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Direct Access to Cumbersome Aminated Quaternary Centers by Hyperbaric Aza-Michael Additions

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The aza-Michael addition of secondary amines to α,β- or β,β-disubstituted α,β-unsaturated esters was efficiently achieved under high pressure (10–16 kbar) in protic solvents in the absence of any catalyst. The expected cumbersome β-aminoesters bearing a tertiary amine directly connected to a quaternary carbon atom could be isolated in fair to good yields. By using α,β,δ,γ-unsaturated esters (alkyl sorbate), the addition took place regioselectively in a 1,6 manner and afforded the β,γ-unsaturated δ-aminoesters.

Introduction

Coordinating the substitution of quaternary carbon centers remains a thorny issue in organic synthesis, particularly when bulky appendages are to be borne by the new center. In most cases, no general solution is available and the fine-tuning of particular reaction conditions is necessary to achieve the target in acceptable yields and selectivities.[1] Aminated quaternary carbon centers are no exception to this rule, even if they are found in many natural products such as important alkaloids, including, FR901483[2] and (+)-lepadiformine C,[3] and the proteosome inhibitors salinosporamide A, omuralide, and lactacystin.[4] The design of efficient routes to these compounds is far from trivial, and significant difficulties lie in the assembling of the aminated quaternary center. Carbon–nitrogen bond formation by conjugate addition of nitrogen nucleophiles to olefins activated by electron-withdrawing groups, better known as the aza-Michael reaction,[5] offers an efficient route to tertiary centers, exemplified particularly well by the lithium amides.[6] Steric hindrance often restricts the application of the aza-Michael, and thus far, such reactions have not been readily applicable to the creation of quaternary centers. In these cases, the yields of 1,4 adducts become disappointingly low,[7] unless appropriate catalysts are used.[8] In addition, the reversibility of this reaction is enhanced by the bulkiness of the partners; the amenability of C–N bond formation is inversely proportional to the steric bulk of the reactants.[9] The application of high pressure (HP, ≥8–10 kbar) brings a solution to this problem, as HP is known to overcome severe steric impairments. More precisely, it has been established that sterically congested reactions are accelerated by pressure to a greater extent than that predicted by comparison with similar reactions free of steric hindrance, at least for reactions with late transition states.[10] Accordingly, we[11] and others[12] have shown previously that HP facilitates to a large extent the aza-Michael addition to the conjugated double bonds of α,β-unsaturated esters. In this paper, we show that the hyperbaric aza-Michael addition of amines is a good way to assemble quaternary centers substituted with tertiary amines.

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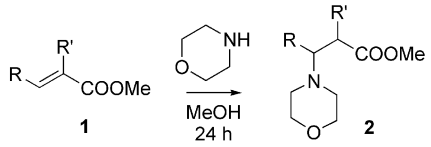
Results and Discussion

Our previous studies had shown that protic solvents such as alcohols are particularly favorable for aza-Michael additions.[11b,13] We first considered the case of β-monosubstituted unsaturated esters that are known to react under thermal or catalytic control, albeit sometimes requiring very harsh conditions. We thus added morpholine to methyl crotonates and cinnamates, taken as model Michael acceptors, and compared the resulting yields of the reactions run by using thermal (uncatalyzed) conditions to those obtained by using HP conditions (Table 1). Even for such simple cases, the application of pressure proved beneficial (Table 1, Entries 1–4), in particular in the case of methyl cinnamate.

However, when the substrate bears two substituents in both the α and β positions to the ester (Table 1, Entry 5), the addition takes place with low diastereoselectivity to afford **2c** as a 3:1 mixture.[14] The origin of this poor stereocontrol is probably related to the N–O–C proton transfer mechanism. First, intramolecular *O*-protonation of the

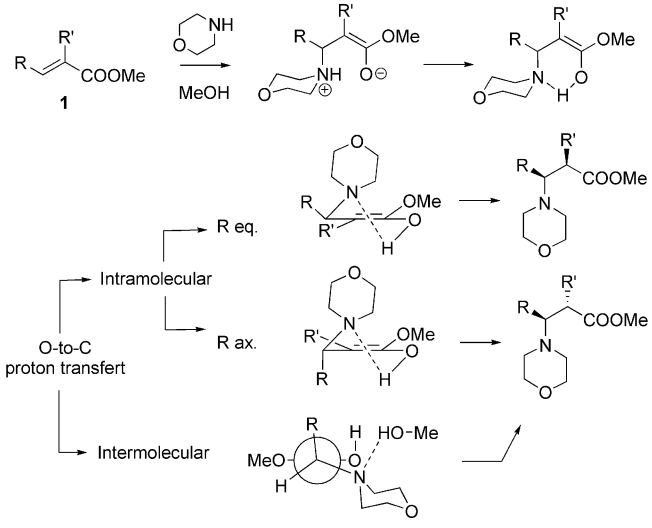
Table 1. Access to amine-substituted tertiary centers by aza-Michael addition to methyl crotonates and cinnamates.



Entry	R	R'	Conditions	Product, % Yield[a]
1	Me	H	1 bar, reflux	**2a**, 82
2	Me	H	12 kbar, r.t.	**2a**, 91[b]
3	Ph	H	1 bar, reflux	**2b**, 0
4	Ph	H	11 kbar, r.t.	**2b**, 62[c]
5	Et	Me	16 kbar, r.t.	**2c**, 70[d]

[a] Isolated yield. [b] After 6 h. [c] Starting ester **1b** was recovered in 27%. [d] Obtained as a mixture (3:1) of two diastereomers.

intermediate enolate by the ammonium is expected. One can thus expect the following enol isomerization to control the stereochemical outcome of the reaction. If a lasting intramolecular interaction between the nitrogen atom and the proton occurs, a semi-rigid six-membered arrangement is likely that can be depicted as two threshold half-chair configurations (Scheme 1). The difference between these two half-chairs lies in the pseudoequatorial or pseudoaxial position of the R group. The more likely equatorial situation would trigger *syn* hydroamination of the double bond. The *anti* diastereomer could then arise either from the pseudoaxial arrangement of R or from an intermolecular protonation (by the solvent) guided by the nitrogen lone pair, pointing *syn* to the R group. Note that the importance of the methanol–amine interaction during the process of the aza-Michael addition has been highlighted in a fine theoretical study by Giessner-Prettre, Dumas, and co-workers.[15]

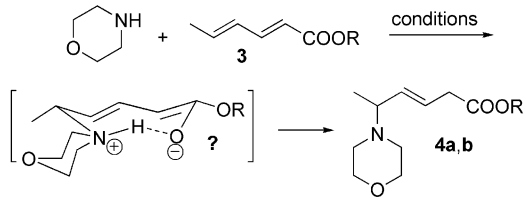


Scheme 1. Proton transfers during the aza-Michael addition on substituted acrylates.

We next tested the reaction of alkyl sorbates with morpholine to evaluate the regioselectivity of reactions involving polyunsaturated systems. It is known for carbon nucleophiles that the controlled addition to electron-deficient dienes can be unpredictable.[16]

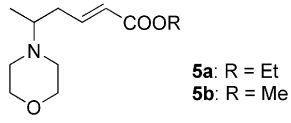
In our hands, δ-aminoester **4a** was obtained regioselectively in good yields after 24 h in EtOH (Table 2, Entries 1 and 2). Because the solvent likely plays a key role in dictating the regioselectivity of the protonation, we repeated the reaction in THF. Interestingly, aminoesters **4a** and **4b** (contaminated with minute amounts of esters **5a** and **5b**) were obtained, suggesting that the source of the proton is, as noted above, the intermediate allylic ammonium species (Table 2). However, proton transfer in this case likely proceeds through an eight-membered transition state that is probably less favored than an intermolecular process. It is interesting to note that (i) no product of 1,2- or 1,4-addition could be observed in these cases and (ii) esters **4a** and **4b** were always obtained selectively as their (*E*) isomers.

Table 2. Aza-Michael addition of morpholine to alkyl sorbates.



Entry	R	Conditions	Product, % Yield[a]
1	Et	1 bar, EtOH, reflux	**4a**, 56
2	Et	12 kbar, EtOH, r.t.	**4a**, 78
3	Et	12 kbar, THF, r.t.	**4a**, 61[b]
4	Me	16 kbar, THF, r.t.	**4b**, 61[b]

[a] Isolated yield. [b] The corresponding (*E*)-α,β-unsaturated δ-aminoesters were also isolated (Entry 3: **5a** 2%; Entry 4: **5b** 8%).

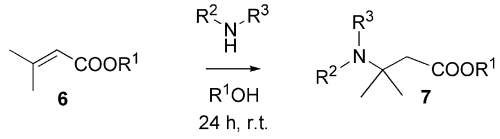


We further pursued this study by using β,β-disubstituted α,β-unsaturated esters as Michael acceptors and decided to use secondary amines to evaluate if the addition could afford highly crowded systems consisting of a quaternary carbon center next to a tertiary amine. The possibility of a retro-Michael addition of the amino group upon release of the pressure posed a serious threat to this strategy. This reversibility is known to limit the utility of hyperbaric oxa-Michael additions, even though its intramolecular version makes feasible a number of interesting synthetic routes.[17]

Initial experiments were run under classical thermal conditions by using senecioic esters **6a** and **6b** (3,3-dimethylacrylate, Table 3) in alcoholic solvent.[18] The data show that even nucleophilic cyclic amines such as morpholine did not react in refluxing MeOH (Table 3, Entry 1). In contrast, these amines added smoothly under pressure (Table 3, Entries 2 and 3). The more sluggish acyclic dialkylamines required an increase in pressure and/or reaction time (Table 3, Entries 4 and 5). At 16 kbar both oxa- and aza-Michael

additions were observed (Table 3, Entry 6) as MeOH behaved under these conditions as a competing nucleophile. At the same pressure, the use of EtOH as solvent (and working with ethyl ester **6b** to avoid transesterification) afforded β-aminoesters **7c** and **7d** in moderate yields (Table 3, Entry 5). Interestingly, the use of *N*,*N*,*N*′-trimethylethylenediamine as nucleophile led to satisfying yields even at 10 kbar (Table 3, Entry 7). In contrast, hexamethyldisilazane (HMDS) did not react at all with **6** under the same conditions (Table 3, Entry 8). The use of ethyl β-methylcinnamate [i.e. (*E*)-ethyl 3-phenylbut-2-enoate] instead of senecioates was also attempted. However, the only reaction observed was the conversion of the ester into the corresponding unsaturated amide, as a result of 1,2-addition of morpholine, in 26% yield (together with 68% starting material).

Table 3. Synthesis of amine-substituted quaternary centers by hyperbaric aza-Michael addition on alkyl senecioates.



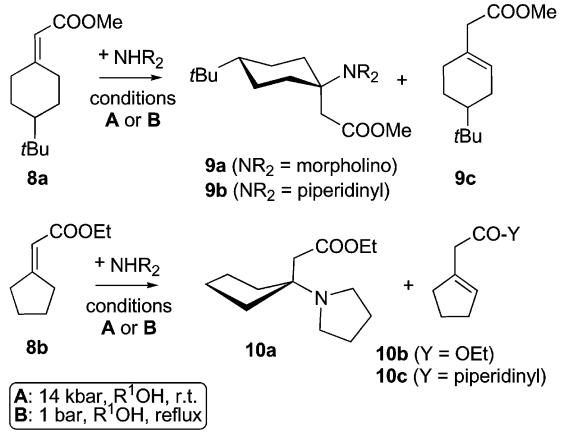
Entry	R^1	R^2	R^3	*P* [kbar]	Product, % Yield[a]
1	Me	$CH_2CH_2OCH_2CH_2$		10^{-3}	– [b]
2	Me	$CH_2CH_2OCH_2CH_2$		16	**7a**, 74
3	Me	$CH_2CH_2CH_2CH_2CH_2$		10	**7b**, 74
4	Et	Me	Me	10	**7c**, 52[c]
5	Et	Et	Et	16	**7d**, 42[d]
6	Me	Et	Et	16	**7e**, trace[e]
7	Me	$(CH_2)_2NMe_2$	Me	10	**7f**, 58
8	Me	$SiMe_3$	$SiMe_3$	10	–

[a] Isolated yield. [b] In refluxing MeOH. [c] Dimethylamine generated in situ by neutralization of its hydrochloride salt with triethylamine. [d] After 48 h. [e] The oxa-Michael adduct (3-methoxy-3-methyl butanoate) was isolated in 46% yield.

More positive results were obtained with cyclic substrates such as cycloalkylidenic esters **8** (Table 4).[11b–11e] Hyperbaric addition was found to be superior to thermal addition (Table 4, Entry 1 vs. 2). However, migration of the double bond of **8** to afford the deconjugated esters **9c** and **10b** or amide **10c** interfered with the desired aza-Michael addition (Table 4, Entries 3–6). Nevertheless, highly nucleophilic amines such as morpholine reacted remarkably well: bicyclic β-aminoester **9a** was obtained in almost quantitative yield and as a single diastereomer. Interestingly, the addition took place in a selective equatorial manner, as evidenced by the X-ray crystal structure of **9a** (Figure 1). Note that such β-aminoesters can be regarded as convenient precursors to spiro β-lactams.[19]

We next tried to extend this protocol to other Michael acceptors such as ketone **11**, sulfone **12**, and nitroalkene **13**.[20] Mesityloxide **11** is commercially available, whereas the two latter substrates were easily prepared (see the Supporting Information). These substrates were treated with the same cyclic secondary amines as above, and the results are presented in Table 5.

Table 4. Synthesis of amino-substituted quaternary centers by hyperbaric aza-Michael addition on alkyl cycloalkylidene esters.

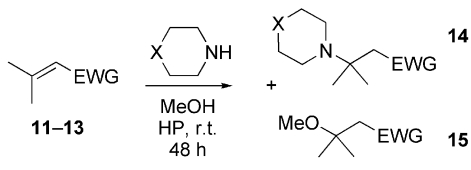


Entry	Ester	R_2	Conditions	R^1	Product, % Yield[a]
1	**8a**	$CH_2CH_2OCH_2CH_2$	B	Me	–
2	**8a**	$CH_2CH_2OCH_2CH_2$	A	Me	**9a**, 98
3	**8a**	$CH_2CH_2CH_2CH_2CH_2$	B	Me	**9c**, 33[b,c]
4	**8a**	$CH_2CH_2CH_2CH_2CH_2$	A	Me	**9b**, 17 / **9c**, 65
5	**8b**	$CH_2CH_2CH_2CH_2$	A	Et	**10a**, 38 / **10c**, 37
6	**8b**	Et_2	B	Et	**10b**, 44[b,c]
7	**8b**	Et_2	A	Et	–

[a] Isolated yield unless otherwise specified. [b] Yield based on integration of the NMR spectroscopy signals. [c] Large amounts of starting material **8** were also recovered.

Figure 1. X-ray crystal structure of **9a**.

Table 5. Hyperbaric aza-Michael addition of morpholine and piperidine on various activated olefins (isolated yields).

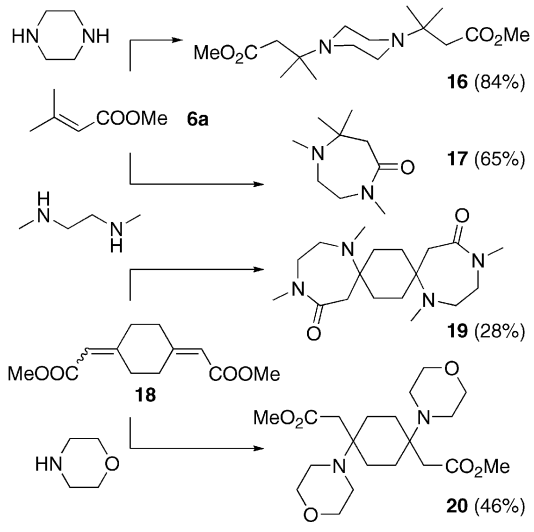


Entry	EWG	X	*P* [kbar]	Product, % Yield
1	COMe (**11**)	O	10	**15a**, 15
2	COMe (**11**)	CH_2	10	**15a**, 10
3	SO_2Ph (**12**)	O	8	**14a**, 80
4	SO_2Ph (**12**)	CH_2	8	**14b**, 71 / **15b**, 10
5	NO_2 (**13**)	O	8	–
6	NO_2 (**13**)	CH_2	8	–

Ketone **11** did not provide any aza-Michael adduct although it is known to react readily with ammonia at atmospheric pressure.[21] A competing, but reversible, 1,2-addition leading to a hemiaminal or iminium intermediate[22] is probably responsible for this failure. Only a small amount of **15a**, resulting from the conjugate addition of MeOH, was recovered under 10 kbar (Table 5, Entries 1 and 2).[23] In contrast, the same amines added easily onto sulfone **12**, leading to β-aminosulfones **14a** and **14b** in good yields (Table 5, Entries 3 and 4), even at lower pressures. Finally, nitroolefin **13** gave only a complex mixture of products under the same reaction conditions (Table 5, Entries 5 and 6), possibly because of uncontrolled polymerization.

These data suggest that unsaturated esters and sulfones might be the most appropriate substrates for these hyperbaric reactions. For reactive substrates (such as unsaturated ketones or nitroolefins), catalytic,[24] neat,[25] or photochemical[26] conditions at atmospheric pressure are perhaps more amenable to aza-Michael additions. Alternatively, an aqueous medium has also been shown to facilitate the addition of amines on nitroolefins.[27]

We finally considered bis-nucleophiles or bis-electrophiles as possible substrates for double additions (Scheme 2). We first evaluated the reaction of diamines and methyl senecioate by using the conditions of Table 1. Depending on the flexibility of the diamine, the simultaneous creation of two quaternary centers or the addition–lactamization occurred. Thus, by using piperazine as the nucleophile, bis(β-aminoester) **16** was recovered in good isolated yield, whereas *N*,*N*′-dimethylethylenediamine gave efficiently seven-membered aminolactam **17** (Scheme 2). Under comparable conditions, two molecules of the latter diamine reacted with diester **18** to furnish dispirocyclic bis(lactam) **19**, albeit in poor yield. The same diester reacted with morpholine to afford cyclic diamino diester **20** in slightly better yield.



Scheme 2. Double hyperbaric aza-Michael additions (r.t., 12–16 kbar, 24 h, MeOH).

Conclusions

The results presented here suggest that the hyperbaric aza-Michael reaction constitutes a direct method to assemble aminated quaternary centers in an atom economical way and without requiring additive. The reaction is performed under mild chemical conditions (room temperature, no catalyst), and depending on the substrate, good yields and selectivities can be achieved. The irreversible character of the addition under HP suggests that the observed selectivities favor the kinetic isomer. Overall, the results presented here indicate that the hyperbaric aza-Michael addition offers attractive solutions to problems in organic methodology that are, otherwise, often tedious to solve. Consequently, the hyperbaric aza-Michael reaction makes available unusual shortcuts for the synthesis of complex molecules bearing cumbersome aminated quaternary centers.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 MHz spectrometer (300 and 75 MHz, respectively) or a JEOL LA-400 spectrometer (400 and 100 MHz, respectively) for solution in $CDCl_3$. Chemical shifts (δ) in ppm are reported by using residual chloroform (7.25 ppm for ^{1}H and 77.20 ppm for ^{13}C) as internal reference. IR spectra were measured with a Perkin–Elmer 16 PC FTIR instrument. Mass spectra were recorded with an ATI-Unicam Automass spectrometer (EI, 70 eV), and ammoniac was used for chemical ionization (CI). High-pressure reactions were performed in a Psika piston-cylinder type apparatus, designed for pressures up to 20 kbar. The silica gel used for flash chromatography was 230–400 mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use.

β,β-Disubstituted α,β-Unsaturated Sulfone 12: To a solution of methyl phenyl sulfone (5.2 g, 0.04 mol) in THF (175 mL), cooled to –78 °C, was added *n*BuLi (1.59 M hexane, 25 mL, 0.04 mol). The mixture was stirred at –78 °C for 30 min before acetone (3 mL, 0.04 mol) was added. The resulting light solution was stirred at –78 °C for 90 min and then treated with aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude resulting alcohol and DMAP (0.5 g, 0.004 mol) were dissolved in CH_2Cl_2. The mixture was cooled to 0 °C before Et_3N (11.2 mL, 0.08 mol) and TFAA (6.7 mL, 0.05 mol) were successively added. The reaction mixture was stirred at 0 °C for 30 min, allowed to reach room temperature, and stirred at room temperature for 3 h. After hydrolysis with aqueous saturated NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 2:1) to afford 2-methyl-1-phenylsulfonyl-1-propene (**12**) as a light yellowish mica crystal (yield 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (d, J = 1.2 Hz, 3 H), 2.15 (d, J = 1.0 Hz, 3 H), 6.2 (q, 1 H), 7.49–7.68 (m, 3 H), 7.87–7.95 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.10, 26.99, 126.06, 126.91 (2 C),129.02 (2 C), 132.91, 142.19, 154.31 ppm.

Typical Procedure for the Aza-Michael Reaction of Sulfone 12 with Amines: A mixture of amine (1.2 mmol), and **12** (1.0 mmol) in MeOH (1.5 mL) was placed in a Teflon reaction vessel, and the mixture was pressurized to 8 kbar at room temperature for 48 h. After the pressure was released, the mixture was concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc).

Typical Procedure for the Treatment of Ester 1 with Amines: A solution of the ester (1 mmol) and amine (1 mmol) in THF (1–1.5 mL) was allowed to stand under 10–16 kbar of pressure at room temperature. After reversion to atmospheric pressure, the solvent was evaporated. The residue was purified by chromatography (silica gel; CH_2Cl_2/MeOH, 9:1; Et_2O/pentane, 1:3) to yield the corresponding products. The following compounds were prepared according to this procedure.

Methyl 3-Morpholin-4-ylbutanoate (2a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, J = 6.6 Hz, 3 H), 2.19 (dd, J = 7.9, 14.3 Hz, 1 H), 2.40–2.55 (m, 5 H), 3.00–3.10 (m, 1 H), 3.55–3.65 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.69 (CH_3CH), 38.12 (CH_2), 48.61 (NCH_2), 51.48 (OCH_3), 56.62 (C-N), 67.27 (OCH_2), 172.83 (C=O) ppm. IR: $\tilde{\nu}$ = 1738 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 187 (8) $[M]^+$, 172 (11), 114 (100). $C_9H_{17}NO_3$ (187.24): calcd. C 57.73, H 9.15, N 7.48; found C 57.32, H 9.23, N 7.76.

Methyl 3-Morpholin-4-ylphenylpropanoate (2b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35–2.45 (m, 4 H), 2.67 (dd, J = 7.4, 14.9 Hz, 1 H), 3.01 (m, 1 H), 3.60 (s, 3 H), 3.65–3.75 (m, 4 H), 3.92 (t, J = 7.5 Hz, 1 H), 7.25–7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.05 (CH_2), 50.39 (NCH_2), 51.60 (OCH_3), 66.25 (CHN), 67.18 (OCH_2), 127.63, 128.23, 128.29, 138.56 (Ph), 172.12 (C=O) ppm. IR: $\tilde{\nu}$ = 1738 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 249 (7) $[M]^+$, 176 (100). $C_{14}H_{19}NO_3$ (249.31): calcd. C 67.45, H 7.68, N 5.62; found C 67.45, H 7.66, N 5.60.

Methyl 2-Methyl-3-morpholin-4-ylpentanoate (2c): ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer): δ = 0.89 (t, J = 7.4 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.20–1.35 (m, 1 H), 1.50–1.60 (m, 1 H), 2.55–2.65 (m, 6 H), 3.55–3.60 (m, 4 H), 3.63 (s, 3 H) ppm. ^{1}H NMR (300 MHz, $CDCl_3$, minor diastereomer): δ = 0.88 (t, J = 7.4 Hz, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), 1.15–1.25 (m, 1 H), 1.30–1.60 (m, 1 H), 2.40–2.65 (m, 6 H), 3.45–3.50 (m, 4 H), 3.56 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ = 12.86 (CH_3CH_2), 15.32 (CH_3CH), 21.72 (CH_2CH_3), 42.89 ($CHCH_3$), 49.85 (NCH_2), 51.64 (OCH_3), 67.91 (OCH_2), 68.25 (CHN), 176.83 (C=O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, minor diastereomer): δ = 13.15 (CH_3CH_2), 14.80 (CH_3CH), 20.67 (CH_2CH_3), 43.50 ($CHCH_3$), 49.52 (NCH_2), 51.25 (OCH_3), 67.90 (OCH_2), 68.95 (CHN), 176.59 (C=O) ppm. IR: $\tilde{\nu}$ = 1737 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 215 (1) $[M]^+$, 186 (8), 128 (100). $C_{11}H_{21}NO_3$ (215.29): calcd. C 61.37, H 9.83, N 6.51; found C 61.23, H 10.14, N 6.28.

Ethyl 5-Morpholin-4-ylhex-3-enoate (4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.7 Hz, 3 H), 1.22 (t, J = 7.2 Hz, 3 H), 2.35–2.55 (m, 4 H), 2.84 (quint., J = 6.7 Hz, 1 H), 3.02 (d, J = 6.8 Hz, 2 H), 3.60–3.75 (m, 4 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.45 (dd, J = 7.8, 15.4 Hz, 1 H), 5.62 (dt, J = 6.8, 15.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.35 (CH_3CH_2), 17.61 (CH_3CH), 37.97 (CH_2CO), 50.62 (NCH_2), 60.83 (CH_2CH_3), 62.60 ($CHCH_3$), 67.33 (OCH_2), 124.04 (CH=), 136.07 (CH=), 171.95 (C=O) ppm. IR: $\tilde{\nu}$ = 1651 (C=C), 1735 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 227 (17) $[M]^+$, 212 (50), 114 (100). $C_{10}H_{19}NO_3$ (201.27): calcd. C 63.41, H 9.31, N 6.16; found C 63.16, H 9.26, N 6.04.

Methyl 5-Morpholin-4-ylhex-3-enoate (4b): ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ = 1.06 (d, J = 6.7 Hz, 3 H), 2.35–2.50 (m, 4 H), 2.84 (quint., J = 6.7 Hz, 1 H), 3.02 (d, J = 6.8 Hz, 2 H), 3.55–3.65 (m, 4 H), 3.59 (s, 3 H), 5.40 (dd, J = 7.8, 15.4 Hz, 1 H), 5.56 (dt, J = 6.8, 15.4 Hz, 1 H) ppm. ^{1}H NMR (300 MHz, $CDCl_3$, minor isomer): δ = 1.04 (d, J = 6.7 Hz, 3 H), 2.35–2.50 (m, 4 H), 2.84 (quint., J = 6.7 Hz, 1 H), 3.02 (d, J = 6.8 Hz, 2 H), 3.55–3.65 (m, 4 H), 3.59 (s, 3 H), 5.40 (dd, J = 7.8, 15.4 Hz, 1 H), 5.56 (dt, J = 6.8, 15.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major isomer): δ = 17.43 (CH_3CH), 37.55 (CH_2CO), 50.48 (NCH_2), 51.90 (OMe), 62.39 ($CHCH_3$), 67.14 (OCH_2), 123.64 (CH=), 136.12 (CH=), 172.17 (C=O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, minor isomer): δ = 18.09 (CH_3CH), 33.10 (CH_2CO), 50.85 (NCH_2), 51.84 (OMe), 57.34 ($CHCH_3$), 67.21 (OCH_2), 122.39 (CH=), 135.34 (CH=), 171.89 (C=O) ppm. IR: $\tilde{\nu}$ = 1653 (C=C), 1741 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 213 (13) $[M]^+$, 198 (100). $C_{11}H_{19}NO_3$ (213.28): calcd. C 61.95, H 8.98, N 6.57; found C 61.68, H 9.11, N 6.65.

Methyl 5-Morpholin-4-ylhex-2-enoate (5b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.6 Hz, 3 H), 2.12 (ddt, J = 1.4, 8.0, 14.3 Hz, 1 H), 2.35–2.50 (m, 5 H), 2.63 (quint., J = 6.6 Hz, 1 H), 3.55–3.65 (m, 4 H), 3.67 (s, 3 H), 5.79 (dt, J = 1.4, 14.3 Hz, 1 H), 6.91 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.93 (CH_3), 36.05 (CH_2), 49.02 (NCH_2), 51.60 (OMe), 58.89 (CH), 67.44 (OCH_2), 122.33 (CH=), 147.56 (CH=), 167.06 (C=O) ppm. IR: $\tilde{\nu}$ = 1656 (C=C), 1723 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 213 (2) $[M]^+$, 185 (4), 140 (25), 114 (100). $C_{11}H_{19}NO_3$ (213.28): calcd. C 61.95, H 8.98, N 6.57; found C 61.72, H 9.09, N 6.61.

Methyl 3-Methyl-3-morpholin-4-ylbutanoate (7a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 6 H), 2.37 (s, 2 H), 2.45–2.60 (m, 4 H), 3.55–3.70 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.11 (CH_3), 43.32 (CH_2), 46.25 (NCH_2), 51.37 (OCH_3), 56.21 (C-N), 67.81 (OCH_2), 172.37 (C=O) ppm. IR: $\tilde{\nu}$ = 1734 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 201 (3) $[M]^+$, 186 (20), 128 (100). $C_{10}H_{19}NO_3$ (201.27): calcd. C 59.68, H 9.52, N 6.96; found C 59.32, H 9.62, N 7.04.

Methyl 3-Methyl-3-piperidin-4-ylbutanoate (7b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 6 H), 1.25–1.35 (m, 2 H), 1.35–1.50 5 (m, 4 H), 2.32 (s, 2 H), 2.35–2.50 (m, 4 H), 3.55 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.78 (CH_3), 24.85, 26.90 (CH_2 piperidine), 42.70 (CH_2), 46.80 (NCH_2), 51.27 (OCH_3), 56.54 (C-N), 172.93 (C=O) ppm. IR: $\tilde{\nu}$ = 1738 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 199 (8) $[M]^+$, 184 (60), 126 (100). $C_{11}H_{21}NO_2$ (199.29): calcd. C 66.29, H 10.62, N 7.03; found C 66.65, H 10.87, N 7.10.

Ethyl 3-(Dimethylamino)-3-methylbutanoate (7c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (s, 6 H), 1.20 (t, J = 7.1 Hz, 3 H), 2.20 (s, 6 H), 2.32 (s, 2 H), 4.06 (q, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.35 (CH_3CH_2), 24.41 (CH_3C), 38.63 (CH_3N), 41.69 (CH_2), 56.14 (C-N), 60.22 (OCH_2), 172.48 (C=O) ppm. IR: $\tilde{\nu}$ = 1732 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 173 (5) $[M]^+$, 158 (14), 86 (100). $C_9H_{19}NO_2$ (173.25): calcd. C 62.39, H 11.05, N 8.08; found C 62.13, H 11.14, N 8.14.

Ethyl 3-(Diethylamino)-3-methylbutanoate (7d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.1 Hz, 6 H), 1.20 (s, 6 H), 1.25 (t, J = 7.2 Hz, 3 H), 2.39 (s, 2 H), 2.54 (q, J = 7.1 Hz, 4 H), 4.10 (q, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.42 (CH_3CH_2O), 16.84 (CH_3CH_2N), 26.30 (CH_3), 43.76 (CH_2), 43.19 (NCH_2), 57.63 (C-N), 60.16 (OCH_2), 172.64 (C=O) ppm. IR: $\tilde{\nu}$ = 1731 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 201 (4) $[M]^+$, 186 (20), 114 (100). $C_{11}H_{23}NO_2$ (201.31): calcd. C 65.63, H 11.52, N 6.96; found C 65.78, H 11.56, N 7.18.

Methyl 3-{[2-(Dimethylamino)ethyl](methyl)amino}-3-methylbutanoate (7f): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 6 H), 2.20 (s, 3 H), 2.23 (s, 6 H), 2.35–2.55 (m, 6 H), 3.62 (s, 3 H) ppm. ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 24.72 (CH_3C), 35.49 (CH_3N), 42.34 (CH_2), 45.82 (CH_3N), 48.91 (NCH_2), 51.31 (OCH_3), 56.81 (C-N), 59.27 (NCH_2), 172.61 (C=O) ppm. IR: $\tilde{\nu}$ = 1736 (C=O) cm^{-1}. MS (IE): *m*/*z* (%) = 216 (4) $[M]^+$, 158 (100). $C_{11}H_{24}N_2O_2$ (216.32): calcd. C 61.07, H 11.18, N 12.95; found C 61.05, H 11.22, N 12.89.

Methyl 3-Methoxy-3-methylbutanoate: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 6 H), 2.46 (s, 2 H), 3.19 (s, 3 H), 3.63 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.23 (CH_3), 44.78 (CH_2), 49.60 (OCH_3), 51.54 ($COOCH_3$), 73.88 ($COCH_3$), 171.46 (C=O) ppm. IR: $\tilde{\nu}$ = 1740 (C=O) cm^{-1}. MS (IC, isobutane): *m*/*z* (%) = 147 (50) $[M + 1]^+$, 115 (82), 85 (82), 71 (100). $C_7H_{14}O_3$ (146.19): calcd. C 57.51, H 9.65; found C 57.39, H 9.62.

Methyl (4-*tert*-Butyl-1-morpholinocyclohexyl)acetate (9a): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 9 H), 0.95–1.05 (m, 1 H), 1.05–1.20 (m, 2 H), 1.30–1.45 (m, 2 H), 1.65–1.80 (m, 2 H), 1.85–2.00 (m, 2 H), 2.51 (s, 2 H), 2.57–2.70 (m, 4 H), 3.57–3.70 (m, 4 H), 3.64 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.74 (C-3,5), 27.69 [$(CH_3)_3C$], 32.44 (CMe_3), 32.55 (C-2,6), 36.98 (CH_2O), 45.96 (NCH_2), 47.80 (C-4), 51.39 (OCH_3), 58.81 (C-1), 62.28 (OCH_2), 172.89 (C=O) ppm. IR: $\tilde{\nu}$ = 1731 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 297 (3) $[M]^+$, 265 (2), 240 (4), 224 (100), 198 (33), 87 (9). $C_{17}H_{31}NO_3$ (297.44): calcd. C 68.65, H 10.51, N 4.71; found C 68.58, H 10.45, N 4.74.

Methyl (4-*tert*-Butyl-1-piperidinocyclohexyl)acetate (9b): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 9 H), 0.95–1.20 (m, 3 H), 1.35–1.75 (m, 10 H), 1.97–2.10 (m, 2 H), 2.51 (s, 2 H), 2.55–2.70 (m, 4 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.90 (C-3,5), 25.11, 27.07 (CH_2 piperidine), 27.66 [$(CH_3)_3C$], 32.39 (CMe_3), 33.35 (C-2,6), 36.35 (CH_2O), 46.59 (NCH_2), 47.48 (C-4), 51.44 (OCH_3), 59.02 (C-1), 173.18 (C=O) ppm. IR: $\tilde{\nu}$ = 1738 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 295 (4) $[M]^+$, 222 (100), 196 (27), 84 (22). $C_{18}H_{33}NO_2$ (295.46): calcd. C 73.17, H 11.26, N 4.74; found C 73.19, H 11.26, N 4.76.

Ethyl (1-Pyrrolidin-1-ylcyclopentyl)acetate (10a): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 1.55–1.90 (m, 12 H), 2.51 (s, 2 H), 2.65–2.75 (m, 4 H), 4.11 (q, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.24 (CH_3), 24.12, 24.46 (C-2–5), 32.28 (CH_2 pyrrolidine), 39.71 (CH_2CO), 46.76 (NCH_2), 60.18 (OCH_2), 67.29 (C-1), 172.64 (C=O) ppm. IR: $\tilde{\nu}$ = 1731 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 225 (2) $[M]^+$, 196 (23), 138 (100). $C_{13}H_{23}NO_2$ (225.33): calcd. C 69.29, H 10.29, N 6.22; found C 69.44, H 10.32, N 6.27.

1-(Cyclopent-1-en-1-ylacetyl)pyrrolidine (10c): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75–1.95 (m, 6 H), 2.25–2.40 (m, 4 H), 3.05 (s, 2 H), 3.35–3.50 (m, 4 H), 5.41 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.39, 24.49, 26.24 (C-3,4,5), 32.53, 35.38 (CH_2 pyrrolidine), 38.39 (CH_2CO), 45.74, 46.89 (NCH_2), 126.98 (C-2), 137.61 (C-1), 169.56 (C=O) ppm. IR: $\tilde{\nu}$ = 1636, (br. s, C=C, C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 179 (33) $[M]^+$, 98 (100). $C_{11}H_{17}NO{\cdot}H_2O$: calcd. C 66.97, H 9.71; found C 66.81, H 9.85.

4-[1,1-Dimethyl-2-(phenylsulfonyl)ethyl]morpholine (14a): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 2.48 (t, *J* = 4.5 Hz, 4 H), 3.21 (s, 2 H), 3.50 (t, *J* = 4.5 Hz, 4 H), 7.53–7.67 (m, 3 H), 7.89–7.98 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.49 (2 C), 45.88 (2 C), 56.92, 62.03, 67.12 (2 C), 127.81 (2 C), 129.10 (2 C), 133.35, 141.74 ppm. $C_{14}H_{21}NO_3S$ (283.38): calcd. C 59.34, H 7.47, N 4.94; found C 59.40, H 7.66, N 5.08.

4-[1,1-Dimethyl-2-(phenylsulfonyl)ethyl]piperidine (14b): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.46 (m, 12 H), 2.42–2.44 (m, 4 H), 3.22 (s, 2 H), 7.53–7.67 (m, 3 H), 7.92–7.97 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.52, 25.37 (2 C), 26.42 (2 C), 46.44 (2 C), 57.11, 61.81, 127.74 (2 C), 129.04 (2 C), 133.18, 141.87 ppm. $C_{15}H_{23}NO_2S$ (281.41): calcd. C 64.02, H 8.24, N 4.98; found C 64.25, H 8.49, N 4.75.

4-Methoxy-4-methylpentan-2-one (15a): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 6 H), 2.22 (s, 3 H), 2.57 (s, 2 H), 3.29 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.83 (3 C), 49.16, 54.10, 74.39, 208.51 ppm.

[(2-Methoxy-2-methylpropyl)sulfonyl]benzene (15b): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 6 H), 3.03 (s, 3 H), 3.40 (s, 2 H), 7.54–7.65 (m, 3 H), 7.90–7.95 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.30 (2 C), 49.24, 64.40, 73.99, 127.96 (2 C), 128.97 (2 C), 133.36, 141.43 ppm.

Dimethyl 3,3′-(Piperazine-1,4-diyl)bis(3-methylbutanoate) (16): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 12 H), 2.32 (s, 4 H), 2.45–2.55 (m, 8 H), 3.56 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.33 (CH_3), 42.80 (CH_2), 46.17 (NCH_2), 51.25 (OCH_3), 55.88 [$C(CH_3)_2$], 172.59 (C=O) ppm. IR: $\tilde{\nu}$ = 1731 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 314 (12) $[M]^+$, 241 (100). $C_{16}H_{30}N_2O_4{\cdot}H_2O$: calcd. C 57.81, H 9.70, N 8.43; found C 58.12, H 9.76, N 8.83.

1,4,7,7-Tetramethyl-1,4-diazepan-5-one (17): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 6 H), 2.05 (s, 3 H), 2.40 (s, 2 H), 2.50–2.55 (m, 2 H), 2.72 (s, 3 H), 3.15–3.25 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.21 [$C(CH_3)_2$], 38.54 (NCH_3), 50.26 (CH_2CO), 50.55, 52.45 (NCH_2), 53.21 [$C(CH_3)_2$], 172.77 (C=O) ppm. IR: $\tilde{\nu}$ = 1635 (C=O) cm^{-1}. MS (EI): *m*/*z* = 171 $[M + H]^+$. $C_9H_{18}N_2O$ (170.25): calcd. C 63.49, H 10.66, N 16.45; found C 63.53, H 10.76, N 16.39.

Bis-1,4-Dimethyl-1,4-diazepan-5-one (19): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.80 (m, 8 H), 2.30 (s, 6 H), 2.33 (s, 4 H), 2.50–2.70 (br. m, 2 H), 2.90 (s, 6 H), 2.90–3.05 (br. m., 4 H), 3.15–3.45 (br. m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.18 (CH_2 cyclohex.), 35.09, 36.02 (NCH_3), 42.35 (CH_2CO), 46.14, 50.38, 53.82 (NCH_2), 50.63 (C-1), 172.91, 173.31 (C=O) ppm. IR: $\tilde{\nu}$ = 1628 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 366 (68) $[M]^+$, 169 (100). $C_{18}H_{32}N_4O_2$ (336.48): calcd. C 64.25, H 9.59, N 16.46; found C 64.42, H 9.45, N 16.46.

Dimethyl 2,2′-(1,4-Dimorpholinocyclohexane-1,4-diyl)diacetate (20): ^1H NMR (300 MHz, $CDCl_3$, minor diastereomer): δ = 1.55–1.85 (m, 8 H), 2.28 (s, 4 H), 2.40–2.50 (m, 8 H), 3.60–3.70 (m, 8 H), 3.67 (s, 6 H) ppm. ^1H NMR (300 MHz, $CDCl_3$, major diastereomer): δ = 1.45–1.90 (m, 8 H), 2.41 (s, 4 H), 2.50–2.60 (m, 8 H), 3.63 (s, 6 H), 3.60–3.70 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, minor diastereomer): δ = 27.00 (CH_2 cyclohex), 38.89 (CH_2O), 44.81 (NCH_2), 51.73 ($COOCH_3$), 57.29 (C-1), 68.12 (OCH_2), 173.13 (C=O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ = 26.96 (C-3,5), 37.90 (CH_2O), 45.27 (NCH_2), 51.53 ($COOCH_3$), 57.75 (C-1), 68.05 (OCH_2), 172.75 (C=O) ppm. IR: $\tilde{\nu}$ = 1731 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 398 (1) $[M]^+$, 240 (100). $C_{20}H_{34}N_2O_6$ (398.50): calcd. C 60.28, H 8.60, N 7.03; found C 60.02, H 8.62, N 6.79.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C spectra for all β-aminoesters.

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