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One-step syntheses of substituted 2-pyrrolidinones and 3-pyrrolidinones from α,β-unsaturated diazoketones and amines. Application in the synthesis of barmumycin

Rafael M.P. Dias, Patrícia B. Momo, Antonio C.B. Burtoloso*

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

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ABSTRACT

A simple and one-pot way to prepare substituted 2- and 3-pyrrolidinones is described. The method uses unsaturated diazoketones (obtained from aldeydes in a single step) and amines, and provide an easy access to these important classes of nitrogen heterocycles. Furthermore, application of this methodology to the synthesis of the natural product barmumycin is achieved in 3 steps from these diazoketones.

1. Introduction

Pyrrolidines are an important class of 5-membered nitrogen heterocycles, being one of the most abundant in nature among nitrogenated compounds.[1] In addition, many molecules of this class exhibit broad biological and pharmaceutical activity, putting them in a special position when compared to the 3-, 4- and 6-membered ring homologous.[2] Fig. 1 gives some examples of natural products, as well as popular pharmaceutical drugs, containing the pyrrolidine ring (Fig. 1).

Due to the vast importance of pyrrolidines, many different synthetic strategies for its preparation appeared in the literature.[3] The most described strategies are: 1) intramolecular cyclization via nucleophilic substitution[4]; 2) olefin metathesis[5]; and 3) reductive amination from 1,4-diketones or iminium ions.[6] Despite the existence of these three main synthetic strategies, as well as of many other methods to synthesize pyrrolidines, only a few can lead to a great structural variety of pyrrolidines starting from a single common intermediate. This type of strategy, a divergent synthesis, becomes very attractive in medicinal chemistry as a tool for obtaining a large number of analogs from the same intermediate.

For many years, our research group has been involved with the chemistry of α,β-unsaturated α'-diazoketones. This class of compounds can be prepared in just one step from aldehydes and have

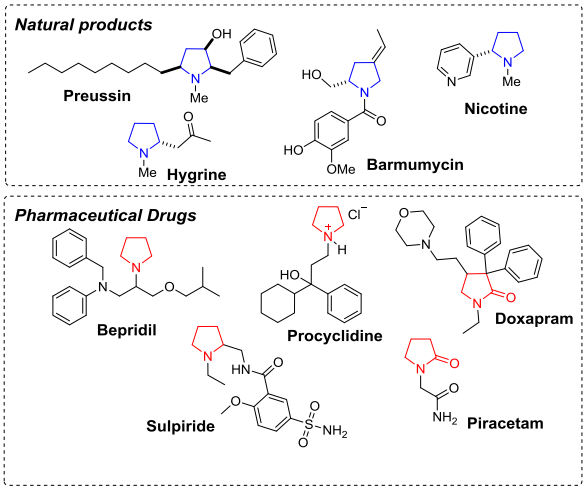

Fig. 1. Example of natural products and important pharmaceutical molecules, containing a pyrrolidine scaffold.

* Corresponding author.
E-mail address: antonio@iqsc.usp.br (A.C.B. Burtoloso).

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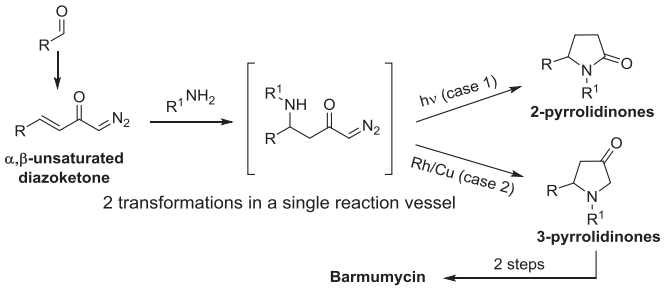
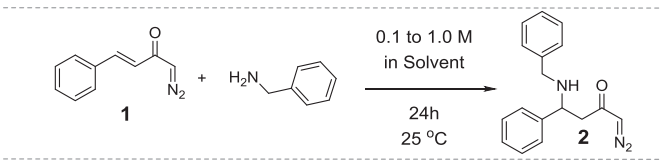
been employed as useful platforms in the divergent synthesis of several compounds, including heterocycles.[7] Herein, we would like to show how we could use α,β-unsaturated α'-diazoketones to construct several 2- and 3-pyrrolidinones in a one pot reaction. Moreover, a three-step synthesis of the alkaloid barmumycin is demonstrated from these intermediates. To accomplish that, we employed these building blocks as aza-Michael acceptors in two different ways: 1) in the presence of amines and light; 2) in the presence of amines and rhodium or copper salts. We envisaged that after the formation of the aza-Michael adduct, a Wolff rearrangement would be prone to happen in the presence of light, leading directly to 2-pyrrolidinones (case 1). In a similar way, an intramolecular N–H insertion reaction would led to 3-pyrrolidinones (case 2) if these adducts were formed in the presence of rhodium or copper catalysts (Scheme 1).



Scheme 1. One-pot synthesis of pyrrolidinones from unsaturated diazoketones and total synthesis of barmumycin.

Table 1
Optimization study for the aza-Michael addition from α,β-unsaturated diazoketones.



Entry	Amine (equiv.)	Solvent	Concentration	Yield %[a]
1[8]	4	Ethyl Ether	0,3 M	64[b]
2	3	Ethyl Ether	0,5 M	89
3	3	DCM	0,5 M	88
4	3	Benzene	0,5 M	80
5	3	THF	0,5 M	90
6	3	MeCN	0,5 M	56
7	3	Ethanol	0,5 M	73
8	3	DMF	0,5 M	75
9	2	THF	0,5 M	71
10	1	THF	0,5 M	32
11	2	Ethyl Ether	0,5 M	53
12	3	THF	1 M	88
13	3	Ethyl Ether	1 M	93
14	3	Ethyl Ether	1 M	90[c]
15	10	THF	0,1 M	0
16	10	THF	0,1 M	73[d]

[a] Yields determined by NMR with 1,2,4,5-tetramethylbenzene as an internal standard.
[b] 48 h.
[c] Isolated yield by column chromatography.
[d] 30 mol% of DBU was used.

2. Results/discussion

We started our work by first optimizing the reaction conditions to perform the Michael reaction, before trying the one-pot transformation (Table 1).

Although Michael reactions with amines are well-described for many types of substrates, it is not in the case of α,β-unsaturated α'-diazoketones. In fact, before our studies,[7] only one single example was described by Clark[8] where the authors used a simple unsaturated α'-diazoketone (1-diazopent-3-en-2-one) and two different amines. This indicates that the aza-Michael reaction from unsaturated α'-diazoketones is still extremely limited with respect to substrates and deserves more attention.[9] Beginning our studies, we choose diazoketone **1** and benzylamine as the model substrates. As a first attempt using Clark's conditions (4.0 equivalents of the amine, 0.3 M in Et_2O, 48 h) we could already obtain a 64% yield for Michael adduct **2** (entry 1, Table 1). In view of the moderate yield and long reaction period, we decided to optimize the yield of this reaction by studying different reaction conditions. For that, other parameters such as solvent, concentration and number of equivalents for the amine were evaluated. Almost doubling the concentration in Clark's condition to 0.5 M furnished **2** in 89% (entry 2, Table 1), even in a lower period of time (24 h). Using this condition, several solvents with different dielectric constant were evaluated next (entries 3–8). In general, less polar solvents proved to be better for the studied aza-Michael addition (THF, Et_2O and DCM being the best and giving basically the same yield). Reducing the amount of amine to two and one equivalents (entries 9–11) dropped the yield from 90% to 71% and 32%, respectively (THF) and from 89% to 53% (Et_2O). Performing the reaction in a higher concentration (entries 12–14), maintaining the amount of amine, didn't cause any substantial change in the yield. It is important to note that very diluted solutions gives no product (even in the presence of 10 equivalents of amine) unless DBU is added (entries 15–16).[10] From all these optimization studies it is clear that at least 3 equivalents of amine and diazoketone concentration of 0.5–1.0 M in DCM, THF or Et_2O should be employed to guarantee the best yields. Using the optimized conditions, described in entry 13 (Table 1), several Michael adducts could be prepared from structurally different amines and unsaturated diazoketones in 71–94% isolated yields (Fig. 2).

We next, started the evaluation of the one-pot formation of 3-pyrrolidines directly from diazoketone **1** (Table 2).

Intramolecular N–H insertion reactions are well-known in the literature[11] and rhodium and copper salts are generally the catalysts of choice, being $Rh_2(OAc)_4$ the most used. Considering that, our first attempt consisted in employing conditions in entry 13, Table 1, in the presence of $Rh_2(OAc)_4$. As shown in entry 1 (Table 2) no reaction was observed, Michael adduct **2** being the only observed product. Performing the reaction with pure isolated **2** also didn't furnish any of 3-pyrrolidine **22**. The same trend was observed when copper(II) acetylacetonate $Cu(acac)_2$ was employed (entry 2). We next turned our attention to dichloromethane (DCM) and benzene as solvents, since they also provided very good yields in the Michael addition optimization studies. According to literature[11] these solvents are also the most employed in insertion reactions. Reaction of $Rh_2(OAc)_4$ and $Cu(acac)_2$ in DCM furnished 10% and 0% of 3-pyrrolidinone **22**, being practically all the aza-Michael adduct **2** recovered (entries 3–4). On the other hand, employing the more reactive copper (II) hexafluoroacetylacetonate $Cu(hfacac)_2$, a complex mixture of products was observed. Probably, formation of the metal carbene from the diazo function was faster than the aza-Michael addition, leading to other reactions (including intermolecular N–H insertion from benzylamine). From this point, we decided to add the catalyst in the flask only after all the diazoketone

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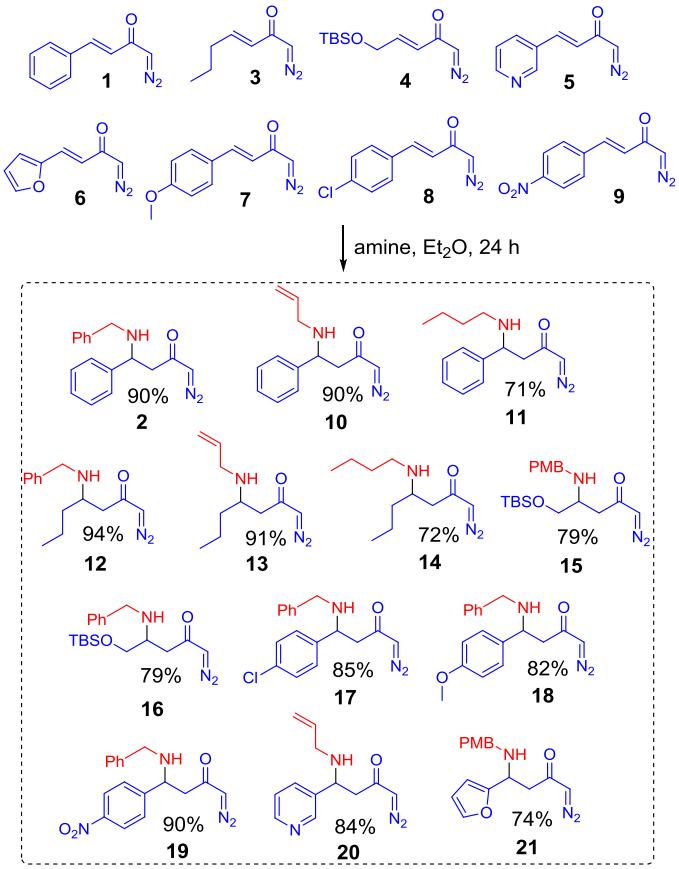
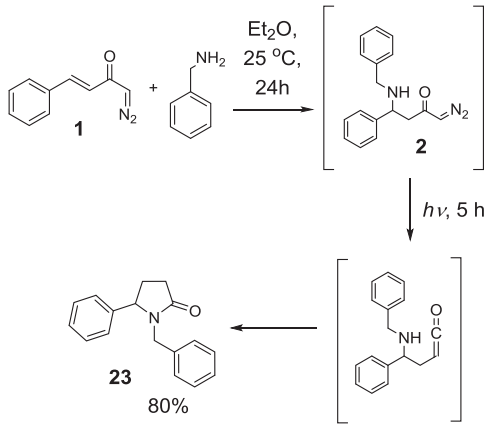
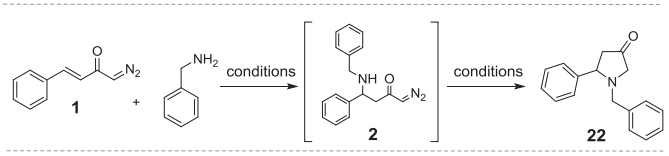


Fig. 2. Aza-Michael adducts prepared from unsaturated diazoketones after the optimization studies.



Scheme 2. One-pot conversion of unsaturated diazoketones to 2-pyrrolidinones.

Table 2
Optimization studies for the one-pot conversion of unsaturated diazoketones to 3-pyrrolidinones.



Entry	Catalyst (mol%)	Solvent	Temp.	Time	Yield %
1[a]	$Rh_2(OAc)_4$ (5)	Et_2O	25 °C	24 h	0
2[a]	$Cu(acac)_2$ (10)	Et_2O	25 °C	24 h	0
3[a]	$Rh_2(OAc)_4$ (5)	DCM	25 °C	24 h	10
4[a]	$Cu(acac)_2$ (10)	DCM	25 °C	24 h	0
5[a]	$Cu(hfacac)_2$ (10)	DCM	25 °C	24 h	0
6[b,c]	$Cu(hfacac)_2$ (10)	DCM	25 °C	25 h	15
7[b,c,d]	$Cu(hfacac)_2$ (10)	DCM	25 °C	25 h	50
8[b,c,d]	$Rh_2(OAc)_4$ (5)	DCM	25 °C	25 h	10
9[b,d,e]	$Rh_2(OAc)_4$ (5)	C_6H_6	80 °C	25 h	55
10[b,d,f]	$Cu(acac)_2$ (10)	C_6H_6	80 °C	5 min	35

[a] 1.0 M solution, 24 h, all reagents mixed together.
[b] Addition of the catalyst only after complete formation of the Michael adduct 2 (24 h).
[c] Stirred by 1 h after addition of the catalyst.
[d] Diluted to 0.05 M with the same solvent before the addition of the catalyst.
[e] Stirred by 30 min after addition of the catalyst.
[f] Stirred by 5 min after addition of the catalyst.

was converted to the Michael adduct **2**. Although the formation of 3-pyrrolidinone **22** could be detected (entry 6), better yields (50%, entry 7) were observed when the reaction was diluted in the same solvent to 0.05 M prior to the addition of the catalyst. This modification did not work well for $Rh_2(OAc)_4$ and low yields of **22**, together with recovery of **2**, were obtained. This scenario changed drastically when the same reaction was performed in benzene under reflux, furnishing **22** in 55% yield (entry 9). From Table 2, conditions in entries 7 and 9 proved to be the best for the one pot transformation. To carry out further studies we selected conditions in entry 7 as the best, since it uses a non-expensive copper catalyst, dichloromethane instead of benzene and the reaction can be performed at room temperature. Attempts to carry out this best condition in ether as solvent provided lower yields.

With respect to the one pot reaction in the presence of light, aiming the synthesis of 2-pyrrolidinones,[12] a less extended screening was necessary. As already observed in our research group, the Wolff rearrangement from unsaturated diazoketones is too fast and probably would occur before the aza-Michael addition reaction, leading to β,γ-unsaturated amides as the main product. In view of that, the reaction was only irradiated with light after all diazoketone **1** was converted to **2**. Repeating condition in entry 13 (Table 1) and then exposing the reaction flask to a 300 W xenon lamp (after dilution to 0.05 M with the same solvent), furnished 2-pyrrolidinone **23** in 80% (Scheme 2) in the first attempt.

Secured with two new protocols for the direct transformation of unsaturated diazoketones into 2- and 3- pyrrolidines, we then extended it to the preparation of other pyrrolidines. Using conditions described in Table 2 and Scheme 2, sixteen pyrrolidinones were prepared in 42–81% isolated yield from five types of diazoketones in the presence of different types of amine (Fig. 3). Moreover, to demonstrate the applicability of this protocol, the total synthesis of the natural product barmumycin[13] was accomplished in 2 steps from pyrrolidinone **36** Scheme 3. Installation of the exocyclic double bond was carried out using Julia-Kocienski olefination[13a,14] to provide olefin **38** in 54% yield in a 3:1 diastereomeric ratio in favor of the desired *E* isomer. Attempts to improve this ratio were fruitless. Next, removal of both PMB and TBS protecting groups was performed in the presence of 1-chloroethyl chloroformate,[15] furnishing the crude alcohol which was used directly in the next step. Coupling the free amine with vanilic acid (or its fenolic TBS ether) in the presence of PyBOP and DIPEA gave barmumycin **39** in approximately 30% overall yield from **38** after three transformations. All the data for **39** are in complete accordance

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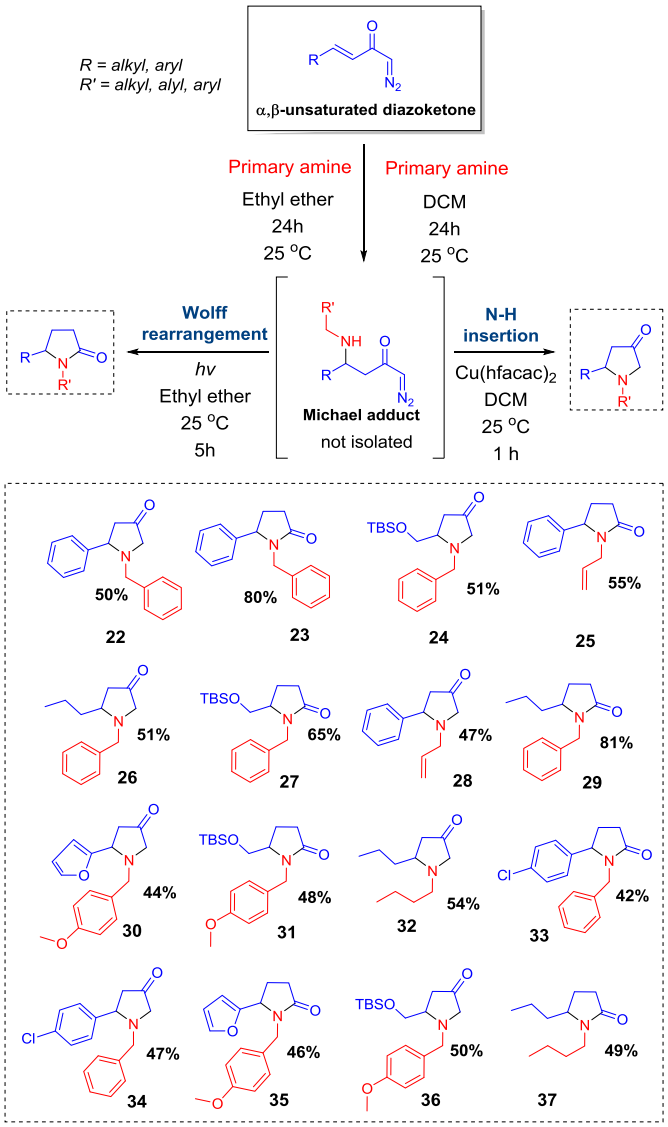
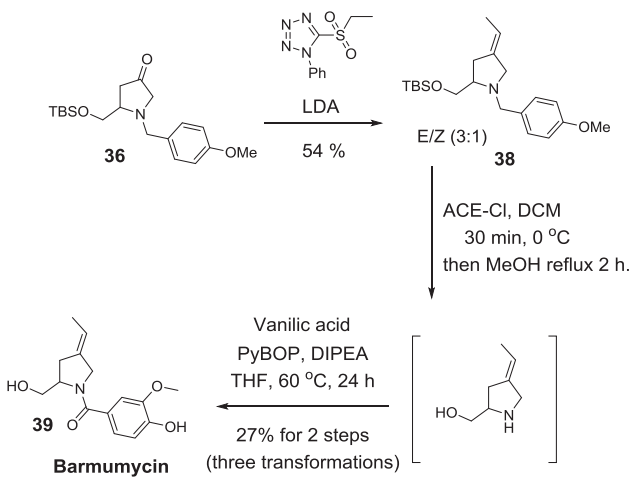


Fig. 3. One-pot synthesis of 2- and 3-pyrrolidinones from unsaturated diazoketones.



Scheme 3. Application in the Barmumycin synthesis.

with those reported in the literature.[13]

3. Conclusion

Pyrrolidines are well distributed in nature and are found in many important pharmaceutical drugs. Herein, we described for the first time the application of unsaturated diazoketones, as useful building blocks to prepare 2- and 3-pyrrolidinones in a divergent and one-pot fashion. The experimental setup is simple and the method permits the synthesis of a library of pyrrolidinones in a direct way and with very good yields. Additionally, we showed an application of this methodology to the short synthesis of the alkaloid barmumycin.

4. Experimental section

4.1. 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 percentages. 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: 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 a NMR spectrometer at 100 or 125 MHz. For ^{13}C NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm) or $(CD_3)_2SO$ (39.5 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).

4.2. General procedure for the Horner-Wadsworth-Emmons reactions

To a solution of diethyl 3-diazo-2-oxopropylphosphonate (400 mg, 1.81 mmol, 1 equiv.) in EtOH (5 mL) was added 185 μL of benzaldehyde (1.81 mmol, 1 equiv.) at room temperature. Thus, 3.6 mL of 0.5 M NaOH solution (water:EtOH 1:1) was added during a period of 1 h (using a syringe pump). After this time, the mixture was stirred and maintained at this temperature for more 30 min. The reaction was finished by the addition of saturated NaCl (20 mL), extracted using CH_2Cl_2 (3 × 20 mL) and dried over $MgSO_4$. Purification by flash column chromatography (10% EtOAc/hexanes) afforded unsaturated diazoketone **1** (233.7 mg, 1.36 mmol, 75%) as a yellow solid.

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4.3. (E)-1-Diazo-4-phenylbut-3-en-2-one **(1)**

Yield: 75%. Yellow solid, m.p. = 63–65 °C. R_f = 0.25 (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 15.8 Hz, 1H), 7.55–7.51 (m, 2H), 7.39–7.37 (m, 3H), 6.60 (d, J = 15.8 Hz, 1H), 5.45 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.3, 140.7, 134.4, 130.3, 128.9, 128.2, 123.7, 56.2 ppm. IR ν_{max} (cm^{-1}): 3072, 3026, 2098, 1637, 1585, 1495, 1448, 1371, 1202, 1149, 1117, 974, 851, 758, 679, 573, 507.

4.4. (E)-1-Diazohept-3-en-2-one **(3)**

Yield: 54%. Yellow oil. R_f = 0.20 (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dt, J = 15.3, 7.0 Hz, 1H), 5.99 (d, J = 15.3 Hz, 1H), 5.29 (s, 1H), 2.18 (dq, J = 7.3, 1.5 Hz, 2H), 1.59–1.38 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.8, 145.1, 127.3, 55.0, 34.3, 21.4, 13.7 ppm. IR ν_{max} (cm^{-1}): 2959, 2930, 2872, 2102, 1653, 1597, 1464, 1367, 1308, 1202, 1153, 1099, 1032, 974, 876, 750, 608, 476.

4.5. (E)-5-((tert-butyldimethylsilyl)oxy)-1-diazopent-3-en-2-one **(4)**

Yield: 74%. Yellow oil. R_f = 0.28 (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, J = 15.0 Hz, 1H), 6.27 (d, J = 14.9 Hz, 1H), 5.33 (s, 1H), 4.36 (2d, J = 3.5 Hz, 2H), 0.92 (s, 9H), 0.04 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 143.4, 125.2, 62.3, 55.6, 25.9 (3C), 18.4, −5.4 (2C) ppm. IR ν_{max} (cm^{-1}): 2953, 2928, 2883, 2856, 2106, 1661, 1614, 1539, 1472, 1362, 1256, 1138, 1007, 939, 837, 608, 501. HRMS (ESI-TOF) calculated for $C_{11}H_{21}N_2O_2Si$ [M+H$^+$] 241.13668, found 241.13622.

4.6. (E)-1-Diazo-4-(pyridin-3-yl)but-3-en-2-one **(5)**

Yield: 72%. Yellow solid, m.p. = 188–190 °C. R_f = 0.25 (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 2.0 Hz, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 15.8 Hz, 1H), 7.33 (dd, J = 7.9, 4.8 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 5.50 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 150.9, 149.8, 137.0, 134.5, 130.3, 128.9, 123.8, 56.7 ppm. IR ν_{max} (cm^{-1}): 3094, 3063, 3021, 2104, 1651, 1595, 1564, 1477, 1373, 1314, 1182, 1124, 1103, 1024, 980, 876, 768, 683, 582, 494. HRMS (ESI-TOF) calculated for $C_9H_8N_3O$ [M+H$^+$] 174.06619, found 174.06580.

4.7. (E)-1-Diazo-4-(furan-2-yl)-but-3-en-2-one **(6)**

Yield: 60%. Yellow solid, m.p. = 66–68 °C. TLC: R_f = 0.26 (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 1.7 Hz, 1H), 7.39 (d, J = 15.4 Hz, 1H), 6.64 (d, J = 3.4 Hz, 1H), 6.56–6.42 (m, 2H), 5.38 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.8, 151.1, 144.6, 127.1, 121.0, 115.6, 112.5, 56.5 ppm. IR ν_{max} (cm^{-1}): 3099, 2106, 1645, 1583, 1552, 1477, 1371,1261, 1151, 1099, 1000, 825.

4.8. (E)-1-Diazo-4-(4-methoxyphenyl)but-3-en-2-one **(7)**

Yield: 50%. Yellow solid, m.p. = 128–129 °C. R_f = 0.20 (30% EtOAc/hexanes). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, J = 15.9, 1H), 7.10 (d, J = 8.9, 2H), 6.6 (d, J = 8.9, 2H), 6.2 (d, J = 15.9, 1H), 4.4 (s, 1H), 3.2 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.1, 161.7, 140.1, 130.1 (2C), 127.7, 122.1, 114.5 (2C), 58.8, 54.5 ppm. IR ν_{max} (cm^{-1}): 3062, 2090, 1643, 1587, 1512, 1421, 1367, 1551, 1172, 1093, 977, 827.

4.9. (E)-4-(4-chlorophenyl)-1-diazobut-3-en-2-one **(8)**

Yield: 83%. Yellow solid, m.p. = 110–112 °C. R_f = 0.25 (30% EtOAc/hexanes). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44 (d, J = 15.9 Hz, 1H), 6.97 (td, J = 2.2, 8.9 Hz, 2H), 6.80 (td, J = 1.9, 8.6 Hz, 2H), 6.03 (d, J = 15.6 Hz, 1H), 4.40 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.9, 136.3, 132.9, 129.3 (2C), 129.2 (2C), 127.2, 123.9, 56.4 ppm. IR ν_{max} (cm^{-1}): 3068, 2100, 1637, 1577, 1490, 1373, 1089, 821.

4.10. (E)-1-Diazo-4-(4-nitrophenyl)but-3-en-2-one **(9)**

Yield: 74%. Yellow solid, m.p. = 135–137 °C. R_f = 0.13 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.9 Hz, 2H), 7.69–7.62 (m, 3H), 6.69 (d, J = 15.8 Hz, 1H), 5.51 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 148.4, 140.7, 137.7, 128.8 (2C), 127.4, 124.2 (2C), 57.2 ppm. IR ν_{max} (cm^{-1}): 3105, 2924, 2853, 2102, 1645, 1603, 1589, 1514, 1416, 1364, 1342, 1151, 1111, 978, 843, 750, 669, 569.

4.11. General procedure for the aza Michael addition

To a 4 mL vial equipped with a magnetic stir-bar and contained an ethereal solution of diazo ketone **1** (20.0 mg, 0.116 mmol,. 1.0 equiv with 0.116 mL of ethyl ether) was added 38 μL of benzylamine (37.3 mg, 0.348 mmol, 3.0 equiv.) at room temperature. The reaction was stirred at room temperature for 24 h. The crude mixture was purified by flash column chromatography [silica gel (230–400 mesh)] using hexanes:AcOEt:TEA (gradient elution 85:10: 5 to 55:40:5) as eluent system to afford the Michael adduct of **2** in 90% yield (29.2 mg, 0.105 mmol) as an orange oil.

4.12. 4-(benzylamino)-1-diazo-4-phenylbutan-2-one **(2)**

Yield: 90%. Yellow oil. R_f = 0.21 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 10H), 5.13 (s, 1H), 4.14 (dd, J = 8.0, 4.8 Hz, 1H), 3.63 (d, J = 13.4 Hz, 1H), 3.54 (d, J = 13.4 Hz, 1H), 2.70–2.58 (m, 2H), 2.07 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 142.8, 140.3, 128.8 (2C), 128.5 (2C), 128.3 (2C), 127.6, 127.3 (2C), 127.0, 59.3, 55.4, 51.6, 49.3 ppm. IR ν_{max} (cm^{-1}): 3325, 3084, 3063, 3026, 2953, 2928, 2856, 2102, 1641, 1495, 1470, 1360, 1256, 1099, 1028, 1006, 970, 937, 837, 779, 698, 613, 492.

4.13. 4-(allylamino)-1-diazo-4-phenylbutan-2-one **(10)**

Yield: 90%. Yellow oil. R_f = 0.22 (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 5.89–5.81 (m, 1H), 5.18 (s, 1H), 5.13–5.09 (m, 1H), 5.07–5.04 (m, 1H), 4.17–4.14 (m, 1H), 3.09 (ddt, J = 14.1, 5.5, 1.5 Hz, 1H), 3.02 (ddt, J = 14.1, 5.6, 1.5 Hz, 1H), 2.72–2.68 (m, 1H), 2.61–2.58 (m, 1H), 1.93 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 142.6, 136.6, 128.6 (2C), 127.5, 127.1 (2C), 116.0, 59.0, 55.3, 49.9, 49.1 ppm. IR ν_{max} (cm^{-1}): 3325, 3084, 3028, 2976, 2924, 2849, 2104, 1637, 1493, 1454, 1371, 1144, 1117, 1074, 1028, 995, 922, 764, 702, 628, 603, 538. HRMS (ESI-TOF) calculated for 230.12879 [M+H$^+$] 223,18049, found 230.12779.

4.14. 4-(butylamino)-1-diazo-4-phenylbutan-2-one **(11)**

Yield: 71%. Yellow oil. R_f = 0.27 (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5H), 5.17 (s, 1H), 4.10 (dd, J = 8.1, 5.0 Hz, 1H), 2.67–2.69 (m, 1H), 2.59–2.57 (m, 1H), 2.46–2.38 (m, 2H), 1.42 (q, J = 7.3 Hz, 2H), 1.30–1.26 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 143.1, 128.6 (2C), 127.4, 127.0 (2C), 59.9, 55.3, 49.2, 47.4, 32.3, 20.4, 14.0 ppm. IR ν_{max} (cm^{-1}): 3327, 3084, 3063, 3028, 2957, 2928, 2872, 2858, 2104, 1639, 1493, 1454, 1367, 1144, 1074, 1028, 980, 945, 914, 762, 702, 631, 592. HRMS (ESI-TOF) calculated for $C_{14}H_{20}N_3O$ [M+H$^+$] 246.1606, found 246.1589.

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4.15. 4-(benzylamino)-1-diazoheptan-2-one **(12)**

Yield: 94%. Yellow oil. $R_f = 0.28$ (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 5.30 (s, 1H), 3.78 (s, 2H), 3.05 (q, $J = 6.0$ Hz, 1H), 2.44 (s, 2H), 1.48–1.33 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 140.6, 128.4 (2C), 128.2 (2C), 126.9, 55.1, 54.5, 51.2, 45.7, 36.7, 19.0, 14.2 ppm. IR ν_{max} (cm^{-1}): 3325, 3086, 3073, 3028, 2959, 2930, 2872, 2102, 1636, 1495, 1454, 1362, 1202, 1149, 1072, 1038, 980, 910, 737, 700, 584, 495. HRMS (ESI-TOF) calculated for $C_{14}H_{20}N_3O$ [M+H$^+$] 246.1606, found 246.1602.

4.16. 4-(allylamino)-1-diazoheptan-2-one **(13)**

Yield: 91%. Yellow oil. $R_f = 0.29$ (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93–5.83 (m, 1H), 5.35 (s, 1H), 5.20–5.15 (m, 1H), 5.10–5.06 (m, 1H), 3.24 (dt, $J = 6.0$, 1.3 Hz, 2H), 3.12–2.97 (m, 1H), 2.41 (s, 2H), 1.46–1.32 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 137.0, 115.9, 55.2, 54.3, 49.7, 45.6, 36.6, 19.0, 14.2 ppm. IR ν_{max} (cm^{-1}): 3325, 3080, 2959, 2930, 2872, 2104, 1636, 1466, 1367, 1148, 995, 920, 748, 702, 635, 576. HRMS (ESI-TOF) calculated for $C_{10}H_{18}N_3O$ [M+H$^+$] 196.1450, found 196.1445.

4.17. 4-(butylamino)-1-diazoheptan-2-one **(14)**

Yield: 71%. Yellow oil. TLC: $R_f = 0.10$ (60% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 1H), 3.01–2.96 (m, 1H), 2.57 (td, $J = 7.0$, 2.9 Hz, 2H), 2.40 (s, 2H), 1.47–1.41 (m, 4H), 1.36–1.32 (m, 4H), 0.93–0.90 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4, 55.0, 46.8, 36.8 (2C), 32.6 (2C), 20.6, 19.1, 14.2, 14.0 ppm. IR ν_{max} (cm^{-1}): 3318, 3081, 2957, 2928, 2873, 2098, 1632, 1465, 1360, 1144, 977, 746. HRMS (ESI-TOF) calculated for $C_{11}H_{22}N_3O$ [M+H$^+$] 212.1763, found 212.1762.

4.18. 5-((tert-butyldimethylsilyl)oxy)-4-((4-methoxybenzyl)amino) -1-diazopentan-2-one **(15)**

Yield: 79%. Yellow oil. TLC: $R_f = 0.20$ (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.31 (s, 1H), 3.79 (s, 3H), 3.73 (s, 2H), 3.64 (dd, $J = 10.0$, 5.2 Hz, 1H), 3.57 (dd, $J = 10.0$, 5.1 Hz, 1H), 3.18–3.06 (m, 1H), 2.46 (s, 2H), 1.80 (s, 1H), 0.89 (s, 9H), 0.05 (d, $J = 1.7$ Hz, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1, 158.8, 132.7, 129.4 (2C), 113.9 (2C), 64.3, 56.2, 55.4, 51.0, 26.0 (3C), 18.4, −5.3 (2C) ppm. IR ν_{max} (cm^{-1}): 3325, 3093, 2951, 2928, 2899, 2854, 2102, 1637, 1612, 1585, 1512, 1466, 1360, 1300, 1248, 1176, 1105, 1038, 1007, 837, 779. HRMS (ESI-TOF) calculated for $C_{19}H_{31}N_3O_3Si$ [M+H$^+$] 378.2213, found 378.2206.

4.19. 4-(benzylamino)-5-((tert-butyldimethylsilyl)oxy)-1-diazopentan-2-one **(16)**

Yield: 79%. Yellow oil. $R_f = 0.25$ (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.31 (m, 4H), 7.25–7.23 (m, 1H), 5.29 (s, 1H), 3.80 (s, 2H), 3.65 (dd, $J = 10.0$, 5.2 Hz, 1H), 3.58 (dd, $J = 10.0$, 5.2 Hz, 1H), 3.12 (q, $J = 6.0$ Hz, 1H), 2.47 (s, 2H), 1.86 (s, 1H), 0.89 (s, 9H), 0.05 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9, 140.4, 128.4 (2C), 128.1 (2C), 126.9, 64.2, 56.1, 55.0, 51.5, 43.1, 25.9 (3C), 18.2, −5.4 (2C) ppm. IR ν_{max} (cm^{-1}): 3327, 3084, 3063, 3026, 2953, 2928, 2895, 2856, 2103, 1641, 1495, 1470, 1360, 1256, 1099, 1028, 1007, 937, 837, 814, 779, 735, 698, 611, 490. HRMS (ESI-TOF) calculated for $C_{18}H_{30}N_3O_2Si$ [M+H$^+$] 348.2107, found 348.2096.

4.20. 4-(benzylamino)-4-(4-chlorophenyl)-1-diazobutan-2-one **(17)**

Yield: 85%. Yellow oil. $R_f = 0.20$ (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 9H), 5.14 (s, 1H), 4.15–4.12 (m, 1H), 3.61 (d, $J = 13.2$ Hz, 1H), 3.52 (d, $J = 13.2$ Hz, 1H), 2.66–2.65 (m, 1H), 2.56–2.54 (m, 1H), 2.00 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.6, 141.2, 140.0, 133.1, 128.8 (2C), 128.6 (2C), 128.4 (2C), 128.1 (2C), 127.0, 58.4, 55.4, 51.4, 49.0 ppm. HRMS (ESI-TOF) calculated for $C_{17}H_{17}ClN_3O$ [M+H$^+$] 314.1060, found 314.1053.

4.21. 4-(benzylamino)-1-diazo-4-(4-methoxyphenyl)butan-2-one **(18)**

Yield: 82%. Yellow oil. $R_f = 0.22$ (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 5H), 7.26–7.24 (m, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 5.13 (s, 1H), 4.09 (dd, $J = 8.2$, 5.1 Hz, 1H), 3.81 (s, 3H), 3.62 (d, $J = 13.2$ Hz, 1H), 3.53 (d, $J = 13.2$ Hz, 1H), 2.72–2.67 (m, 1H), 2.59–2.56 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 159.0, 140.3, 134.6, 128.3 (2C), 128.2 (2C), 128.2 (2C), 126.9, 114.0 (2C), 58.5, 55.3, 51.4, 49.4 ppm. HRMS (ESI-TOF) calculated for $C_{18}H_{20}N_3O_2$ [M+H$^+$] 310.1556, found 310.1556.

4.22. 4-(benzylamino)-1-diazo-4-(4-nitrophenyl)butan-2-one **(19)**

Yield: 90%. Yellow oil. $R_f = 0.17$ (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, $J = 8.7$ Hz, 2H), 7.57 (d, $J = 8.7$ Hz, 2H), 7.32–7.29 (m, 2H), 7.26–7.23 (m, 3H), 5.18 (s, 1H), 4.29 (dd, $J = 8.5$, 4.8 Hz, 1H), 3.61 (d, $J = 13.2$ Hz, 1H), 3.54 (d, $J = 13.2$ Hz, 1H), 2.72–2.67 (m, 1H), 2.59–2.56 (m, 1H), 2.07 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.9, 150.6, 147.4, 139.6, 128.5 (2C), 128.2 (2C), 128.1 (2C), 127.2, 124.0 (2C), 58.5, 55.6, 51.6, 48.4 ppm. IR ν_{max} (cm^{-1}): 3327, 3105, 3065, 3028, 2924, 2851, 2104, 1636, 1605, 1520, 1495, 1454, 1371, 1346, 1200, 1178, 1143, 1109, 1028, 1014, 982, 945, 856, 752, 737, 700, 644, 584, 496. HRMS (ESI-TOF) calculated for $C_{17}H_{17}N_4O_3$ [M+H$^+$] 325.1301, found 325.1291.

4.23. 4-(allylamino)-1-diazo-4-(pyridin-3-yl)butan-2-one **(20)**

Yield 84%. Yellow oil. $R_f = 0.15$ (50% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, $J = 2.0$ Hz, 1H), 8.52 (dd, $J = 4.8$, 1.6 Hz, 1H), 7.71 (dt, $J = 7.8$, 1.9 Hz, 1H), 7.29–7.26 (m, 1H), 5.87–5.79 (m, 1H), 5.23 (s, 1H), 5.14–5.07 (m, 2H), 4.23 (dd, $J = 8.5$, 4.9 Hz, 1H), 3.11–3.00 (m, 2H), 2.76–2.71 (m, 1H), 2.62–2.59 (m, 1H), 2.19 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 149.3, 149.1, 138.1, 136.2, 135.0, 123.7, 116.5, 56.6, 55.7, 50.0, 48.5 ppm. IR ν_{max} (cm^{-1}): 3317, 3078, 3036, 2976, 2922, 2818, 2104, 1634, 1477, 1425, 1373, 1144, 1026, 995, 924, 808, 715, 633, 613, 553, 504, 490. HRMS (ESI-TOF) calculated for $C_{12}H_{15}N_4O$ [M+H$^+$] 231.12404, found 231.12311.

4.24. 4-(Furan-2-yl)-4-((4-methoxybenzyl)amino)-1-diazobutan-2-one **(21)**

Yield: 74%. Yellow oil. TLC: $R_f = = 0.10$ (35% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, $J = 1.8$, 0.8 Hz, 1H), 7.22–7.15 (m, 2H), 6.89–6.80 (m, 2H), 6.33 (dd, $J = 3.2$, 1.8 Hz, 1H), 6.20 (d, $J = 3.2$ Hz, 1H), 5.21 (s, 1H), 4.20 (dd, $J = 7.3$, 6.3 Hz, 1H), 3.79 (s, 3H), 3.67 (d, $J = 12.9$ Hz, 1H), 3.54 (d, $J = 12.9$ Hz, 1H), 2.85–2.64 (m, 2H), 1.89 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 158.7, 154.9, 141.8, 132.0 (2C), 129.4, 113.8 (2C), 110.1, 107.1, 55.3 (2C), 52.2, 50.6, 46.5 ppm. IR ν_{max} (cm^{-1}): 3314, 3099, 2955, 2928, 2836, 2098, 1642, 1612, 1593, 1511, 1463, 1360, 1300, 1245, 1177, 1148, 1032, 1016, 814, 742. HRMS (ESI-TOF) calculated for $C_{16}H_{18}N_3O_3$ [M+H$^+$] 300.1348, found 300.1343.

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4.25. General procedure for one-pot N–H insertion

To a 10 mL round-bottom flask equipped with a magnetic stir-bar and contained the diazoketone **1** (20.0 mg, 0.116 mmol,. 1.0 equiv) and 232 mL of DCM, was added 38 μL of benzylamine (37.3 mg, 0.348 mmol, 3.0 equiv) at room temperature. The reaction was stirred at room temperature for 24 h. After this time, 2.0 mL of DCM and 5.5 mg Cu(hfacac)$_2$ (0.0116 mmol,. 0.1 equiv) were added to this solution at room temperature. The reaction mixture was stirred at this temperature for 30 min (the reaction proceeded with N_2 release). After the reaction time, the solvent was partially removed under reduced pressure in a rotary evaporator and the crude material was purified by flash chromatography employing an eluent system 9:1 hexanes:EtOAc and the 3-pyrrolidinone **22** was obtained in 50% yield (14.6 mg, 0.058 mmol) as an orange oil.

4.26. 1-Benzyl-5-phenylpyrrolidin-3-one **(22)**

Yield: 50%. Yellow oil. R_f = 0.27 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2H), 7.41–7.38 (m, 2H), 7.33–7.23 (m, 6H), 3.96 (d, J = 13.2 Hz, 1H), 3.86 (dd, J = 10.6, 6.3 Hz, 1H), 3.45 (d, J = 17.5 Hz, 1H), 3.16 (d, J = 13.2 Hz, 1H), 2.75–2.70 (m, 2H), 2.44 (dd, J = 17.5, 10.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4, 140.9, 137.9, 129.0 (2C), 128.6 (2C), 128.5 (2C), 128.1, 127.6 (2C), 127.4, 66.9, 61.6, 57.7, 48.2 ppm. IR ν_{max} (cm^{-1}): 3086, 3063, 3030, 2918, 2833, 2795, 1757, 1672, 1603, 1495, 1454, 1429, 1400, 1364, 1310, 1234, 1198, 1178, 1136, 1074, 1028, 970, 893, 860, 758, 700, 636, 582, 484, 459.

4.27. 1-Benzyl-5-(((tert-butyldimethylsilyl)oxy)methyl) pyrrolidin-3-one **(24)**

Yield: 51%. Yellow oil. R_f = 0.26 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7. 25 (m, 5H), 4.19 (d, J = 13.2 Hz, 1H), 3.84 (dd, J = 10.5, 4.5 Hz, 1H), 3.78 (dd, J = 10.4, 4.2 Hz, 1H), 3.57 (d, J = 13.2 Hz, 1H), 3.28 (d, J = 17.4 Hz, 1H), 3.24–3.20 (m, 1H), 2.84 (d, J = 17.4 Hz, 1H), 2.55 (dd, J = 18.2, 7.2 Hz, 1H), 2.29 (dd, J = 18.2, 7.3 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.6, 138.3, 128.5 (2C), 128.4 (2C), 127.2, 65.1, 62.0, 61.8, 58.1, 41.7, 25.8 (3C), 18.2, −5.4, −5.5 ppm. IR ν_{max} (cm^{-1}): 3063, 3030, 2955, 2930, 2897, 2857, 1759, 1716, 1682, 1495, 1472, 1458, 1443, 1362, 1256, 1186, 1096, 1009, 839, 779, 742, 700, 669, 636, 517. HRMS (ESI-TOF) calculated for $C_{18}H_{30}NO_2Si$ [M+H$^+$] 320.2046, found 320.2043.

4.28. 1-Benzyl-5-propylpyrrolidin-3-one **(26)**

Yield: 51%. Yellow oil. R_f = 0.25 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.24 (m, 5H) 4.22 (d, J = 13.1 Hz, 1H), 3.26–3.23 (m, 2H), 2.90–2.86 (m, 1H), 2.62 (d, J = 17.5, 1H), 2.48 (dd, J = 17.5, 6.3 Hz, 1H), 2.16 (dd, J = 18.0, 10.1 Hz, 1H), 1.98–1.90 (m, 1H), 1.51–1.32 (m, 3H), 0.98 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7, 138.2, 128.8 (2C), 128.6 (2C), 127.4, 62.2, 62.0, 57.7, 43.8, 35.1, 19.2, 14.5 ppm. IR ν_{max} (cm^{-1}): 3086, 3063, 3030, 2959, 2932, 2872, 2797, 1757, 1495, 1454, 1402, 1371, 1337, 1296, 1252, 1186, 1148, 1070, 1028, 953, 741, 700, 638, 521. HRMS (ESI-TOF) calculated for $C_{14}H_{20}NO$ [M+H$^+$] 218.15394, found 218.15306.

4.29. 1-Allyl-5-phenylpyrrolidin-3-one **(28)**

Yield: 47%. Yellow oil. R_f = 0.24 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.38–7.29 (m, 3H), 5.84–5.76 (m, 1H), 5.19–5.15 (m, 1H), 5.13–5.10 (m, 1H), 3.77 (dd, J = 10.6, 6.3 Hz, 1H), 3.64 (d, J = 17.4 Hz, 1H), 3.37 (dd, J = 13.7, 4.9 Hz, 1H), 2.77 (d, J = 17.5 Hz, 1H), 2.73–2.68 (m, 2H), 2.41 (dd, J = 18.2, 10.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.5, 140.6, 134.4, 128.8 (2C), 128.0, 127.4 (2C), 117.6, 66.6, 61.6, 56.1, 48.0 ppm. IR ν_{max} (cm^{-1}): 3065, 3030, 2978, 2922, 2799, 2766, 1761, 17151 1697, 1690, 1607, 1495, 1456, 1420, 1369, 1287, 1200, 1179, 1134, 1074, 995, 758, 702, 581. HRMS (ESI-TOF) calculated for $C_{13}H_{16}NO$ [M+H$^+$] 202.12264, found 202.12192.

4.30. 5-(Furan-2-yl)-1-(4-methoxybenzyl)pyrrolidin-3-one **(30)**

Yield: 44%. Yellow oil. TLC: R_f = 0.45 (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, J = 1.8, 0.8 Hz, 1H), 7.20–7.13 (m, 2H), 6.90–6.76 (m, 2H), 6.38 (dd, J = 3.2, 1.8 Hz, 1H), 6.33 (dd, J = 3.2, 0.8 Hz, 1H), 4.10 (t, J = 7.5 Hz, 1H), 3.82 (d, J = 13.1 Hz, 1H), 3.79 (s, 3H), 3.35 (d, J = 13.1 Hz, 1H), 3.31 (d, J = 17.3 Hz, 1H), 2.86 (d, J = 17.3 Hz, 1H), 2.70 (d, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.2, 158.9, 153.0, 142.5, 130.0, 129.5, 129.3, 114.4, 113.8, 110.2, 108.4, 60.2, 58.3, 56.4, 55.3, 43.8 ppm. IR ν_{max} (cm^{-1}): 3137, 2998, 2953, 2932, 2836, 1758, 1612, 1593, 1513, 1463, 1346, 1300, 1249, 1177, 1150, 1034, 820, 744. HRMS (ESI-TOF) calculated for $C_{16}H_{18}N_3O$ [M+H$^+$] 272.1287, found 272.1283.

4.31. 1-Butyl-5-propylpyrrolidin-3-one **(32)**

Yield: 49%. Yellow oil. TLC: R_f = 0.40 (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49 (d, J = 17.4 Hz, 1H), 3.00–2.94 (m, 1H), 2.71–2.67 (m, 1H), 2.61 (d, J = 17.4 Hz, 1H), 2.46 (dd, J = 18.0, 6.2 Hz, 1H), 2.14–2.07 (m, 2H), 1.83–1.80 (m, 1H), 1.49–1.34 (m, 7H), 0.97–0.92 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 62.6, 62.3, 53.5, 43.8, 35.1, 30.3, 20.6, 19.3, 14.3, 13.9 ppm. IR ν_{max} (cm^{-1}): 2959, 2930, 2873, 1760, 1667, 1459, 1379, 1253, 1187, 1144, 746. HRMS (ESI-TOF) calculated for $C_{11}H_{22}NO$ [M+H$^+$] 184.1701, found 184.1699.

4.32. 1-Benzyl-5-(4-chlorophenyl)pyrrolidin-3-one **(34)**

Yield: 47%. Yellow oil. TLC: R_f = 0.27 (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.32–7.29 (m, 2H), 7.26–7.22 (m, 3H), 3.92 (d, J = 13.2 Hz, 1H), 3.85 (dd, J = 10.5, 6.4 Hz, 1H), 3.45 (d, J = 17.5 Hz, 1H), 3.17 (d, J = 13.2 Hz, 1H), 2.76–2.69 (m, 2H), 2.38 (dd, J = 17.5, 10.5 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 139.5, 137.5, 133.7, 129.1 (2C), 128.8 (2C), 128.5 (2C), 128.4 (2C), 127.4, 66.0, 61.4, 57.5, 47.9 ppm. IR ν_{max} (cm^{-1}): 2978, 2953, 2852, 1758, 1671, 1462, 1231, 1198, 1022, 891, 701. HRMS (ESI-TOF) calculated for $C_{17}H_{17}NOCl$ [M+H$^+$] 286.0999, found 286.0999.

4.33. 5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxybenzyl)pyrrolidin-3-one **(36)**

Yield: 50%. Yellow oil. TCC: Rf = 0.20 (15% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.12 (d, J = 13.1 Hz, 1H), 3.84–3.77 (m, 5H), 3.52 (d, J = 13.1 Hz, 1H), 3.26 (d, J = 17.4 Hz, 1H), 3.28–3.18 (m, 1H), 2.82 (d, J = 17.4 Hz, 1H), 2.54 (dd, J = 18.2, 7.2 Hz, 1H), 2.28 (dd, J = 18.2, 7.3 Hz, 1H), 0.90 (s, 9H), 0.07 (d, J = 7.5 Hz, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.6, 158.8, 130.2, 129.7 (2C), 113.8 (2C), 65.1, 61.9, 61.7, 57.4, 55.3, 41.7, 25.8 (3C), 18.2, −5.4 (2C) ppm. IR ν_{max} (cm^{-1}): 2955, 2930, 2899, 2857, 1759, 1612, 1514, 1472, 1464, 1362, 1302, 1252, 1180, 1105, 1038, 1010, 939, 839, 779, 702, 636, 584. HRMS (ESI-TOF) calculated for $C_{19}H_{32}NO_3Si$ [M+H$^+$] 350.2151, found 350.2144.

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4.34. General procedure for the one-pot photochemical Wolff rearrangement

To a vial of 4 mL contained an ethereal solution of diazoketone **1** (15.0 mg, 0.087 mmol, 1.0 equiv. in 87 μL of anhydrous ethyl ether) was added 29 μL of benzylamine (28.5 mg, 0.261 mmol, 3.0 equiv) at room temperature. The reaction was stirred at this temperature for 24 h. Then, 3.2 mL of anhydrous ethyl ether was added and the solution was transferred to a quartz cuvette of 1 cm light path. The reaction mixture was irradiated with an Osram 150 Xenon arc lamp for five hours under magnetic stirring at room temperature (gas evolution was observed during the first four hours). Then, the solvent was removed under reduced pressure in a rotary evaporator and the crude material was purified by flash chromatography employing as eluent system a mixture of hexanes:EtOAc (gradient elution - 8:2 to 6:4). The pyrrolidinone **19** was obtained in 80% (17.5 mg, 0.069 mmol) yield as a yellow oil. Osram 150 Xenon arc lamp can also be replaced by an 18 W white LED lamp. In this case, irradiation for 3 days is necessary.

4.35. 1-Benzyl-5-phenylpyrrolidin-2-one **(23)**

Yield: 80% (68% using the LED lamp). Yellow oil. $R_f = 0.30$ (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.26 (m, 6H), 7.15–7.13 (m, 2H), 7.13–7.07 (m, 2H), 5.12 (d, $J = 14.6$ Hz, 1H), 4.41 (dd, $J = 8.1$, 5.5 Hz, 1H), 3.48 (d, $J = 14.6$, 1H), 2.68–2.61 (m, 1H), 2.53–2.48 (m, 1H), 2.44–2.36 (m, 1H), 1.93–1.86 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 140.9, 136.4, 129.0 (2C), 128.5 (2C), 128.5 (2C), 128.1, 127.5, 126.7 (2C), 61.3, 44.3, 30.3, 28.3 ppm. IR ν_{max} (cm^{-1}): 3063, 3026, 3005, 2970, 2941, 2897, 1680, 1634, 1495, 1456, 1437, 1412, 1371, 1356, 1306, 1288, 1256, 1217, 1200, 1167, 1153, 1078, 1028, 970, 708, 677, 596, 555.

4.36. 1-Allyl-5-phenylpyrrolidin-2-one **(25)**

Yield: 55%. Yellow oil. $R_f = 0.29$ (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.00 (m, 5H), 5.71–5.61 (m, 1H), 5.12–5.10 (m, 1H), 4.99–4.95 (m, 1H), 4.65–4.62 (m, 1H), 4.40 (dd, $J = 15.2$, 4.6 Hz, 1H), 3.10–3.04 (m, 1H), 2.63–2.46 (m, 3H), 1.96–1.88 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 141.0, 132.0, 129.0 (2C), 128.1, 126.6 (2C), 118.1, 61.6, 43.3, 30.2, 28.3 ppm. IR ν_{max} (cm^{-1}): 3082, 3065, 3030, 2970, 2922, 2855, 1693, 1547, 1495, 1456, 1439, 1410, 1366, 1285, 1258, 1246, 1150, 1078, 993, 928, 829, 770, 704, 636, 584. HRMS (ESI-TOF) calculated for $C_{13}H_{16}NO$ [M+H$^+$] 202.12264, found 202.12184.

4.37. 1-Benzyl-5-(((tert-butyldimethylsilyl)oxy)methyl) pyrrolidin-2-one **(27)**

Yield: 65%. Yellow oil. Rf = 0.29 (30% EtOAc/hexanes). 1H NMR (500 MHz, CDCl3) δ 7.31–7.24 (m, 5H), 5.00 (d, $J = 15.0$ Hz, 1H), 4.04 (d, $J = 15.0$ Hz, 1H), 3.68–3.66 (m, 1H), 3.54–3.49 (m, 2H), 2.57–2.50 (m, 1H), 2.40–2.33 (m, 1H), 2.06–2.01 (m, 1H), 1.92–1.86 (m, 1H), 0.88 (s, 9H). 0.03 (s, 6H) ppm. 13C NMR (126 MHz, CDCl3) δ 175.6, 137.0, 128.6 (2C), 128.0 (2C), 127.4, 63.5, 58.4. 44.6, 30.4, 25.8 (3C), 21.5, 18.2, −5.52 (2C) ppm. IR νmax (cm-1): 3030, 2955, 2930, 2895, 2857, 1694, 1497, 1472, 1445, 1418, 1360, 1254, 1180, 1115, 1078, 1030, 1007, 974, 939, 883, 814, 779, 702, 650, 507.

4.38. 1-Benzyl-5-propylpyrrolidin-2-one **(29)**

Yield: 81%. Yellow oil. $R_f = 0.32$ (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 4.98 (d, $J = 15.0$ Hz, 1H), 3.96 (d, $J = 15.0$ Hz, 1H), 3.44–3.40 (m, 1H), 2.51–2.35 (m, 2H), 2.12–2.05 (m, 1H), 1.71–1.64 (m, 2H), 1.35–1.27 (m, 2H), 1.22–1.17 (m, 1H), 0.89 (t, $J = 7.3$ Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 136.8, 128.6 (2C), 128.0 (2C), 127.4, 56.8, 44.1, 35.0, 30.3, 24.0, 17.7, 14.1 ppm. IR ν_{max} (cm^{-1}): 3063, 3030, 2961, 2932, 2872, 1688, 1495, 1454, 1420, 1371, 1313, 1254, 1204, 1177, 1084, 1030, 920, 704, 633, 606, 511.

4.39. 5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxybenzyl)pyrrolidin-2-one **(31)**

Yield: 48%. Yellow oil. TCC: $R_f = 0.25$ (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 4.94 (d, $J = 14.8$ Hz, 1H), 3.97 (d, $J = 14.8$ Hz, 1H), 3.79 (s, 3H), 3.67 (dd, $J = 10.4$, 3.7 Hz, 1H), 3.55–3.48 (m, 2H), 2.57–2.48 (m, 1H), 2.38–2.30 (m, 1H), 2.04–1.98 (m, 1H), 1.91–1.86 (m, 1H), 0.88 (s, 9H), 0.03 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 159.1, 129.5 (2C), 129.2, 114.1 (2C), 63.6, 58.3, 55.4, 44.1, 30.6, 26.0 (3C), 21.6, 18.3, −5.4 (2C). ppm. IR ν_{max} (cm^{-1}): 2953, 2930, 2856, 1682, 1612, 1513, 1461, 1418, 1247, 1177, 1113, 1032, 837, 777. HRMS (ESI-TOF) calculated for $C_{19}H_{32}NO_3Si$ [M+H$^+$] 350.2151, found 350.2144.

4.40. 1-Benzyl-5-(4-chlorophenyl)pyrrolidin-2-one **(33)**

Yield: 42%. Yellow oil. TLC: $R_f = 0.30$ (40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, $J = 8.5$ Hz, 2H), 7.28–7.26 (m, 3H), 7.08–7.04 (m, 4H), 5.10 (d, $J = 14.6$ Hz, 1H), 4.37 (dd, $J = 8.0$, 5.7 Hz, 1H), 3.47 (d, $J = 14.6$ Hz, 1H), 2.66–2.59 (m, 1H), 2.54–2.37 (m, 2H), 1.89–1.82 (m, 1H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 139.4, 136.1, 133.9, 129.2 (2C), 128.6 (2C), 128.5 (2C), 128.1 (2C), 127.6, 60.7, 44.4, 30.2, 28.2 ppm. IR ν_{max} (cm^{-1}): 3029, 2955, 2924, 2854, 1688, 1492, 1407, 1269, 1253, 1152, 1088, 1014, 822, 703. HRMS (ESI-TOF) calculated for $C_{17}H_{17}NOCl$ [M+H$^+$] 286.0999, found 286.0995.

4.41. 5-(Furan-2-yl)-1-(4-methoxybenzyl)pyrrolidin-2-one **(35)**

Yield: 46%. Yellow oil. TLC: Rf = 0.15 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, $J = 1.8$, 0.7 Hz, 1H), 7.10 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 6.34 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.19 (dd, $J = 3.2$, 0.5 Hz, 1H), 4.94 (d, $J = 14.6$ Hz, 1H), 4.48 (dd, $J = 8.3$, 4.9 Hz, 1H), 3.79 (s, 3H), 3.53 (d, $J = 14.6$ Hz, 1H), 2.71–2.64 (m, 1H), 2.50–2.42 (m, 1H), 2.27–2.16 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 159.0, 152.7, 142.8, 129.7 (2C), 128.6, 113.9 (2C), 110.2, 108.3, 55.3, 54.4, 43.8, 30.3, 24.5 ppm. IR ν_{max} (cm^{-1}): 2955, 2926, 2838, 1682, 1612, 1513, 1440, 1414, 1245, 1175, 1152, 1032, 1012, 905, 818, 744. HRMS (ESI-TOF) calculated for $C_{16}H_{17}N_3ONa$ [M+Na$^+$] 294.1106, found 294.1110.

4.42. 1-Butyl-5-propylpyrrolidin-2-one **(37)**

Yield: 54%. Yellow oil. TLC: $R_f = 0.25$ (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65–3.56 (m, 2H), 2.89 (ddd, $J = 13.8$, 8.8, 5.0 Hz, 1H), 2.39–2.26 (m, 2H), 2.16–2.04 (m, 1H), 1.69–1.64 (m, 2H), 1.52–1.29 (m, 7H), 0.98–0.91 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 57.4, 39.9, 35.4, 30.4, 29.5, 24.2, 20.2, 18.0, 14.2, 13.8 ppm. IR ν_{max} (cm^{-1}): 2957, 2928, 2873, 1667, 1457, 1422, 1375, 1315, 1284, 1261, 1193, 1131, 1113, 917, 820, 742, 661. HRMS (ESI-TOF) calculated for $C_{11}H_{22}NO$ [M+H$^+$] 184.1701, found 184.1700.

4.43. General procedure for the Julia-Kocienski olefination

To a 25 mL round-bottom flask equipped with a magnetic stir-bar and containing a solution of 5-(ethylsulfonyl)-1-phenyl-1*H*-tetrazole (0.69 mmol, 1.2 equiv., 198.0 mg in 5.0 mL of THF) at −78 °C, was added dropwise a solution of LDA (1.5 M in THF, 0.69 mmol, 0.46 mL). The mixture was stirred at −78 °C for 10 min. After this time, a solution of pyrrolidin-3-one (**36**) (0.69 mmol, 1.0

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equiv., 240.0 mg in 0.7 mL of THF) was added and the reaction mixture was stirred at this temperature for 1 h. The mixture was quenched with saturated NH_4Cl (20 mL), extracted using CH_2Cl_2 (3 × 20 mL) and dried over $MgSO_4$. The crude material was purified by flash chromatography employing a mixture of 9:1 hexanes:EtOAc as eluent. The ethylidene pyrrolidine **38** was obtained in an inseparable 3:1 *E/Z* ratio (135.0 mg, 0.37 mmol, 54%) as a yellow oil.

4.44. (E)-2-(((tert-butyldimethylsilyl)oxy)methyl)-4-ethylidene-1-(4-methoxybenzyl)pyrrolidine (38)

Yield: 54%. Yellow oil. TLC: $R_f = 0.30$ (20% EtOAc/hexanes). Ratio 3:1 *E/Z*. *E isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.23 (m, 2H), 6.84–6.82 (m, 2H), 5.23–5.21 (m, 1H), 4.15 (d, J = 12.8 Hz, 1H), 3.85–3.80 (m, 1H), 3.79 (s, 3H), 3.62–3.58 (m, 1H), 3.37–3.30 (m, 1H) 3.23 (d, J = 12.8 Hz, 1H), 2.85–2.75 (m, 1H), 2.58–2.53 (m, 1H), 2.25–2.11 (m, 1H), 1.56–1.53 (m, 3H), 1.47 (d, J = 6.8 Hz, 1H), 0.90 (s, 9H), 0.06 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 137.5, 131.6, 130.0 (2C), 114.4, 113.6 (2C), 67.0, 65.5, 60.1, 59.0, 55.2, 36.3, 32.5, 26.0 (3C), 18.3, 14.3, −5.3 (2C) ppm. *Z isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 6.86–6.84 (m, 2H), 5.23–5.21 (m, 1H), 4.15 (d, J = 12.8 Hz, 1H), 3.85–3.80 (m, 1H), 3.80 (s, 3H), 3.59–3.49 (m, 2H), 3.37–3.32 (m, 1H), 2.85–2.75 (m, 1H), 2.58–2.53 (m, 1H), 2.22–2.11 (m, 1H), 1.47–1.45 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 137.5, 131.6, 130.0 (2C), 114.4, 113.6 (2C), 67.0, 65.5, 60.1, 59.0, 55.2, 36.3, 32.5, 26.0 (3C), 18.3, 14.3, −5.3 (2C) ppm. IR ν_{max} (cm^{-1}):. HRMS (ESI-TOF) calculated for $C_{21}H_{36}NO_2Si$ [M+H$^+$] 362.2515, found 362.2511.

4.44.1. Barmumycin synthesis

To a 10 mL round-bottom flask equipped with a magnetic stir-bar and containing a solution of pyrrolidine **38** (80.0 mg, 0.221 mmol, 1.0 equiv., 3:1 *E/Z* mixture) in dry DCM (480 μL), was slowly added a solution of 1-chloroethyl chloroformate (49 μL, 64.5 mg, 0.442 mmol, 2.0 equiv.) in dry DCM (540 μL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min. After the solvent was removed, the residue containing the chloridrate was dissolved in MeOH and refluxed for 2 h. The reaction was finished by the addition of saturated K_2CO_3 (10 mL), extracted using CH_2Cl_2 (20 × 10 mL) and dried over Na_2SO_4. After removal of the solvent, the crude alcohol was dissolved in dry THF (2.40 mL) and added to the activated vanilic acid [to a solution of vanilic acid (57.5 mg, 0.332 mmol, 1.5 equiv.) and PyBOP (176 mg, 0.332 mmol, 1.5 equiv.) in dry THF (2.40 mL) was added DIPEA (116 μL, 85.8 mg, 0.664 mmol, 3.0 equiv.). The mixture was stirred at ambient temperature for 30 min]. After that, the reaction mixture was stirred at 60 °C for 24 h. The solvent was then removed under reduced pressure and the crude material dissolved in DCM and washed with saturated $NaHCO_3$ and NH_4Cl. After concentration, purification by flash column chromatography with EtOAc afforded barmumycin **39** (16.5 mg, 0.06 mmol, 27% overall yield) as a colorless oil and as an inseparable 3:1 mixture of E/Z isomers. The isomers can be separated only by HPLC as described by Álvarez.[12a]

Yield: 27%. Yellow oil. TLC: $R_f = 0.33$ (5% MeOH/DCM). Ratio 3:1 *E/Z*. *E isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.12 (bs, 1H), 5.34 (bs, 1H), 4.66 (bs, 1H), 4.07–4.20 (m 2H), 3.90 (s, 3H), 3.74 (bs, 2H), 2.69–2.76 (m, 1H), 2.23–2.34 (m, 1H), 1.63 (3H, d, J = 6.8 Hz) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 147.6, 146.5, 134.5, 128.1, 120.8, 117.4, 113.8, 110.4, 67.0, 60.4, 56.1, 54.9, 29.9, 14.3 ppm. *Z isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 5.34–5.42 (m, 1H), 4.64 (bs, 1H), 4.07–4.20 (m 2H), 3.90 (s, 3H), 3.74 (bs, 2H), 2.69–2.76 (m, 1H), 2.27–2.40 (m, 1H), 1.60 (bs, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 147.6, 146.5, 134.5, 128.1, 120.9, 117.4, 113.9, 110.7, 67.0, 60.1, 56.0, 34.2, 29.7, 14.6 ppm. HRMS (ESI-TOF) calculated for $C_{15}H_{19}NO_4$ [M+Na$^+$] 300.1212, found 300.1210.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.05.040.

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