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Tandem aza-Michael additions under high pressure: a shortcut to the azanorbornyl skeleton

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Abstract—The hyperbaric aza-Michael addition of mono- and diamines on α,β-unsaturated β,β-disubstituted mono- and diesters has been studied. While in the case of monoester, this reaction provides a β-aminoester presenting a quaternary center, a direct and efficient access to diester or lactams featuring an azanorbornyl skeleton was obtained when starting from a diester, following an unprecedented double aza-Michael addition.

1. Introduction

The β-lactam, which was derived directly from β-amino-acids, and the azanorbornane skeletons are nitrogen heterocycles sharing two characteristics. First, their biological activity and their extensive use as fundamental building blocks in the synthesis of pharmaceuticals and analogues of natural products such as alkaloids and antibiotics fuels up a permanent attention from the organic chemistry community.[1] For instance, the β-lactam nuclei featuring new characteristics such as quaternary centers in α of the nitrogen position[2] or spirocyclic arrangements[3] are regarded as valuable assets in antibiotherapy. Spiro-β-lactams exhibit other attractive biological activities illustrated by the cholesterol absorption inhibitor Sch 58053 (Fig. 1, left).[4] It is also now well established that the replacement of α-aminoacid residues with β-amino or α,β-diaminoacid residues at specific positions in some peptides leads to improved biological activity due to increased metabolic stability against peptidases.[5]

Meanwhile, the discovery of the alkaloid, epibatidine, found in trace amounts from skin extracts of an Ecuadoran poison frog, *Epipedobates tricolor*, has generated considerable interest in the 7-azanorbornane nucleus.[6] Indeed, epibatidine (Fig. 1, right) was first reported to be a highly potent, nonopioid analgesic, and nicotinic acetylcholine receptor agonist, but its high toxicity soon prompted the development and screening of new analogues.[7]

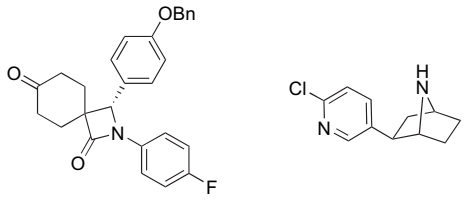

Figure 1. Cholesterol absorption inhibitor Sch 58053 (left) and analgesic epibatidine (right).

On a synthetic point of view, and this constitutes the second common point between β-aminoacids and azanorbornanes, the access to analogues of above structures can be envisaged through an aza-Michael addition on simple or double acetylidenic cyclohexanes (Fig. 2). The combination of this reaction with a substitution–condensation sequence (tandem aza-Michael reactions) can thus provide a short and atom-economical route to cyclic and polycyclic complex molecules including these heterocyclic moieties.

The aza-Michael addition on unsaturated esters is probably the most direct method to prepare β-aminoesters.[8] However, and despite its atom-economical character, this reaction is severely limited by steric factors such as those imposed by the presence of α and/or β-substituent(s), as evidenced by Pfau's pioneering results.[9] An elegant way to circumvent this problem is to resort to the addition of enantiomerically pure chiral lithium amides as homochiral ammonia equivalents. This strategy has proved to be remarkably general and is probably regarded as the most efficient route to these

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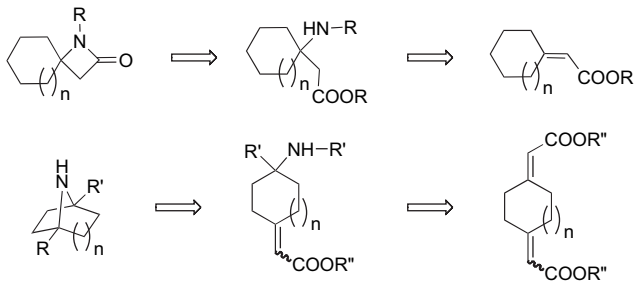


Figure 2. Access to spiro-β-lactams and to aza-bridged carbocyclic structures by aza-Michael additions.

compounds to date.[10] Another alternative consists in resorting to high pressure, which is known to help overcoming steric barriers. It has been previously shown that this technique indeed opens direct routes toward tertiary β-aminoesters,[11] and Jenner has measured a highly negative (≈ -50 mL/mol)[12] activation volume associated to this reaction, explaining its efficiency under hyperbaric conditions.

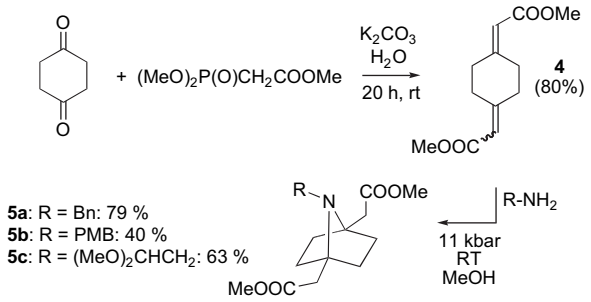
Our first results in the field led us to suggest that *exo*-cyclic olefins bearing an electron-withdrawing group are substrates for the hyperbaric (11 kbar) conjugate addition of primary amines, provided the reaction is run in alcohols.[13] Actually, α-brominated α,β-unsaturated esters give access, in these same conditions, to spiroaziridines in high yields and stereoselectivities.[14] In this paper, we report developments dealing with polyfunctional nucleophiles allowing an aza-Michael–condensation reaction sequence.

2. Results and discussion

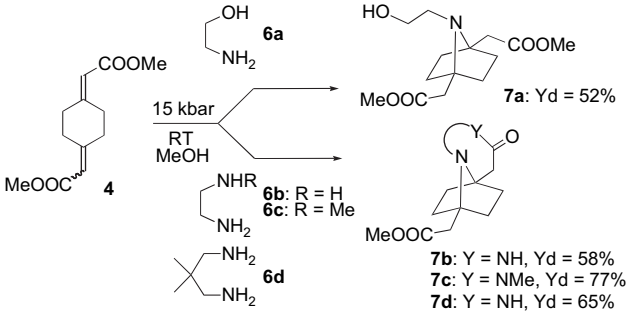
In a preliminary step, we checked that simple *exo*-cyclic olefins such as **1** react with nucleophilic primary amines such as benzylamine in comparable conditions. The expected β-aminoester **2** (featuring a quaternary center) was indeed obtained in 46% yield under 11 kbar (Scheme 1). Actually, the nucleophilic attack of the amine on the ester group (providing the corresponding unsaturated benzylamide) is the main competing reaction. No double 1,2- and 1,4-additions were noted. An efficient conjugate addition was also observed with a secondary amine such as morpholine.[15]

We next moved to binucleophiles and compressed *N*-methylethylenediamine with **1** in identical conditions. The spirolactam **3** was directly obtained in 57% yield (Scheme 1). The two diastereomers of the resulting lactams, present in a 5:1 ratio, could be separated by flash chromatography. Their NMR analysis showed that the major isomer **3a** resulted from an axial attack of the amine, in contrast with our own previous observations.[14a] About 15% of β-methoxyester **2c**, resulting from the conjugate addition of methanol on **1**, was also obtained in this case.

Bielectrophiles were also expected to trigger cascade reactions, of potential interest in the perspective of the synthesis of polyheterocyclic cation-chelating molecules. We thus turned our hands to the known[16] diester **4**, which was prepared and reacted with primary amines (Scheme 2) as well as with commercially available *N*,*N*- and *N*,*O*-binucleophiles (Scheme 3).

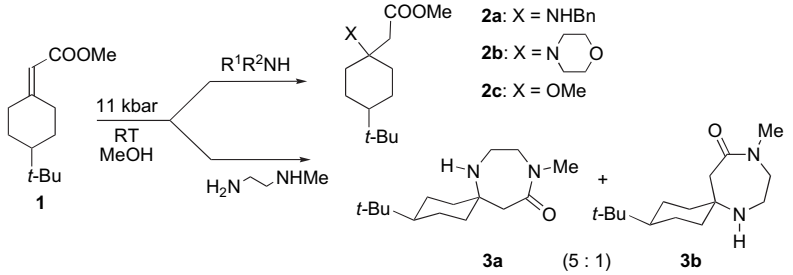


Scheme 2. Synthesis of diester **4** and their reactions with primary amines.

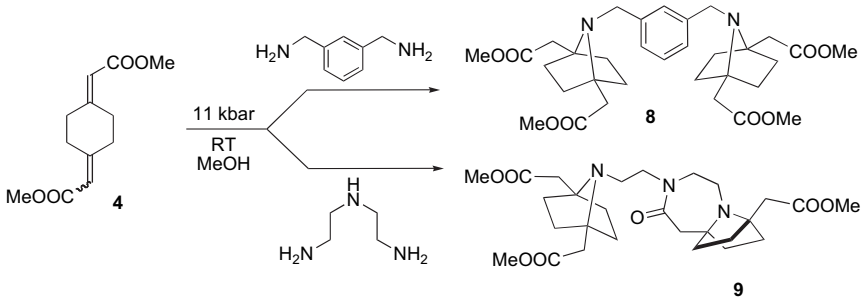


Scheme 3. Reactions of diester **4** with *N*,*N*- and *N*,*O*-binucleophiles.

The diester **4** was obtained efficiently as a 1:1 mixture of (*Z*)- and (*E*)-isomers from 1,4-cyclohexanedione resorting to the aqueous Horner–Emons conditions described by Villieras and Rambaud (Scheme 2).[17] The room temperature hyperbaric addition of a series of primary amines led to the bridged structure **5** in relatively good yields. This direct access to bridged β-aminodiesters, never described before to our knowledge, was relatively surprising considering the low



Scheme 1. Reactions of ester **1** with *N*-nucleophiles.



Scheme 4. Reactions of diester **4** with *N*,*N*-binucleophiles.

reactivity of secondary amines in conjugate additions, even under high pressure.[11a] Note that the reaction requires a protic solvent such as methanol and that only small amounts of the corresponding amides are formed, except in the case of *p*-methoxybenzylamine. Compound **5b** was indeed recovered together with 28% of its monoamide derivative.

We next wondered whether the combination of binucleophiles and bielectrophiles could afford polycyclic molecules in a single hyperbaric step. Thus, diamines **6** and diester **4** in methanol were put under 15 kbar at room temperature. The tricyclic derivatives **7b–d** were isolated in reasonable yields (Scheme 3). It is worth underlining that: (i) the same reaction can be performed under atmospheric pressure at refluxing methanol. However, the conversion rate is only 50% after one week; (ii) neither in the case of **6b** nor in that of **6d**, any product resulting from the double aza-Michael addition of the two primary amines on the two double bonds was obtained; (iii) in all cases, the intramolecular conjugate addition of the intermediate secondary amine on the remaining double bond takes place efficiently while no intermolecular addition of a secondary amine could be observed in comparable conditions. Note also that resorting to 2-aminoethanol **6a** led to the double addition of the amine while no lactonization was observed. The corresponding aminoalcohol **7a** was recovered in 52% yield after 24 h at 15 kbar and room temperature.

Extending this reaction to binucleophiles in which longer tethers separate the two primary amines revealed impossible. Actually, two separate additions take place leading to dimeric bridged structures, a supplementary lactam ring closure occurring with diethylenetriamine (Scheme 4). However, these reactions lead to large amounts of polymeric

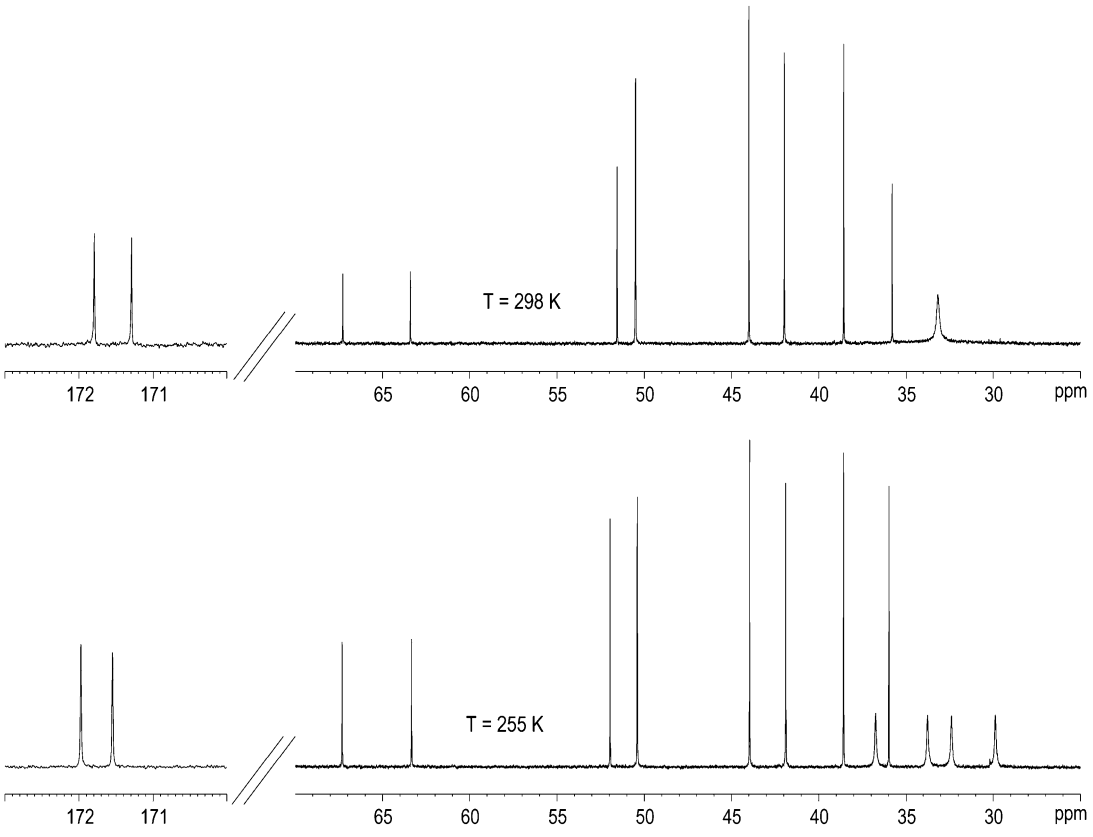


Figure 3. ^{13}C (150 MHz) spectrum of **7c** at variable temperature.

materials, adducts **8** and **9** being recovered in 10 and 16%, respectively.

Some physicochemical properties of tricyclic derivatives **7b–d** deserve comments. First, the floppiness of their seven-membered ring lactams is associated to poorly resolved ^{1}H and ^{13}C NMR spectra at room temperature. At 255 K, a dramatic improvement of the resolution was observed (see for instance the 20–40 ppm region of the ^{13}C NMR spectrum of **7c** in Fig. 3).

Interestingly, an elemental analysis revealed that the folded lactamic ring traps one molecule of water. This stable cluster can be dehydrated in refluxing benzene using a Dean–Stark apparatus. The water removal could be confirmed by a quick IR spectrum recording as well as by elemental analysis. The ability of this highly chelating ring to trap polar molecules (and ions?) could be of interest in the perspective of supramolecular applications.

3. Conclusion

In conclusion, the conjugate addition of primary amines on α,β-unsaturated β,β-disubstituted esters can be efficient under hyperbaric conditions, even in the case of β,β-disubstituted esters reacting with secondary amines. Resorting to *N*,*N*-binucleophiles and bielectrophiles such as diester **4** leads to polycyclic lactams in reasonable yields through a yet unknown double aza-Michael step. Extensions of these results to other substrates, their application to the synthesis of skeletons of biological relevance, and efforts toward an asymmetric version[18] of this tandem reaction are in progress.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 300 (default) or 600 (specified) MHz and ^{13}C NMR spectra at 75 (default) or 150 (specified) MHz; chemical shifts (δ) are given in parts per million (ppm) and the coupling constants (J) in hertz. The solvent was deuterochloroform. IR spectra were recorded by transmission. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; ammonia was used for chemical ionization (CI). The silica gel used for flash chromatography was 230–400 mesh. High pressure reactions were performed in a piston–cylinder type apparatus, designed for pressures up to 20 kbar. All reagents were of reagent grade and were used as such or distilled prior to use. Methyl 4-*tert*-butylcyclohexylidene acetate **1** and diester **4** were prepared as reported previously.[13,14a]

4.2. Typical procedure for the treatment of esters 1 and 4 with amines and binucleophiles

A solution of the ester (1 mmol) and amine or binucleophile (1 mmol) in methanol (1–1.5 mL) was allowed to stand under 11–15 kbar at room temperature. After reversion to atmospheric pressure, the solvent was evaporated. The residue was chromatographed (CH_2Cl_2/MeOH 9:1) to yield the corresponding products. The following compounds were all prepared according to this procedure.

4.2.1. Methyl 2-[1-(benzylamino)-4-(*tert*-butyl)cyclohexyl]acetate (2a). Oil. IR (KBr, ν, cm^{-1}): 1731 (C=O). ^{1}H NMR ($CDCl_3$): δ 0.91 (s, 9H), 1.25–1.07 (m, 3H), 1.47 (br t, 2H), 1.77 (br d, 2H), 1.89 (br d, 2H), 2.67 (s, 2H), 3.73 (s, 3H), 3.79 (s, 2H), 7.82–7.24 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 23.8 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 32.7, 37.1 (CH_2 cycl.), 44.1 (C_q), 46.2 (CH_2CO), 48.3 (CH), 51.7 (CH_3O), 55.0 (NCH_2), 127.9, 128.8, 129.1, 141.6 (C_6H_5), 172.9 (C=0). MS (CI) *m*/*z* (relative intensity): 318 (M^++1), 244 (7), 106 (20), 91 (60), 57 (100). Calcd for $C_{20}H_{32}NO_2$: C, 75.67; H, 9.84; N, 4.41; found C, 75.65; H, 9.89; N, 4.49.

4.2.2. Methyl 2-[4-(*tert*-butyl)-1-morpholinocyclohexyl] acetate (2b). Oil. ^{1}H NMR ($CDCl_3$): δ 0.77 (s, 9H), 0.90–1.15 (m, 3H), 1.30 (br t, 2H), 1.63 (br d, 2H), 1.85 (br d, 2H), 2.43 (s, 2H), 2.50–2.60 (m, 4H), 3.50–3.60 (m, 4H), 3.57 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 23.62 ($C(CH_3)_3$), 27.58 ($C(CH_3)_3$), 32.32, 37.42 (CH_2 cycl.), 36.82 (C_q), 45.84 (CH_2CO), 47.67 (CH), 51.24 (CH_3O), 58.70 (NCH_2), 68.10 (OCH_2), 172.70 (C=O).

4.2.3. Methyl 2-[4-(*tert*-butyl)-1-methoxycyclohexyl] acetate (2c). Oil. IR (KBr, ν, cm^{-1}): 1741 (C=O). ^{1}H NMR ($CDCl_3$): (major diastereomer): δ 0.83 (s, 9H), 1.00–1.10 (m, 2H), 1.30–1.50 (m, 2H), 1.70–1.80 (m, 2H), 1.90–2.00 (m, 2H), 2.58 (s, 2H), 3.26 (s, 3H), 3.66 (s, 3H); (minor diastereomer): δ 0.82 (s, 9H), 1.20–1.35 (m, 7H), 1.45–1.55 (m, 2H), 1.90–2.00 (m, 2H), 2.42 (s, 2H), 3.19 (s, 3H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$): (major diastereomer): δ 24.31 (CH_2 cycl.), 27.77 (CH_3, Bu^t), 35.20 (CH_2 cycl.), 37.56 (CH_2CO), 47.69 (CH), 49.09 (OCH_3), 51.70 (OCH_3), 76.20 (C–O cycl.), 171.76 (C=O); (minor diastereomer): δ 22.26 (CH_2 cycl.), 27.72 (CH_3, Bu^t), 34.60 (CH_2 cycl.), 43.04 (CH_2CO), 47.50 (CH), 48.93 (OCH_3), 51.70 (OCH_3), 74.14 (C–O cycl.), 171.51 (C=O). MS (EI) *m*/*z* (relative intensity): 210 (16, M^+-CH_3OH), 169 (49), 143 (98), 57 (100). Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81; found C, 69.19; H, 10.72.

4.2.4. 4-(*tert*-Butyl)-10-methyl-7,10-diazaspiro[5,6]dodecan-11-one (3a). Solid. Mp 148 °C. IR (KBr, ν, cm^{-1}): 1624 (C=O), 3309 (NH). ^{1}H NMR ($CDCl_3$): δ 0.81 (s, 9H), 0.90–1.15 (m, 2H), 1.04 (dt, J=3.0, 13.5 Hz, 2H), 1.45–1.85 (m, 5H), 2.54 (s, 2H), 2.85–2.90 (m, 2H), 2.95 (s, 3H), 3.35–3.40 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.02 (CH_2 cycl.), 27.69 ($C(CH_3)_3$), 32.50 ($C(CH_3)_3$), 36.10 (NCH_3), 42.30 (CH_2 cycl.), 47.83 (C^4), 50.20 (C^3), 52.98 (CH_2N), 53.79 (CH_2N), 173.33 (C=O). MS (EI) *m*/*z* (relative intensity): 252 (38, M^+), 237 (18), 153 (100). Calcd for $C_{15}H_{28}N_2O$: C, 71.38; H, 11.18; N, 11.10; found C, 71.24; H, 11.26; N, 11.08.

4.2.5. 3-(*tert*-Butyl)-10-methyl-7,10-diazaspiro[5,6]dodecan-11-one (3b). Solid. Mp 110 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.79 (s, 9H), 1.01 (m, 1H), 1.32 (m, 4H), 1.74 (br s, 2H), 1.97 (br d, J=7.3 Hz, 2H), 2.80 (s, 2H), 3.06 (s, 3H), 3.13 (t, J=4.6 Hz, 2H), 3.55 (br s, 2H), 5.10 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.28 (CH_2 cycl.), 27.67 ($C(CH_3)_3$), 32.44 ($C(CH_3)_3$), 35.94 (NCH_3), 42.19 (CH_2 cycl.), 43.67 (C^4), 47.86 (C^3), 51.76 (CH_2N), 53.00

(CH_2N), 172.14 (C=O). MS (EI) *m/z* (relative intensity): 252 (35, M^+), 237 (18), 153 (100).

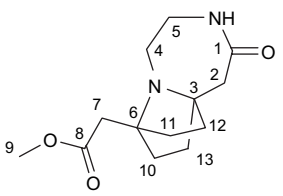
4.2.6. Methyl 2-[7-benzyl-4-(2-methoxy-2-oxoethyl)-7-azabicyclo[2.2.1]hept-1-yl]acetate (5a). Solid. Mp 65–66 °C. IR (KBr, ν, cm^{-1}): 1751 (C=O). ^1H NMR ($CDCl_3$): δ 1.64–1.78 (m, 8H), 2.44 (s, 2H), 3.52 (s, 2H), 3.56 (s, 6H), 7.10–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 33.90 (CH_2 cycl.), 40.50 (CH_2), 46.80 (NCH_2), 51.80 (OCH_3), 67.40 (C cycl.), 126.70, 128.10, 128.50, 142.10 (C_6H_5), 172.10 (C=O). MS (EI) *m/z* (relative intensity): 331 (1, M^+), 272 (2), 258 (12). Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23; found C, 68.94; H, 7.59; N, 4.28.

4.2.7. Methyl 2-[7-(4-methoxybenzyl)-4-(2-methoxy-2-oxoethyl)-7-azabicyclo[2.2.1]hept-1-yl]acetate (5b). Solid. Mp 62–64 °C. IR (KBr, ν, cm^{-1}): 1742 (C=O). ^1H NMR ($CDCl_3$): δ 1.63–1.78 (m, 8H), 2.46 (s, 2H), 3.47 (s, 2H), 3.59 (s, 6H), 3.77 (s, 3H), 6.82–7.27 (dd, J=8.7 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 33.90 (CH_2 cycl.), 40.50 (CH_2), 46.20 (NCH_2), 51.80 (OCH_3), 55.60 (OCH_3 phenyl), 67.30 (C cycl.), 113.90, 129.10 (C_6H_5), 172.20 (C=O). MS (EI) *m/z* (relative intensity): 361 (34, M^+), 330 (2), 232 (31), 121 (100). Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88; found: C, 66.65; H, 7.66; N, 4.02.

4.2.8. Methyl 2-[7-(2,2-dimethoxyethyl)-4-(2-methoxy-2-oxoethyl)-7-azabicyclo[2.2.1]hept-1-yl]acetate (5c). Oil. IR (KBr, ν, cm^{-1}): 1747 (C=O). ^1H NMR ($CDCl_3$): δ 1.64–1.78 (m, 8H), 2.38 (d, J=4.9 Hz, 1H), 2.64 (s, 2H), 3.37 (s, 6H), 3.65 (s, 6H), 4.22 (t, J=4.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 33.70 (CH_2 cycl.), 40.40 (CH_2), 46.10 (NCH_2), 51.90 (OCH_3), 55.20 (OMe), 67.50 (C cycl.), 106.40 (CHO), 172.30 (C=O). MS (EI) *m/z* (relative intensity): 298 (4, $[M-MeO]^+$), 254 (100), 224 (6), 193 (15), 151 (17). Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25; found C, 58.07; H, 8.31; N, 4.32.

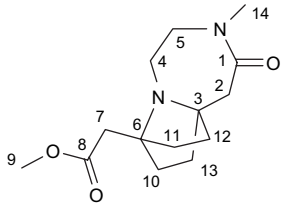
4.2.9. Methyl 2-[7-(2-hydroxyethyl)-4-(2-methoxy-2-oxoethyl)-7-azabicyclo[2.2.1]hept-1-yl]acetate (7a). Oil. IR (KBr, ν, cm^{-1}): 1737 (C=O), 3449 (OH). ^1H NMR ($CDCl_3$): δ 1.63 (br s, 8H), 2.45 (t, J=5.3 Hz, 2H), 2.61 (s, 4H), 3.46 (t, J=5.3 Hz, 2H), 3.60 (br s, 1H), 3.64 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 33.40 (CH_2 cycl.), 39.48 (CH_2), 43.69 (NCH_2), 51.80 (OCH_3), 61.36 (C cycl.), 67.29 (OCH_2), 171.73 (C=O). MS (EI) *m/z* (relative intensity): 254 (100, M^+-CH_3OH), 198 (25); (CI) *m/z* (relative intensity): 286 (100, M^+), 254 (17, M^+-CH_3OH). Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91; found C, 58.89; H, 8.16; N, 4.92.

4.2.10. Methyl 2-(6-oxo-2,5-diazatricyclo[6.2.2.0^{2,8}]-dodec-1-yl)acetate (7b).



Solid. Mp 151 °C. IR (KBr, ν, cm^{-1}): 1660, 1732 (C=O). ^1H NMR (600 MHz, $CDCl_3$, T=298 K): δ 1.50–1.80 (m, 8H), 2.56 (s, 2H), 2.60 (br s, 2H), 2.77 (br s, 2H), 3.35 (br s, 2H), 3.63 (s, 3H), 6.88 (br s, 1H); (T=255 K): δ 1.50–1.90 (m, 8H, CH_2-10–CH_2-13), 2.37, 2.89 (2m, 2H, CH_2-4), 2.54, 3.13 (2m, CH_2-2), 2.64 (s, 2H, CH_2-7), 3.32, 3.53 (2m, 2H, CH_2-5), 3.70 (s, 3H, OCH_3), 7.58 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, T=298 K): δ 33.35 (br s, C-10–C-13), 38.84 (C-7), 41.69 (C-5), 42.18 (C-2), 46.03 (C-4), 51.82 (OCH_3), 63.25 (C-3), 67.68 (C-6), 171.56 (C-8), 175.05 (C-1); (T=255 K): δ 29.96, 32.40, 33.77, 36.77 (C-10–C-13), 38.68 (C-7), 41.53 (C-2), 45.69 (C-4), 41.85 (C-5), 52.00 (OCH_3), 63.01 (C-3), 67.54 (C-6), 171.62 (C-8), 175.50 (C-1). MS (EI) *m/z* (relative intensity): 252 (35, M^+), 224 (30), 179 (37), 165 (100). Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10; found C, 61.93; H, 8.03; N, 10.89.

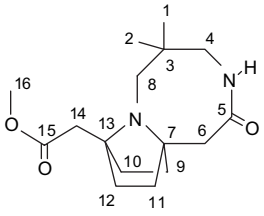
4.2.11. Methyl 2-(5-methyl-6-oxo-2,5-diazatricyclo[6.2.2.0^{2,8}]dodec-1-yl)acetate (7c).



Solid. IR (KBr, ν, cm^{-1}): 1650, 1736 (C=O). ^1H NMR (600 MHz, $CDCl_3$, T=298 K): δ 1.45–1.75 (m, 8H), 2.56 (s, 2H), 2.60 (br s, 2H), 2.82 (br s, 2H), 2.96 (s, 3H), 3.50 (br s, 2H), 3.64 (s, 3H); (T=255 K): δ 1.50–1.80 (m, 8H, CH_2-10,11,12,13), 2.40, 2.90 (2m, 2H, CH_2-4), 2.65, 3.12 (2m, 2H, CH_2-2), 2.67 (s, 2H, CH_2-7), 2.96 (s, 3H), 3.30, 3.85 (2m, 2H, CH_2-5), 3.64 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$, T=298 K): δ 33.37 (br s, C-10,11,12,13), 36.04 (NCH_3), 38.81 (C-7), 42.21 (C-2), 44.23 (C-4), 50.74 (C-5), 51.81 (OCH_3), 63.58 (C-3), 67.46 (C-6), 171.56 (C-8), 172.03 (C-1); (T=255 K): δ 29.89, 32.40, 33.77, 36.77 (C-10,11,12,13), 36.01 (NCH_3), 38.61 (C-7), 41.92 (C-2), 43.98 (C-4), 50.44 (C-5), 51.97 (OCH_3), 63.34 (C-3), 67.31 (C-6), 171.59 (C-8), 172.01 (C-1). MS (EI) *m/z* (relative intensity): 266 (59, M^+), 238 (42), 193 (63), 179 (100); (CI) *m/z* (relative intensity): 267 (100, MH^+). Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52; found C, 63.03; H, 8.39; N, 10.27.

7c·1H$_2$O: Solid. IR (KBr, ν, cm^{-1}): 1650, 1736 (C=O), 3467 (OH). ^1H NMR (CD_3CN, T=298 K): δ 1.45–1.75 (m, 8H), 2.20 (br s, 2H), 2.56 (s, 2H), 2.60 (br s, 2H), 2.82 (br s, 2H), 2.96 (s, 3H), 3.50 (br s, 2H), 3.64 (s, 3H); (T=323 K): δ 1.50–1.80 (m, 8H, CH_2-10–CH_2-13), 2.10 (br s, 2H), 2.40, 2.90 (2m, CH_2-4), 2.62 (s, 2H, CH_2-7), 2.65, 3.12 (2m, 2H, CH_2-2), 2.96 (s, 3H, NCH_3), 3.30, 3.85 (2m, 2H, CH_2-5), 3.64 (s, 3H, OCH_3); ($(CD_3)_2CO$, T=298 K): δ 1.45–1.75 (m, 8H), 2.20 (br s, 2H), 2.56 (s, 2H), 2.60 (br s, 2H), 2.77 (br s, 2H), 2.82 (br s, 2H), 2.96 (s, 3H), 3.50 (br s, 2H), 3.64 (s, 3H); (T=323 K): δ 1.50–1.80 (m, 8H, CH_2-10–CH_2-13), 2.10 (br s, 2H), 2.40, 2.90 (2m, CH_2-4), 2.47 (br s, 2H), 2.62 (s, 2H, CH_2-7), 2.65, 3.12 (2m, 2H, CH_2-2), 2.96 (s, 3H, NCH_3), 3.30, 3.85 (2m, 2H, CH_2-5), 3.64 (s, 3H, OCH_3). Calcd for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85; found C, 58.91; H, 8.43; N, 9.75.

4.2.12. Methyl 2-(4,4-dimethyl-7-oxo-2,6-diazatricyclo-[7.2.2.0^{2,9}]tridec-1-yl)acetate (7d).



Solid. Mp 179 °C. IR (KBr, ν, cm^{-1}): 1661, 1736 (C=O), 31.98, 32.91 (NH). ^{1}H NMR (600 MHz, $CDCl_3$, T=260 K) major isomer: δ 0.80 (s, 3H), 0.90 (s, 3H), 1.45–1.75 (m, 8H, CH_2-9–CH_2-12), 1.83 (A-part of AB system, J=14.8 Hz, 1H), 2.04 (B-part of AB system, J=14.8 Hz, 1H), 2.40 (A-part of AB system, J=13.2 Hz, 1H), 2.56 (m, 2H), 2.60 (d, J=4.4 Hz, 1H), 2.88 (B-part of AB system, J=13.2 Hz, 1H), 3.38 (dd, J=14.8, 11.1 Hz, 1H), 3.67 (s, 3H), 6.62 (br s, 1H); minor isomer: δ 0.78 (s, 3H), 0.98 (s, 3H), 1.45–1.75 (m, 8H, CH_2-9–CH_2-12), 2.06 (A-part of AB system, J=14.8 Hz, 1H), 2.24 (B-part of AB system, J=14.8 Hz, 1H), 2.29 (A-part of AB system, J=13.0 Hz, 1H), 2.54 (m, 2H), 2.72 (d, J=7.2 Hz, 1H), 2.75 (B-part of AB system, J=13.0 Hz, 1H), 3.20 (dd, J=13.5, 7.2 Hz, 1H), 3.67 (s, 3H), 6.70 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, T=298 K) major isomer: δ 23.16, 24.01 (C-1, C-2), 30.54 (C-9 or C-11), 32.73 (C-10 or C-12), 33.70 (C-10 or C-12), 36.57 (C-3), 38.08 (C-9 or C-11), 39.99 (C-14), 40.15 (C-6), 48.79 (C-8), 50.51 (C-4), 51.40 (C-16), 67.46 (C-7), 68.11 (C-13), 171.75 (C-15), 174.93 (C-5); minor isomer: δ 22.05, 27.03 (C-1, C-2), 32.18, 33.31, 33.87, 34.58 (C-9–C-11), 35.33 (C-3), 36.57 (C-6), 39.99 (C-14), 51.40 (C-16), 53.53 (C-8), 54.76 (C-4), 67.16 (C-13), 67.86 (C-7), 171.82 (C-15), 174.33 (C-5). MS (EI) *m/z* (relative intensity): 294 (11, M$^+$), 265 (42), 221 (100). Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52; found C, 65.02; H, 8.97; N, 9.48.

Compound ***8***: Solid. IR (KBr, ν, cm^{-1}): 1738 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.55–1.80 (m, 16H), 2.39 (s, 8H), 3.47 (AB system, 4H), 3.52 (s, 12H), 7.10–7.25 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 33.70 (CH_2 cycl.), 40.34 (CH_2), 46.70 (NCH_2), 51.60 (OCH_3), 67.12 (C cycl.), 126.19, 127.11, 128.12, 141.64 (C_6H_4), 171.98 (C=O). MS (EI) *m/z* (relative intensity): 584 (100, M$^+$), 553 (43), 511 (32).

Compound ***9***: Solid. IR (KBr, ν, cm^{-1}): 1650, 1736 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.51–1.70 (m, 16H), 2.36 (t, J=2.6 Hz, 2H), 2.59 (br s, 2H), 2.68 (br s, 6H), 2.75–2.85 (m, 2H), 3.25–3.35 (m, 2H), 3.55–3.65 (m, 2H), 3.65 (s, 6H), 3.66 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 33.51 (br s, C-10–C-13), 38.75, 39.70 ($CH_2C(O)O$), 40.23 (CH_2CON), 42.31, 45.12, 50.23, 51.00 (CH_2N), 51.71, 51.83 (OCH_3), 63.61, 67.27, 67.56 (C_q), 171.53, 171.83, 171.88 (C=O). MS (EI) *m/z* (relative intensity): 519 (5, M$^+$), 488 (10), 254 (100).

References and notes

1. Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117–128 and references therein.
2. (a) Ponsford, R. J.; Roberts, P. M.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1979**, 846–847; (b) Nagao, Y.; Kumagai, T.; Tamai, S.; Matsunaga, H.; Abe, T.; Inoue, Y. *Heterocycles* **1996**, *42*, 849–859; (c) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, *38*, 2519–2520; (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Odriozola, B.; Urchegui, R.; Goerls, H. *Chem. Commun.* **1996**, 1269–1271.
3. (a) Manhas, M. S.; Chib, J. S.; Chiang, Y. H.; Bose, A. K. *Tetrahedron* **1969**, *25*, 4421–4426; (b) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron* **1983**, *39*, 75–82; (c) Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1763–1768.
4. For an elegant enantioselective synthesis of this compound, see: Kambara, T.; Tomioka, K. *J. Org. Chem.* **1999**, *64*, 9282–9285.
5. Review about β-aminoesters as peptido mimetics: Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M.-I. *Curr. Med. Chem.* **2002**, *9*, 811–822; About α,β-diamino acids: Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3196.
6. See for instance: Gonzalez, J.; Koontz, J. I.; Hodges, L. M.; Nilsson, K. R.; Neely, L. K.; Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1995**, *117*, 3405–3421.
7. See for instance: (a) Ellis, J. L.; Harman, D.; Gonzalez, J.; Spera, M. L.; Liu, R.; Shen, T. Y.; Wypij, D. M.; Zuo, F. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 1143–1150; (b) Boyce, S.; Webb, J. K.; Shepheard, S. L.; Russell, M. G. N.; Hill, R. G.; Rupniak, N. M. J. *Pain* **2000**, *85*, 443–450; (c) Kassiou, M.; Bottlaender, M.; Loc'h, C.; Dolle, F.; Musachio, J. L.; Coulon, C.; Ottaviani, M.; Dannals, R. F.; Maziere, B. *Synapse* **2002**, *45*, 95–104.
8. (a) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639; (b) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290–4299; (c) Gorobets, E. N.; Miftakhov, M. S.; Valeev, F. A. *Russ. Chem. Rev.* **2000**, *69*, 1001–1019; (d) Volontiero, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827–1830.
9. Pfau, M. *Bull. Soc. Chim. Fr.* **1967**, 1117–1125.
10. For an extensive and recent review, see: Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891.
11. (a) D'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112–8114; (b) Jenner, G. *Tetrahedron* **1996**, *52*, 13557–13568.
12. Jenner, G. *New J. Chem.* **1995**, *19*, 173–178.
13. Rulev, A. Y.; Maddaluno, J. *J. Phys. Org. Chem.* **2002**, *15*, 590–598.
14. (a) Rulev, A. Y.; Maddaluno, J.; Plé, G.; Plaquevent, J.-C.; Duhamel, L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1397–1401; (b) Rulev, A. Y.; Maddaluno, J. *Eur. J. Org. Chem.* **2001**, 2569–2576.
15. Rulev, A. Y.; Maddaluno, J. Unpublished results.
16. Bryce, M. R.; Coates, H. M.; Cooper, J.; Murphy, L. C. *J. Org. Chem.* **1984**, *49*, 3399–3401.
17. Villieras, J.; Rambaud, M. *Synthesis* **1983**, 300–303.
18. For reviews on the asymmetric aza-Michael addition on esters and amides, see Refs. 1 and 11, as well as: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582; (b) *Enantioselective Synthesis of β-aminoacids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: Hoboken, NJ, USA, 2005; (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061.