C), 115.8 (q, *J*= 288.4, 1C), 59.4, 43.0, 39.8, 36.4, 31.9, 27.7 ppm; HRMS (ESI-Orbitrap) calcd for $C_9H_{17}F_3NO_2$ $[M+H]^+$ 228.12059 found 228.11937.

2,2,2-trifluoro-*N*-(5-hydroxy-3-phenylpentyl)acetamide 8b.

Colorless oil; 55% yield (366.0 mg, 1.33 mmol); R_f = 0.45 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3333, 3083, 3060, 2927, 2866, 1568, 1493, 1432, 1319, 1049, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 7.26-7.21 (m, 1H), 7.20-7.15 (m, 2H), 6.44 (bs, 1H), 3.56 (ddd, *J* = 10.6, 6.2, 5.4 Hz, 1H), 3.48-3.41 (m, 1H), 3.37-3.26 (m, 1H), 3.22-3.09 (m, 1H), 2.80 (tt, *J* = 10.0, 5.1 Hz, 1H), 2.05-1.89 (m, 2H), 1.88-1.79 (m, 2H), 1.69 (bs, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (q, *J* = 36.6 Hz, 1C), 143.3, 128.9, 127.4, 126.9, 115.7 (q, *J* = 287.8 Hz, 1C), 60.4, 40.2, 39.1, 38.6, 35.4 ppm; HRMS (ESI-Orbitrap) calcd for $C_{13}H_{17}F_3NO_2$ $[M+H]^+$ 276.12059 found 276.11876.

Synthesis of *N*-terminal amino alcohols 8e and 8f from the nitro esters 10a[23] and 10b.

The synthesis of the *N*-terminal amino alcohols **8e** and **8f** was conducted according to the experimental procedure previously described for *N*-protected amino alcohols **8a** and **8b**.

2,2,2-trifluoro-N-(4-hydroxy-2-phenylbutyl)acetamide 8e.

Colorless oil; 35% yield (500.0 mg, 1.91 mmol); R_f = 0.16 (Hexanes/AcOEt 1:1); IR ν_{max} = 3304, 3068, 3029, 2937, 2883, 1708, 1454, 1375, 1156, 1002 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H), 7.30-7.24 (m, 1H), 7.21-7.15 (m, 2H), 6.89 (bs, 1H), 3.75-3.61 (m, 2H), 3.52 (ddd, *J* = 13.4, 8.1, 5.4 Hz, 1H), 3.45 (ddd, *J* = 13.5, 8.0, 5.5 Hz, 1H), 3.06-2.99 (m, 1H), 2.03 (bs, 1H), 2.00-1.85 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.3 (q, *J* = 36.9 Hz, 1C), 141.2, 129.0, 127.5, 127.4, 115.8 (q, *J* = 287.7 Hz, 1C), 60.3, 45.2, 42.1, 36.1 ppm; HRMS (ESI-Orbitrap) calcd for $C_{12}H_{14}F_3NNaO_2$ $[M+Na]^+$ 284.08688 found 284.08610.

2,2,2-trifluoro-N-(5-hydroxy-2-phenylpentyl)acetamide 8f.

Colorless oil; 51% yield (205.0 mg, 0.74 mmol); R_f = 0.37 (Hexanes/AcOEt 1:1 run twice); IR ν_{max} = 3310, 3087, 3031, 2940, 2884, 1707, 1554, 1454, 1209, 1156 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.32 (m, 2H), 7.30-7.25 (m, 1H), 7.19-7.15 (m, 2H), 6.19 (bs, 1H), 3.83-3.73 (m, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.34 (ddd, *J* = 13.9, 9.2, 5.1 Hz, 1H), 2.85 (tt, *J* = 9.3, 5.4 Hz, 1H), 1.85-1.77 (m, 1H), 1.76-1.66 (m, 1H), 1.56 -1.40 (m, 2H), 1.34 (bs, 1 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1 (q, *J* = 36.9 Hz, 1C), 141.1, 129.1, 127.6, 127.4, 115.7 (q, *J* = 287.9 Hz, 1C), 62.5, 45.3, 45.0, 30.1, 29.5 ppm; HRMS (ESI-TOF) calcd for $C_{13}H_{16}F_3NNaO_2$ $[M+Na]^+$ 298.1025 found 298.1026.

Synthesis of *N*-terminal amino aldehydes 3a-d by Parikh-Doering oxidaditon. [16]

2,2,2-trifluoro-*N*-(3-oxopropyl)acetamide 3a.

White Solid; 30% yield (583.0 mg, 3.45 mmol); m.p. 82-86 °C; R_f = 0.46 (Silica gel, Hexanes/AcOEt 1:1); IR ν_{max} = 2934, 2864, 1703, 1559, 1448, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.03 (bs, 1H), 3.65 (q, *J* = 5.9 Hz, 2H), 2.85 (t, *J* = 5.8 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 157.3 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 287.5 Hz), 42.6, 33.3 ppm; HRMS (ESI-TOF) calcd for $C_5H_7F_3NO_2$ $[M+H]^+$ 170.0423 found 170.0427.

2,2,2-trifluoro-*N*-(4-oxobutyl)acetamide 3b.

Colorless oil; 70% yield (1.40 g, 7.56 mmol); R_f = 0.43 (Silica gel, Hexanes/AcOEt 1:1); IR ν_{max} = 3106, 2954, 2897, 2844, 1705,1557, 1449,

1139 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.20 (bs, 1H), 3.39 (q, 6.6 Hz, 2H), 2.60 (t, *J* = 6.8 Hz, 2H), 1.95-1.85 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7, 157.5 (q, *J*= 36.7 Hz, 1C), 115.8 (q, *J*= 287.5 Hz, 1C), 41.2, 39.3, 21.0 ppm; HRMS (ESI-Orbitrap) calcd for $C_6H_8F_3NNaO_2$ $[M+Na]^+$ 206.03993 found 206.03979.

2,2,2-trifluoro-*N*-(5-oxopentyl)acetamide 3c.

Colorless oil; 91 % yield (1.93 g, 9.13 mmol); R_f = 0.43 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 3096, 2941, 2868, 1701, 1560, 1148, 1054 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.2 Hz, 1H), 6.83 (bs, 1H), 3.38 (q, *J* = 6.4 Hz, 2H), 2.54 (td, *J* = 6.7, 1.1 Hz, 2H), 1.72-1.59 (m, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 157.4 (q, *J* = 37.0 Hz, 1C), 115.8 (q, *J* = 287.7 Hz, 1C), 43.1, 39.4, 28.2, 18.7 ppm; HRMS (ESI-Orbitrap) calcd for $C_7H_{10}F_3NNaO_2$ $[M+Na]^+$ 220.05558 found 220.05525.

2,2,2-trifluoro-*N*-(6-oxohexyl)acetamide 3d.

White solid; 83% yield (890.0 mg, 4.21 mmol); m.p. 99-104 ºC; R_f = 0.51 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 3115, 2923, 2861, 1697, 1563, 1348, 1177, 1150 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.5 Hz, 1H), 6.60 (bs, 1H), 3.38 (q, *J* = 6.8 Hz, 2H), 2.48 (td, *J* = 7.2, 1.5 Hz, 2H), 1.71-1.58 (m, 4H), 1.43-1.34 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3; 157.3 (q, *J* = 36.5 Hz, 1C); 115.8 (q, *J* = 288.5 Hz, 1C); 43.5; 39.6; 28.6; 26.0; 21.3 ppm; HRMS (ESI-TOF) calcd for $C_8H_{12}F_3NNaO_2$ $[M+Na]^+$ 234.0712 found 234.0724

General procedure for the Horner-Wadsworth-Emmons (H.W.E.) olefination.

The Horner-Wadsworth-Emmnos Olefinations were conducted according to the procedure described by Masamune-Roush.[18]

(*E*)-*N*-(6-diazo-5-oxohex-3-en-1-yl)-trifluoroacetamide 4a.

Yellow solid; 70% yield (97.0 mg, 0.41 mmol); m.p. 88-90 ºC; R_f = 0.29 (Silica gel, Hexanes/AcOEt 7:3); IR v_{max} = 3087, 2105, 1709, 1656, 1594, 1561, 1365, 1149 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (bs, 1H), 6.74 (dt, *J* = 15.4, 7.1 Hz, 1H), 6.06 (d, *J* = 15.5 Hz, 1H), 5.34 (s, 1H), 3.52 (q, *J* = 6.5 Hz, 2H), 2.52 (qd, *J* = 6.8, 1.5 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.3, 157.5 (q, *J* = 37.1 Hz, 1C), 139.8, 129.5, 115.7 (q, *J* = 287.4 Hz, 1C), 55.9, 38.4, 31.4 ppm; HRMS (ESI-TOF) calcd for $C_8H_8F_3N_3NaO_2$ $[M+Na]^+$ 258.0461 found 258.0454.

(*E*)-*N*-(7-diazo-6-oxohept-4-en-1-yl)-trifluoroacetamide 4b.

Yellow solid; 61% yield (82.0 mg, 0.33 mmol); m.p. 61-63 ºC; R_f = 0.35 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 2940, 2852, 2101, 1706, 1653, 1596, 1558, 1361, 1143 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 15.4, 6.9 Hz, 1H), 6.59 (bs, 1H), 6.03 (d, *J* = 15.4 Hz, 1H), 5.31 (s, 1H), 3.40 (q, *J* = 6.8 Hz, 2H), 2.31-2.23 (m, 2H), 1.78 (quint, *J* = 7.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6, 157.4 (q, *J* = 36.8 Hz), 143.0, 128.0, 115.8 (q, *J* = 287.8 Hz), 55.6, 39.3, 29.2, 27.4 ppm; HRMS (ESI-Orbitrap) calcd for $C_9H_{10}F_3N_3NaO_2$ $[M+Na]^+$ 272.06173 found 272.06161.

(*E*)-*N*-(8-diazo-7-oxooct-5-en-1-yl)-trifluoroacetamide 4c.

Yellow solid; 79% yield (21.0 mg, 0.08 mmol); m.p. 64-67 ºC; R_f = 0.31 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 3089, 2937, 2864, 2101, 1707, 1652, 1598, 1558, 1362, 1143 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 15.4, 7.0 Hz, 1H), 6.51 (bs, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 5.31 (s, 1H), 3.38 (q, *J* = 6.7 Hz, 2H), 2.25 (qd, *J* = 7.1, 1.6 Hz, 2H), 1.69-1.58 (m, 2H), 1.59-1.47 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.5, 157.3 (q, *J* = 36.9 Hz), 143.8 , 127.8, 115.8 (q, *J* = 287.8 Hz), 55.4, 39.6, 31.5, 28.5, 25.2 ppm; HRMS (ESI-Orbitrap) calcd for $C_{10}H_{13}F_3N_3O_2$ $[M+H]^+$ 264.09544 found 264.09521.

(*E*)-*N*-(9-diazo-8-oxonon-6-en-1-yl)-trifluoroacetamide 4d.

Orange semisolid; 71% yield (92.51 mg, 0.33 mmol); R_f = 0.37 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 3093, 2935, 2862, 2102, 1706, 1652, 1598, 1558, 1365, 1149 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 15.4, 7.0 Hz, 1H), 6.54 (bs, 1H), 5.99 (d, *J* = 15.5 Hz, 1H), 5.31 (s, 1H), 3.36 (q, *J* = 6.8 Hz, 2H), 2.22 (qd, *J* = 7.2, 1.5 Hz, 2H), 1.60 (quint, *J* = 7.5 Hz, 2H), 1.51 (quint, *J* = 7.5 Hz, 2H), 1.42-1.32 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7, 157.2 (q, *J* = 36.8 Hz, 1C), 144.5, 127.6, 115.8 (q, *J* = 287.8 Hz, 1C), 55.2, 39.8, 31.9, 28.7, 27.6, 26.1 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{14}F_3N_3NaO_2$ $[M+Na]^+$ 300.0930 found 300.0944.

General procedure for the synthesis of *N*-terminal *α,β*-unsaturated diazoketones in 2 steps from *N*-terminal amino alcohols

In previously flamed 10 mL two-neck round-bottom flask with a connected condenser were added 100.0 mg (0.44 mmol, 1.0 equiv.) of 2,2,2-trifluoro-N-(5-hydroxy-3,3-dimethylpentyl)acetamide **8a** and 4.5 mL of anhydrous ethyl acetate. Then 370.0 mg of 2-Iodoxybenzoic acid (1.64 mmol, 3.0 equiv.) was added in portions and the reaction was allowed to stir over reflux for 5 hours. After this period, the reaction solution was cooled to room temperature, filtered with celite pad and concentrated. To a 25.0 mL round-bottom flask with the crude reaction mixture of the first step was added 6.40 mL of acetonitrile and 24.5 mg (0.58 mmol, 1.30 equiv.) of dried LiCl. The reaction was cooled to 0 °C and the solution of diazophosphonate **5a** in acetonitrile (127.1 mg, 0.6 M, 1.3 equiv.) was added dropwise. Then 54.1 mg of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.36 mmol, 0.8 equiv.) was added and the reaction was allowed to stir for 2 hours. After this period the reaction was concentrated and the crude reaction mixture was purified by flash column chromatography (Silica Gel, Hexanes/AcOEt 7:3→1:1) to afford the *N*-terminal *α,β*-unsaturated diazoketone **9a** in 31% yield (40.0 mg, 0.14 mmol) as a viscous yellow oil.

(*E*)-*N*-(8-diazo-3,3-dimethyl-7-oxooct-5-en-1-yl)-trifluoroacetamide 9a.

Viscous yellow oil; 31% yield (40.0 mg, 0.14 mmol); R_f = 0.39 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 2959, 2917, 2873, 2851, 2103, 1708, 1652, 1601, 1557, 1155 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (dt, *J* = 15.4, 7.7 Hz, 1H), 6.57 (bs, 1H), 6.02 (d, *J* = 15.3 Hz, 1H), 5.35 (s, 1H), 3.51-3.24 (m, 2H), 2.14 (dd, *J* = 7.8, 1.3 Hz, 2H), 1.55 -1.47 (m, 2H), 0.98 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.4 , 157.1 (q, *J* = 36.9 Hz, 1C), 141.0, 130.0, 115.7 (q, *J* = 287.5 Hz, 1C), 55.6, 44.6, 40.3, 36.1, 33.4, 27.0 ppm. HRMS (ESI-Orbitrap) calcd for $C_{12}H_{17}F_3N_3O_2$ $[M+H]^+$ 292.12674 found 292.12485.

(*E*)-*N*-(8-diazo-7-oxo-3-phenyloct-5-en-1-yl)-trifluoroacetamide 9b.

Viscous yellow oil; 56% yield (62.0 mg, 0.18 mmol); R_f = 0.41 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 3064, 2928, 2104, 1709, 1557, 1364, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H), 7.27-7.22 (m, 1H), 7.17-7.12 (m, 2H), 6.62 (dt, *J* = 15.4, 7.7 Hz, 1H), 6.30 (bs, 1H), 5.92 (d, *J* = 15.4 Hz, 1H), 5.23 (s, 1H), 3.29 (dq, *J* = 13.8, 7.0 Hz, 1H), 3.21-3.09 (m, 1H), 2.80-2.71 (m, 1H), 2.55-2.41 (m, 2H), 2.06-1.96 (m, 1H), 1.93-1.81 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.3, 157.0 (q, *J* = 36.9 Hz), 142.4, 141.8, 129.0, 128.8, 127.2, 127.2, 115.7 (q, *J* = 287.4 Hz), 55.4, 43.4, 39.5, 38.5, 34.8 ppm; HRMS (ESI-Orbitrap) calcd for $C_{16}H_{17}F_3N_3O_2$ $[M+H]^+$ 340.12674 found 340.12453.

(*E*)-*N*-(2-((5-diazo-4-oxopent-2-en-1-yl)oxy)ethyl)-trifluoroacetamide 9e.

Viscous yellow oil; 45% yield (50.0 mg, 0.22 mmol); R_f = 0.37 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 2942, 2876, 2107, 1714, 1658, 1602, 1558, 1363, 1178, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (dt, *J* = 15.6, 4.4 Hz, 1H + bs, 1H, N-H), 6.19 (d, *J* = 15.6 Hz, 1H), 5.35 (s, 1H), 4.19 (dd, *J* = 4.4, 2.0 Hz, 2H), 3.68-3.54 (m, 4H) ppm; ^3C NMR (101 MHz, $CDCl_3$) δ 183.9, 157.3 (q, *J* = 37.1 Hz), 139.1, 126.9, 115.8 (q, *J* = 287.7 Hz), 69.8, 68.4, 56.0, 39.6 ppm; HRMS (ESI-TOF) calcd for $C_9H_{10}F_3N_3NaO_3$ $[M+Na]^+$ 288.0567 found 288.0577.

***(E)*-*N*-(2-((5-diazo-4-oxopent-2-en-1-yl)thio)ethyl) trifluoroacetamide 9f.**

Yellow solid; 30% yield (150.0 mg, 0.53 mmol); m.p. 56-59 ºC; R_f = 0.35 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 2955, 2924, 2854, 2105, 1706, 1555, 1365, 1149 cm^{-1};.^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (bs, 1H), 6.72 (dt, *J* = 15.1, 7.4 Hz, 1H), 6.08 (d, *J* = 15.3 Hz, 1H), 5.39 (s, 1H), 3.53 (q, *J* = 6.5 Hz, 2H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.66 (t, *J* = 6.7 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8, 157.3 (q, *J* = 37.2 Hz), 138.3, 129.2, 115.7 (q, *J* = 287.7 Hz), 56.0, 38.6, 32.4, 29.7 ppm. HRMS (ESI-Orbitrap) calcd for $C_9H_{10}F_3N_3NaO_2S$ [M+Na] 304.03380 found 304.03292.

(*E*)-*N*-(7-diazo-6-oxo-2-phenylhept-4-en-1-yl)-trifluoroacetamide 9g.

Yellow solid; 52% yield (64.0 mg, 0.20 mmol); m.p. 75-78 ºC; R_f = 0.32 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 3089, 3031, 2954, 2923, 2850, 2102, 1709, 1653, 1362, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (m, 2H), 7.33-7.25 (m, 1H), 7.19-7.13 (m, 2H), 6.64 (dt, *J* = 15.5, 7.2 Hz, 1H), 6.26 (bs, 1H), 5.98 (d, *J* = 15.4 Hz, 1H), 5.24 (s, 1H), 3.83-3.73 (m, 1H), 3.39 (ddd, *J* = 13.7, 8.9, 5.2 Hz, 1H), 3.08-2.99 (m, 1H), 2.60-2.54 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.1, 157.2 (q, *J* = 37.2 Hz), 140.8, 139.8, 129.4, 129.2, 127.7, 127.4, 115.7 (q, *J* = 288.5 Hz), 55.5, 44.7, 44.3, 36.0 ppm; HRMS (ESI-TOF) calcd for $C_{15}H_{14}F_3N_3NaO_2$ $[M+Na]^+$ 348.0930 found 348.0944.

(*E*)-*N*-(8-diazo-7-oxo-2-phenyloct-5-en-1-yl)-trifluoroacetamide 9h.

Viscous yellow oil; 32% yield (47.0 mg, 0.14 mmol); R_f = 0.43 (Silica gel, Hexanes/AcOEt 1:1); IR v_{max} = 3089, 3065, 3031, 2951, 2856, 2104, 1713, 1653, 1365, 1266, 1207, 1152 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (m, 2H), 7.32-7.27 (m, 1H), 7.19-7.12 (m, 2H), 6.72 (dt, *J* = 15.4, 6.9 Hz, 1H), 6.19 (bs, 1H), 5.90 (d, *J* = 15.5 Hz, 1H), 5.26 (s, 1H), 3.83-3.71 (m, 1H), 3.34 (ddd, *J* = 13.8, 9.2, 5.0 Hz, 1H), 2.84 (tt, *J* = 9.5, 5.5 Hz, 1H), 2.25-2.06 (m, 2H), 1.92-1.71 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.4, 157.1 (q, *J* = 37.1 Hz, 1C), 143.6, 140.3, 129.2, 128.9, 127.6, 127.6, 115.7 (q, *J* = 287.8 Hz, 1C), 55.3, 45.1, 44.7, 31.6, 29.7 ppm; HRMS (ESI-TOF) calcd for $C_{16}H_{16}F_3N_3NaO_2$ $[M+Na]^+$ 362.1087 found 362.1085.

General procedure for Horner-Wadsworth-Emmons Olefination (H.W.E.) with diethyl (4-diazo-3-oxobutan-2-yl) phosphonate 5b.

The *N*-terminal diazoketones **9c** and **9d** were prepared following the methodology previously described for the synthesis of *N*-terminal diazoketones in 2 steps from *N*-terminal amino alcohols, with the diazophosphonate **5b.**

(*E*)-*N*-(7-diazo-5-methyl-6-oxohept-4-en-1-yl)-trifluoroacetamide 9c.

Yellow solid; 40% yield (87.0 mg, 0.33 mmol); m.p. 66-69 ºC; R_f = 0.32 (Silica gel, Hexanes/AcOEt 7:3); IR v_{max} = 2933, 2103, 1709, 1647, 1594, 1556, 1344, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (bs, 1H), 6.27 (tq, *J* = 7.3, 1.4 Hz, 1H), 5.56 (s, 1H), 3.40 (q, *J* = 6.8 Hz, 2H), 2.29-2.22 (m, 2H), 1.84-1.82 (m, 3H), 1.76 (quint, *J* = 7.4 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.3, 157.3 (q, *J* = 37.1 Hz), 136.3, 135.7, 115.8 (q, *J* = 287.9 Hz), 53.3, 39.5, 28.0, 25.6, 12.2 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_{12}F_3N_3NaO_2$ $[M+Na]^+$ 286.0774 found 286.0779.

(*E*)-*N*-(8-diazo-6-methyl-7-oxooct-5-en-1-yl)-trifluoroacetamide 9d.

Yellow solid; 35% yield (50.0 mg, 0.18 mmol); m.p. 47-50 ºC; R_f = 0.27 (Silica gel, Hexanes/AcOEt 7:3); IR v_{max} = 2953, 2852, 2104, 1709, 1596, 1557, 1368, 1342, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (bs, 1H), 6.26 (tq, *J* = 7.3, 1.4 Hz, 1H), 5.55 (s, 1H), 3.39 (q, *J* = 6.8 Hz, 2H), 2.28-2.20 (m, 2H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.68-1.58 (m, 2H), 1.56-1.44 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.5, 157.3 (q, *J* = 36.8 Hz), 136.9, 135.9, 115.8 (q, *J* = 288.0 Hz), 53.1, 39.7, 28.7, 28.0, 25.7, 12.2 ppm. HRMS (ESI-TOF) calcd for $C_{11}H_{14}F_3N_3NaO_2$ $[M+Na]^+$ 300.0930 found 300.0943.

General procedure for the syntheses of *N*-heterocycles cores.[20]

To a 10 mL round-bottom flask equipped with a magnetic stir-bar flask were added 20.0 mg of *N*-terminal *α,β*-unsaturated diazoketone **4c** (0.075 mmol, 1.0 equiv.) and 1.5 mL of methanol. Then 0.32 mL of K_2CO_3 5% aqueous solution (0.11 mmol, 1.5 equiv.) was added and the reaction was allowed to stir over reflux for 45 minutes. After this period, the reaction solution was cooled to room temperature and concentrated. In a quartz cell of 1 cm light path, containing a magnetic stirrer and fitted with a rubber septum, were added the crude reaction mixture of the first step and anhydrous acetonitrile (2.5 mL, 0.025 M) under argon atmosphere. The reaction mixture was irradiated with an Osram 150 xenon arc lamp and allowed to stir at room temperature for 4 hours. The solvent was then removed under reduced pressure in a rotatory evaporator and the crude product was purified by flash chromatography with a short pad of silica ($CHCl_3$ as the eluent) to furnish the hexahydroindolizin-3(2H)-one **6c** in 57% yield as a yellowish oil.

Tetrahydro-1H-pyrrolizin-3(2H)-one 6b.

Yellowish oil; 40% yield (4.0 mg, 0.032 mmol); R_f = 0.33 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2962, 2925, 2881, 1664, 1421, 1308, 1204 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95-3.83 (m, 1H), 3.61-3.50 (m, 1H), 3.10- 3.01 (m, 1H), 2.74 (dddt, *J* = 16.6, 11.4, 9.1, 1.3 Hz, 1H), 2.44 (ddd, *J* = 16.6, 9.5, 2.0 Hz, 1H), 2.30 (dddd, *J* = 12.7, 8.9, 6.8, 2.0 Hz, 1H), 2.17-1.95 (m, 3H), 1.73 (dddd, *J* = 12.7, 11.1, 9.4, 7.7 Hz, 1H), 1.41-1.24 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 62.1, 41.0, 35.4, 32.2, 27.2, 27.0 ppm.

Hexahydroindolizin-3(2H)-one 6c.

Yellowish oil; 57% yield (6.0 mg, 0.043 mmol); R_f = 0.35 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2925, 2854, 1657, 1445, 1423, 1370, 1260, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17-4.06 (m, 1H), 3.40 (dtd, *J* = 10.8, 7.2, 3.4 Hz, 1H), 2.68-2.55 (m, 1H), 2.41-2.31 (m, 2H), 2.26-2.13 (m, 1H), 1.93-1.81 (m, 2H), 1.74-1.64 (m, 1H), 1.66-1.53 (m, 1H), 1.46-1.28 (m, 2H), 1.23-1.08 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 57.3, 40.2, 33.6, 30.3, 25.3, 24.4, 23.7 ppm.

Hexahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one 6d.

Light brown oil; 15% yield (4.1 mg, 0.027 mmol); R_f = 0.45 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2925, 2854, 1651, 1458, 1436, 1171, 1126, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80-3.65 (m, 2H), 3.22-3.01 (m, 1H), 2.42-2.30 (m, 2H), 2.15-2.00 (m, 1H), 1.85-1.74 (m, 1H), 1.68-1.52 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 59.3, 42.5, 35.2, 31.1, 29.8, 27.8, 26.4, 25.0 ppm.

7,7-dimethylhexahydroindolizin-3(2H)-one 13a.

Yellowish oil; 37% yield (4.3 mg, 0.026 mmol); R_f = 0.39 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2950, 2923, 2869, 1669, 1457, 1295, 1128 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (ddd, *J* = 13.5, 5.3, 2.0 Hz, 1H), 3.67-3.55 (m, 1H), 2.85-2.74 (m, 1H), 2.41-2.31 (m, 2H), 2.24-2.11 (m, 1H), 1.61-1.49 (m, 2H), 1.40-1.33 (m, 1H), 1.33-1.25 (m, 2H), 1.01 (s, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 53.2, 46.4, 37.1, 36.3, 32.6, 30.5, 30.0, 25.5, 23.0 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_{18}NO$ $[M+H]^+$ 168.1383 found 168.1387.

(7R,8aR)-7-phenylhexahydroindolizin-3(2H)-one 13b.

Yellowish oil; 49% yield (4.0 mg, 0.019 mmol) [diastereoisomers mixture: *cis:trans* (3:1)]; R_f = 0.52 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 3084, 3060, 2927, 2856, 1673, 1452, 1421, 1282, 1269, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) [major diastereoisomer] δ 7.36-7.29 (m, 2H), 7.25-7.17 (m, 3H), 4.26 (ddd, *J* = 13.3, 4.9, 1.7 Hz, 1H), 3.71-3.54 (m, 1H), 2.86-2.68 (m, 2H), 2.46-2.38 (m, 2H), 2.31-2.14 (m, 2H), 2.11-2.03 (m, 1H), 1.95-1.84 (m, 1H), 1.73-1.61 (m, 1H), 1.39 (q, *J* = 12.5 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) [major diastereoisomer] δ 173.6, 145.0, 128.6, 126.6, 126.5, 57.2, 41.9, 41.0, 39.9, 32.0, 30.4, 25.1 ppm.

1-methyltetrahydro-1H-pyrrolizin-3(2H)-one 13c.

Yellowish oil; 30% yield (3.1 mg, 0.022 mmol) [diastereoisomers mixture *cis:trans* (1:1)]; R_f = 0.39 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2956, 2924, 2873, 1666, 1456, 1377, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) [diastereoisomer mixture] δ 3.97 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.59-3.46 (m, 3H), 3.11 -3.00 (m, 2H), 2.90 (ddt, *J* = 16.4, 8.0, 1.2 Hz, 1H), 2.62-2.48 (m, 2H), 2.40 (ddt, *J* = 16.1, 11.2, 1.3 Hz, 1H), 2.19-1.98 (m, 6H), 1.76-1.65 (m, 2H), 1.60-1.50 (m, 1H), 1.42-1.36 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) [diastereoisomer mixture] δ 174.3, 174.3, 69.0, 65.1, 43.9, 43.1, 41.4, 41.2, 38.0, 30.8, 29.6, 27.0, 26.9, 25.1, 18.0, 16.0 ppm.

1-methylhexahydroindolizin-3(2H)-one 13d.

Yellowish oil; 56% yield (6.0 mg, 0.039 mmol) [diastereoisomers mixture *cis:trans* (1:1)]; R_f = 0.45 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2924, 2853, 1670, 1454, 1377, 1200, 1126 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) [diastereoisomer mixture] δ 4.15-4.06 (m, 2H), 3.44-3.37 (m, 1H), 2.90 (ddd, *J* = 10.9, 7.0, 3.5 Hz, 1H), 2.68-2.44 (m, 5H), 2.06-1.85 (m, 6H), 1.74-1.57 (m, 3H), 1.47-1.19 (m, 6H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) [diastereoisomer mixture] δ 173.5, 173.3, 64.2, 60.7, 40.6, 40.1, 39.1, 38.7, 34.6, 31.8, 28.9, 26.6, 24.6, 24.3, 23.9, 23.6, 18.2, 15.1 ppm.

Tetrahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6(7H)-one 13e.

Yellowish oil; 47% yield (5.0 mg, 0.035 mmol); R_f = 0.41 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2933, 2857, 1664, 1450, 1364, 1267, 1196, 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.00 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.96-3.89 (m, 2H), 3.72-3.65 (m, 1H), 3.34 (ddd, *J* = 11.8, 11.7, 3.2 Hz, 1H), 3.08 (t, *J* = 11.0 Hz, 1H), 3.04-2.92 (m, 1H), 2.47-2.34 (m, 2H), 2.18-2.09 (m, 1H), 1.59-1.49 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 72.8, 66.0, 54.9, 40.2, 29.9, 20.7 ppm.

6-phenyltetrahydro-1H-pyrrolizin-3(2H)-one 13g.

Yellow oil; 35% yield (4.3 mg, 0.021 mmol) [diastereoisomers mixture *cis:trans* (1:1)]; R_f = 0.36 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 2924, 2854, 1683, 1454, 1376, 1286, 1203, 1178, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) [diastereoisomers mixture] δ 7.37-7.29 (m, 4H), 7.28-7.19 (m, 6H), 4.22-4.05 (m, 3H), 3.73-3.63 (m, 1H), 3.61-3.49 (m, 2H), 3.47 (q, *J* = 7.4 Hz, 1H), 3.07 (ddd, *J* = 11.9, 7.0, 1.4 Hz, 1H), 2.85-2.67 (m, 2H), 2.56-2.30 (m, 5H), 2.19-2.10 (m, 1H), 1.97 (ddd, *J* = 12.9, 8.6, 6.6 Hz, 1H), 1.86 (dddd, *J* = 12.7, 11.2, 9.5, 7.7 Hz, 1H), 1.75 (tt, *J* = 12.1, 8.8 Hz, 1H), 1.60-1.49 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) [diastereoisomers mixture] δ 175.9, 174.6, 142.5, 141.3, 128.7, 128.7, 127.1, 127.0, 127.0, 126.8, 62.5, 60.3, 48.9, 47.9, 47.3, 45.2, 41.5, 39.9, 35.1, 34.7, 28.9, 27.0 ppm.

(6R,8aR)-6-phenylhexahydroindolizin-3(2H)-one 13h.

Yellowish oil; 51% yield (4.1 mg, 0.019 mmol) [diastereoisomers mixture *cis:trans* (1:4)]; R_f = 0.44 (Silica gel, AcOEt/Methanol 9:1); IR ν_{max} = 3084, 3060, 2927, 2854, 1666, 1446, 1310, 1031 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) [major diastereoisomer] δ 7.57-7.06 (m, 5H), 4.10 (ddd, *J* = 12.9, 4.5, 1.8 Hz, 1H), 3.67-3.59 (m, 1H), 2.77 (dd, *J* = 12.4, 12.4 Hz, 1H), 2.66-2.57 (m, 1H), 2.52-2.33 (m, 2H), 2.37-2.21 (m, 1H), 2.14-1.94 (m, 2H), 1.88-1.75 (m, 1H), 1.75-1.61 (m, 1H), 1.49-1.34 (m, 1H) ppm; ^{13}C NMR (101 MHz, CD_3OD) [major diastereoisomer] δ 176.1, 144.1 129.7, 128.1, 127.9, 58.6, 47.6, 43.4, 34.4, 32.1, 31.5, 25.7 ppm .

Synthesis of the intermediate 12 via diazomethane acylation methodology from the activated nitro acid 11.

The 1-diazo-5-nitro-4-phenylpentan-2-one **12** were prepared following the methodology previously described [20]

1-diazo-5-nitro-4-phenylpentan-2-one 12.

Viscous yellow oil; 65% yield (136.0 mg, 0.58 mmol); R_f = 0.33 (Silica gel, Hexanes/AcOEt 7:3); IR ν_{max} = 3106, 3032, 2920, 2104, 1788, 1729, 1633, 1547, 1376, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.33-7.25 (m, 1H), 7.26-7.20 (m, 2H), 5.20 (s, 1H), 4.77 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.66 (dd, *J* = 12.6, 8.0 Hz, 1H), 4.04 (quint, *J* = 7.2 Hz, 1H), 2.85-2.67 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1, 138.5, 129.1, 128.0, 127.3, 79.4, 55.6, 43.3, 40.1 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{11}N_3NaO_3$ $[M+Na]^+$ 256.0693 found 256.0681.

Synthesis of the nitro ester 10b via photochemical Wollf rearrangement of the diazoketone 12.

Methyl 5-nitro-4-phenylpentanoate 10b.

Colorless oil; 61% yield (75.0 mg, 0.32 mmol); R_f = 0.58 (Silica gel, Hexanes/AcOEt 7:3); IR ν_{max} = 3062, 3031, 2953, 2923, 2869, 2852, 1732, 1551, 1378, 1265, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 2H), 7.31-7.24 (m, 1H), 7.21-7.16 (m, 2H), 4.65-4.51 (m, 2H), 3.62 (s, 3H), 3.56-3.43 (m, 1H), 2.24-2.15 (m, 2H), 2.16-2.04 (m, 1H), 2.03-1.92 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 138.1, 129.1, 128.0, 127.6, 80.5, 51.7, 43.6, 31.3, 28.0 ppm. HRMS (ESI-TOF) calcd for $C_{12}H_{15}NNaO_4$ $[M+Na]^+$ 260.0893 found 260.0901.

Procedure for the synthesis of the Diethyl (4-diazo-3-oxobutan-2-yl) phosphonate 5b.

The diazophosphote **5b** was prepared in 2 steps via the Arbuzov reaction for the synthesis of the 2-(diethoxyphosphoryl)propanoic acid,[26] followed by the methodology described by Pinho and Burtoloso[17] for the synthesis of diazophosphonate **5a**.

Diethyl (4-diazo-3-oxobutan-2-yl) phosphonate 5b.

Yellow oil; 30% yield (153.0 mg, 0.65 mmol); R_f = 0.33 (Silica gel, Et_2O/MeOH 95:5); IR ν_{max} = 2984, 2941, 2909, 2101, 1733, 1634, 1352, 1244, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 (s, 1H), 4.23-4.03 (m, 4H), 3.10-2.87 (m, 1H), 1.41 (dd, *J* = 17.9, 7.2 Hz, 3H), 1.34 (td, *J* = 7.0, 2.6 Hz, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.4, 62.8 (d, *J* = 6.8 Hz), 62.6 (d, *J* = 6.9 Hz), 55.8, 44.6 (d, *J* = 129.8 Hz), 16.3 (d, *J* = 6.1 Hz), 11.2 (d, *J* = 6.1 Hz) ppm; HRMS (ESI-TOF) calcd for $C_8H_{15}N_2NaO_4P$ $[M+Na]^+$ 257.0662 found 257.0657.

Acknowledgements ((optional))

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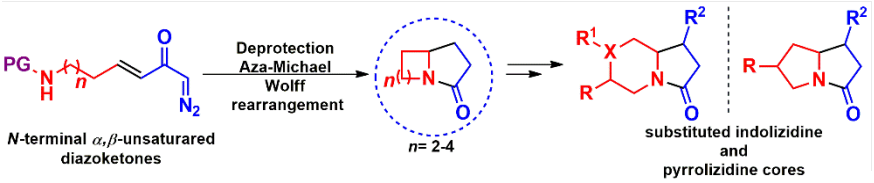

Synthesis of *N*-heterocycles*

*João Victor Santiago, Antonio C. B. Burtoloso**

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Rapid synthesis of bicyclic *N*-heterocyclic cores from *N*-terminal α,β-unsaturated diazoketones

The synthesis of bicyclic *N*-heterocycles cores from *N*-terminal α,β-unsaturated diazoketones is described. The transformation consists in just three sequential steps and involves a one-pot *N*-deprotection/intramolecular aza-Michael reaction, followed by a photochemical Wolff rearrangement.

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