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A versatile PIFA-mediated approach to structurally diverse pyrrolo(benzo)diazepines from linear alkynylamides

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Dedicated to the memory of our colleague and friend José Manuel Concellón

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ABSTRACT

The addition of the hypervalent iodine reagent PIFA [phenyliodine(III) bis(trifluoroacetate)] to a series of properly substituted *N*-(3-aminopropyl)alkynylamides results in the efficient formation of a functionalized 5-aroyl-2-pyrrolidinone skeleton. By proper manipulations of the N(1)-substituents, through consecutive deprotection and/or reductive amination steps, a second cyclization process occurs yielding the target heterocycles. As it will be disclosed, the overall process is open to structural modifications that gives rise to a series of pyrrolo(benzo)diazepine derivatives.

1. Introduction

The performance of synthetic studies on a particular structural motif with well-recognized biological or pharmacological actions has been a recurrent approach for the development of new methodologies in organic synthesis. Not surprisingly, the pyrrolo[1,2-*c*][1,4]benzodiazepine skeleton (PBD), as being part of the naturally-occurring DNA-interactive antitumor antibiotics known as the 'anthramycines',[1] has been the target for a number of different approaches. In general terms,[2] the use of adequately substituted *N*-(2-aminobenzoyl)proline derivatives[3] and isatoic anhydrides[4] are still the two main entrances to the synthesis of PBD derivatives. Such little options for the preparation of a type of heterocycle that requires as much structural diversity as possible for biological studies were recently enlarged by our group in a novel design for the enantiocontrolled synthesis of the antibiotic (−)-DC-81 that featured the intramolecular PIFA-assisted cyclization[5] of *N*-methoxyamides of type **1**, derived from L-proline, to render optically pure **2** (see Fig. 1).[6] From a mechanistic point of view, it is accepted that in this transformation the deficient *N*-acylnitrenium intermediate **I**, generated by the action of the I(III) reagent,[7] is intramolecularly captured by the arene system to perform the ring closure process.[8]

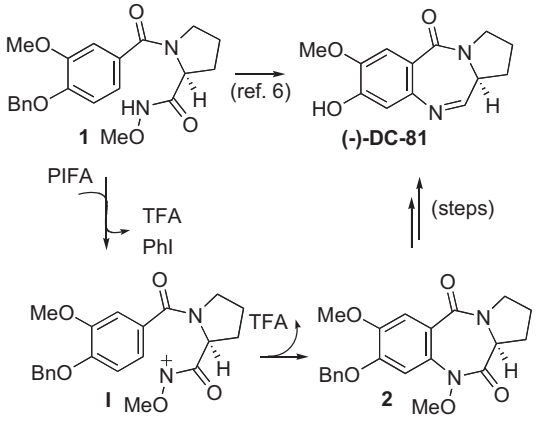

Figure 1. First approach to a PIFA-mediated synthesis of a pyrrolo(benzo)diazepine skeleton designed in our group.

Convinced of the need for developing novel and more versatile approaches to the preparation of PBD derivatives, we wish to report here a new routine to prepare such type of heterocycles based on the intramolecular formal double addition of a diamino fragment across both positions of a triple bond (from **3** to **4** in Fig. 2) assisted,

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once again, by the hypervalent iodine reagent PIFA. This proposal, adapted from our previous communications,[9] is based on the alternative activation of the electronically enriched triple bond by PIFA (instead of nitrogen oxidation) to give an electrophilic intermediate **II** that reacts intramolecularly with the nucleophilic amide to give **III**. Reaction of **III** with a free trifluoroacetate ligand delivered by PIFA results in the formation of a nonisolable ester **IV**, which after basic hydrolysis during the work up affords the substituted pyrrolidinone skeleton **V**. Finally, subtle selection of fragment $\sum$ will eventually lead to the final heterocycle **4** through application of reductive amination conditions.

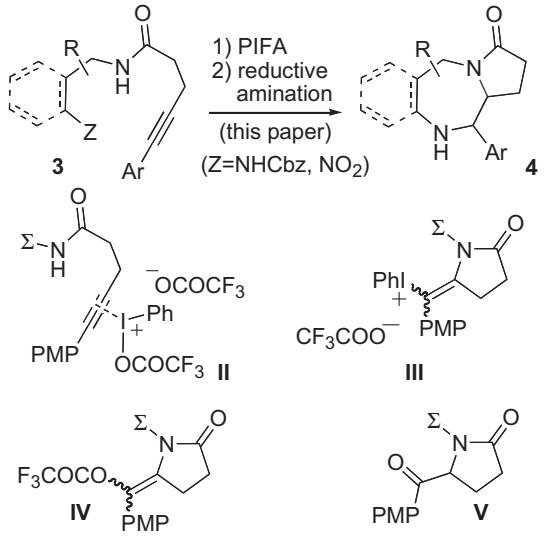
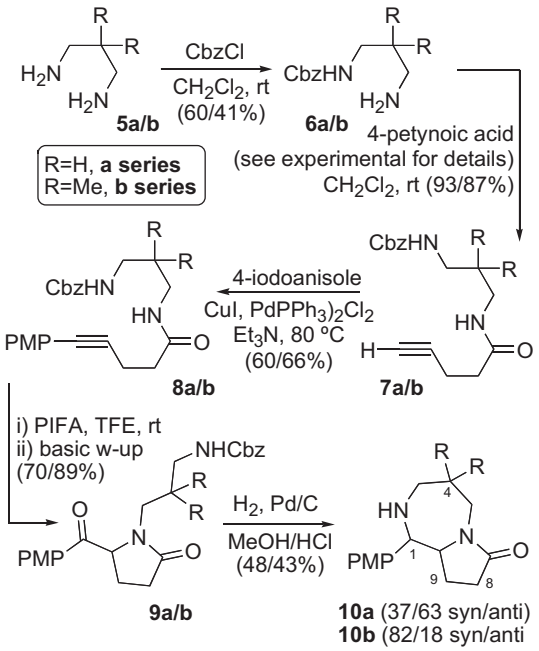


Figure 2. Second approach to a PIFA-mediated synthesis of a pyrrolo(benzo)diazepine skeleton designed in our group.

The fact that the present approach allows the preparation of both pyrrolodiazepine and pyrrolobenzodiazepine derivatives[10] by a common route and, additionally, with a less common oxygenated function at the C-3 position of the PBD skeleton, reinforces the interest for its development.[11]

2. Results and discussion

According to our synthetic plan, the preparation of the target molecules required bringing a number of different components together in a linear multifunctional molecule using 1,3-diaminopropane (**5a**) and 1,3-diamino-2,2-dimethylpropane (**5b**) as starting materials (see Scheme 1). Therefore, these compounds were first protected[12] as carbamates **6a**,**b** and then transformed into amides **7a**,**b** using pentynoic acid under standard conditions in very high yields. To accomplish the first part of the synthesis, a Sonogashira coupling reaction[13] was envisaged to include an activated *para*-methoxyphenyl group (PMP) at the terminal position of the triple bond. When all parts of substrates **8a**,**b** were assembled, they were submitted to the PIFA-mediated cyclization conditions. Thus, treatment of amides **8a**,**b** with a slight excess (1.5 equiv) of the hypervalent iodine reagent in trifluoroethanol (TFE) as solvent at room temperature, followed by a basic aqueous work up, rendered the 5-aroyl-2-pyrrolidinones **9a**,**b** in which the protected 3-aminopropyl appendage remained unaltered and ready to be used in the second cyclization step. Accordingly, treatment of derivatives **9a**,**b** under an atmosphere of H_2 (70 psi) using Pd(C) as catalyst in acidic methanol rendered pyrrolodiazepines **10a**,**b** in 48 and 43% yields, respectively, through a combination of three consecutive single processes (deprotection, intramolecular addition to the carbonyl group, and reduction of the resultant imine). It must be mentioned that an intensive spectroscopic study led to the conclusion that both substrates **10a**,**b** were formed as inseparable mixtures of *syn*/*anti* diastereoisomers in different proportions and with opposed preferences for the relative configuration of the new stereogenic center generated at C-1.

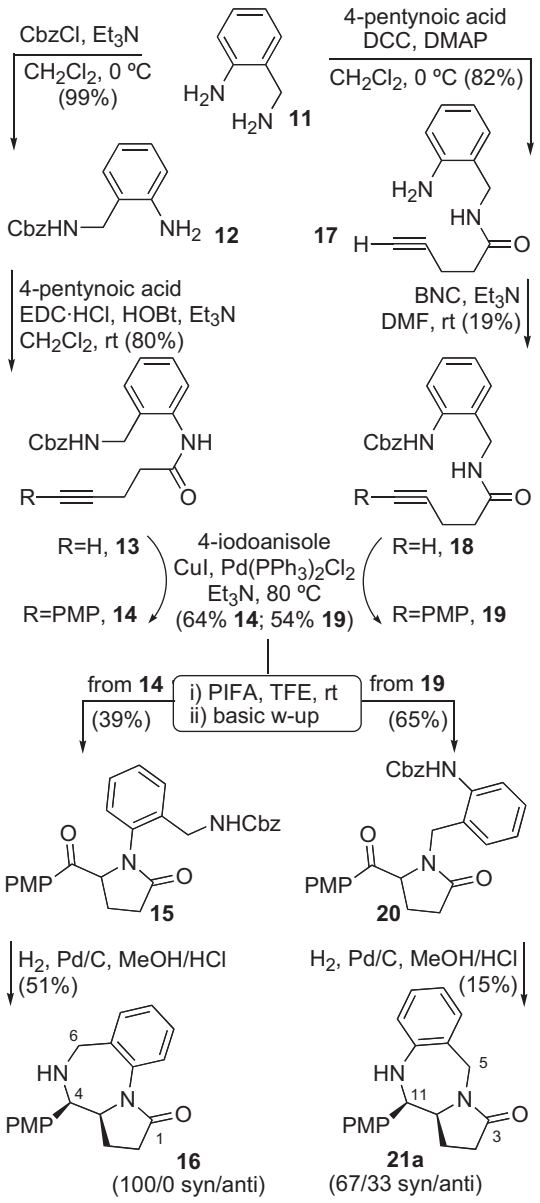


Scheme 1. Preparation of pyrrolodiazepinones **10a**,**b**.

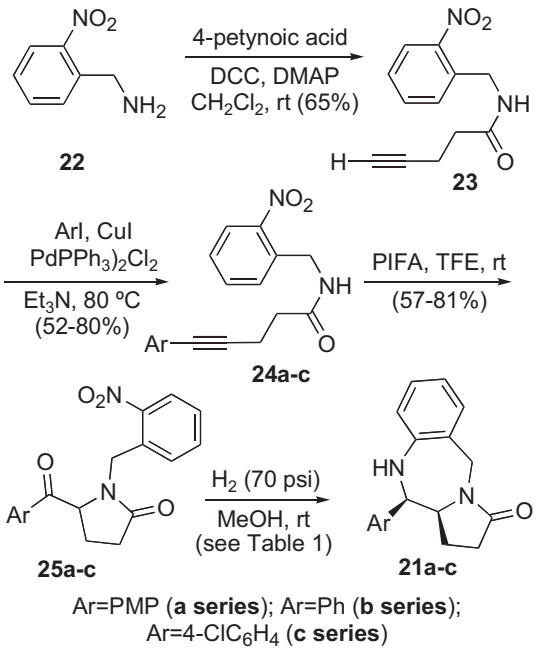
To the view of these results we planned to extend this synthetic strategy to the preparation of the PBD skeleton and, coherently, we selected 2-aminobenzylamine (**11**) as the starting material. As opposed to the previous design that started from symmetric diamines **5a**,**b**, the alteration in the order of protection/amidation events when applied to diamine **11** will eventually lead to two different regioisomers. Therefore, in order to demonstrate the versatility of this approach, we embarked in the preparation of both tricyclic derivatives following the route depicted in Scheme 2.

Taking advantage of the markedly different nucleophilicity of both amino groups in **11**, regioisomers **13** and **18** could be independently prepared by altering the sequence of amidation and protection steps. Successive Sonogashira coupling reaction under standard conditions, and PIFA-mediated cyclization rendered, respectively, pyrrolidinones **15** and **20** that were finally submitted to hydrogenation conditions. We were happy to find that, as anticipated, both regioisomeric pyrrolo-benzo[*f*]-1,4-diazepin-1-one **16** and pyrrolo-benzo[*e*]-1,4-diazepin-3-one **21a** were obtained, although with different results. In fact, while PBD **16**, which features a less common fusion of the three rings, was obtained from **15** in a reasonable yield (51%) and with complete *syn* diastereoselectivity, the efficiency of the synthesis of PBD **21a**, on the contrary, was not satisfactory at all (extremely low overall yield and poor diastereoselectivity in the final step), especially due to the difficulties associated to the protection step (from **17** to **18**)[14] and in the final cyclization (from **20** to **21a**).

As a consequence, we decided to explore a new protection-free synthetic alternative, outlined in Scheme 3, which starts now from 2-nitrobenzylamine (**22**) following a similar routine as before. Thus, after successive steps of amidation, Sonogashira coupling, and PIFA-mediated intramolecular cyclization, pyrrolidinone **25a** was prepared and submitted to the final reductive cyclization step. This part of the synthesis was optimized with respect to the use of



Scheme 2. Preparation of PBDs **16** and **21a**.



Scheme 3. Synthetic alternative for the preparation of PBDs **21a**–**c**.

Table 1
Optimization of the reductive cyclization of **25a**–**c** into **21a**–**c**

Entry	25	21	Conditions[a]	Yield (%)	(*syn*/*anti*)[b]
1	**a**	**a**	PtO_2/MeOH	92	(84/16)
2	**a**	**a**	Ra-Ni/MeOH[c]	58	(38/62)
3	**a**	**a**	$Pd(OH)_2$, MeOH	72	(53/47)
4	**a**	**a**	Pd(C)/MeOH-HCl	0[d]	—
5	**a**	**a**	Pd black/MeOH	71[e]	—
6	**b**	**b**	PtO_2/MeOH	95	(77/23)
7	**c**	**c**	PtO_2/MeOH	49	(71/29)

[a] A 10 wt % quantity of catalyst was employed.
[b] Determined from the crude ^1H NMR.
[c] The reduction of the NO_2 group to render *N*-(2′-aminobenzyl)-5-(4-methoxybenzoyl)-2-pyrrolidinone (**26a**) (98% yield) was the only process that could be detected when a limited amount (5 wt %) of catalyst was employed. The reaction progressed to the final compound in 58% yield with an additional amount of catalyst.
[d] A complex mixture of products was obtained.
[e] Isolated yield for pyrrolidinone **26a**.

different catalysts able to accomplish the reduction of the nitro group and the in situ heterocyclization under hydrogenation conditions. The results, summarized in Table 1, show that the best conditions to transform **25a** into PBD **21a** required the use of PtO_2 as catalyst (entry 1) working under a H_2 atmosphere (70 psi) at room temperature.[15] Some other attempts that include the use of other catalysts (entries 2 and 3) resulted in a less efficient transformation. It must be also mentioned that while the same conditions employed to transform **9** into **10**, and **15** into **16**, happened to be unproductive for **25a** (entry 4), the use of Pd black resulted exclusively in the reduction of the nitro group as the final stage of the reaction (entry 5). The addition of an extra amount of catalysts did not result in a further progress. In addition, the diastereoselectivity of the process was clearly favored with the use of PtO_2.

To the view of these results we decided to extend the synthetic strategy depicted in Scheme 3 to the preparation of a small series of derivatives **21a**–**c**, in which the aryl fragment located at C-11 is modified. Under such circumstances, 11-phenylPBD **21b** and 11-(4-chlorophenyl)PBD **21c** were obtained in reasonable good yields with good diastereoselectivities (entries 6–7 in Table 1).

3. Conclusions

In conclusion, we have shown that the intramolecular PIFA-mediated alkyne amidation reaction on *N*-(3-aminopropyl), *N*-(2-aminomethylphenyl), *N*-(2-aminobenzyl), and *N*-(2-nitrobenzyl) substituted substrates has proven to be an efficient alternative to prepare highly functionalized pyrrolidinones. As a demonstration of its usefulness, when this transformation is coupled with a second intramolecular amination step, the overall process results in a simple and rapid protocol for the synthesis of a series of pyrrolodiazepinone and pyrrolobenzodiazepinone derivatives.

4. Experimental section

4.1. General procedures

All reagents were purchased and used as received. All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140 °C) overnight and purged with argon prior to use. Melting points were measured

using open glass capillaries and are uncorrected. Infrared spectra were recorded as thin films and peaks are reported in cm^{-1}. Only representative absorptions are given. Flash chromatography was carried out on SiO_2 (silica gel 60, 230–400 mesh ASTM). NMR spectra were recorded on a 300 instrument (300 MHz for ^1H and 75.4 MHz for ^{13}C) at 20–25 °C unless otherwise stated. Chemical shifts (δ) were measured in parts per million relative to chloroform (δ=7.26 for ^1H or 77.0 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT and several bidimensional NMR experiments (COSY, HSQC, NOESY) were used to assist with the assignation of the signals and structural and stereochemical determinations. Mass spectra were recorded under electron impact (70 eV) or chemical ionization conditions.

4.2. Typical procedure for the benzyloxycarbonylation of diamines 5

*4.2.1. Synthesis of N-benzyloxycarbonyl-1,3-propanediamine (**6a**).* A stirred solution of benzyl chloroformiate (2.9 mL, 21 mmol) in 50 mL of CH_2Cl_2 was added dropwise over 85 min to a solution of 1,3-propanediamine **5a** (3.11 g, 42 mmol) in 70 mL of the same solvent at 0 °C. The mixture was stirred for additional 90 min, the temperature was raised to rt, and stirring was continued for 24 h. Then, the solid that was formed (the HCl salt of the excess of starting material) was filtered, and the solution was washed with brine (3×40 mL), decanted and dried over Na_2SO_4 (anhyd). Removal of the solvent under vacuum afforded an oil that was purified by column chromatography (EtOAc) to render carbamate **6a** as a colorless oil (60%): ^1H NMR ($CDCl_3$) δ (ppm) 7.32–7.26 (m, 5H), 5.55 (br s, 1H), 5.06 (s, 2H), 3.26–3.22 (m, 2H), 2.80–2.67 (m, 2H), 1.61–1.56 (m, 2H), 1.46 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 156.6, 136.7, 128.5, 128.0, 66.5, 39.6, 39.1, 33.0; IR ν (cm^{-1}) 3325, 2931, 1683; MS [M+1] *m*/*z*: 209 (41), 165 (10), 108 (26), 101 (100).

*4.2.2. N-Benzyloxycarbonyl-2,2-dimethyl-1,3-propanediamine (**6b**).* According to the typical procedure, carbamate **6b** was obtained from diamine **5b** in a 41% yield and purified by column chromatography (EtOAc) as a colorless oil: ^1H NMR ($CDCl_3$) δ (ppm) 7.37–7.12 (m, 5H), 6.05 (br s, 1H), 5.02 (s, 2H), 2.99 (s, 2H), 2.42 (s, 2H), 1.88 (s, 2H), 0.79 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 157.1, 136.8, 128.4, 128.0, 66.5, 50.4, 49.1, 35.6, 23.3; IR ν (cm^{-1}) 3320, 2944, 1702; MS [M+1] *m*/*z*: 237 (8), 129 (100), 108 (22), 107 (13); HRMS calcd for $C_{13}H_{20}N_2O\cdot H^+$: 237.1603, found: 237.1611.

*4.2.3. Synthesis of 2-amino-N-(benzyloxycarbonyl)benzylamine (**12**).* A stirred solution of benzyl chloroformiate (0.3 mL, 2.05 mmol) in 50 mL of CH_2Cl_2 was added dropwise over 85 min to a solution of benzylamine **11** (0.5 g, 4.1 mmol)[16] and Et_3N (0.3 mL, 6.1 mmol) in 6 mL of the same solvent at 0 °C. The mixture was stirred for additional 90 min, the temperature was raised to rt, and stirring was continued for 24 h. Then, a white precipitate was filtered, and the solution was washed with brine (3×40 mL), decanted and dried over Na_2SO_4 (anhyd). Removal of the solvent under vacuum afforded an oil that was purified by column chromatography (MeOH) to render carbamate **12** as a yellowish solid that was triturated in hexanes (99%): mp 52–53 °C (hexanes); ^1H NMR ($CDCl_3$) δ (ppm) 7.36 (s, 5H), 7.15–7.03 (m, 2H), 6.74–6.65 (m, 2H), 5.32 (br s, 1H), 5.12 (s, 2H), 4.28 (d, *J*=6.1, 2H), 4.09 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 157.0, 145.4, 136.4, 129.2, 128.6, 128.2, 128.1, 122.3, 118.1, 116.0, 67.0, 42.5; IR ν (cm^{-1}) 3349, 3029, 1692; MS [M+1] *m*/*z*: 257 (32), 256 (100), 196 (38), 149 (47), 148 (25), 121 (26), 106 (39); HRMS calcd for $C_{15}H_{16}N_2O_2\cdot H^+$: 257.1290, found: 257.1293.

*4.2.4. Synthesis of N-[(2-N′-benzyloxycarbonylamino)benzyl]-4-pentyamide (**18**).* Benzyl *para*-nitrophenyl carbonate (683 mg, 2.5 mmol) and Et_3N (1.1 mL, 7.5 mmol) were added, successively, into a solution of amide **17** (1.0 g, 4.9 mmol) in DMF (15 mL). The mixture was magnetically stirred at rt for 12 h under inert atmosphere. Then, solvent was removed under vacuum; the residue was taken in 40 mL of CH_2Cl_2 and washed with a saturated solution of Na_2CO_3 (30 mL). The decanted organic phase was dried with Na_2SO_4 (anhyd), the solvent removed under vacuum, and the resulting residue was purified by column chromatography (hexanes/EtOAc, 1/1) to afford **18** as a white solid that was triturated in hexanes (19%): mp 110–111 °C (hexanes); ^1H NMR ($CDCl_3$) δ (ppm) 8.79 (br s, 1H), 7.90 (d, *J*=8.4, 1H), 7.44–7.04 (m, 8H), 6.29 (m, 1H), 5.23 (s, 2H), 4.37 (d, *J*=6.4, 2H), 2.51–2.46 (m, 2H), 2.38–2.34 (m, 2H), 1.92 (t, *J*=2.6, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.0, 154.5, 136.8, 136.6, 128.5, 128.0, 123.9, 123.8, 122.4, 82.5, 69.6, 66.7, 40.6, 35.1, 14.8; IR ν (cm^{-1}) 3290, 3073, 1650, 1559; MS [M+1] *m*/*z*: 230 (11, M+1−Cbz), 229 (75), 227 (21), 149 (30), 147 (100), 132 (20); HRMS calcd for [$C_{20}H_{20}N_2O_3\cdot H^+$−Cbz] 230.1055, found: 230.1024.

4.3. Typical procedure for the acylation of amines. Method 1

*4.3.1. Synthesis of N-(3-N′-benzyloxycarbonyl-aminopropyl)-4-pentynamide (**7a**).* Amine **6a** (1.6 g, 7.7 mmol) was added to a cold (0 °C) solution of DCC (1.7 g, 8.5 mmol), DMAP (50 mg, 0.4 mmol), and 4-pentynoic acid (833 mg, 8.5 mmol) in CH_2Cl_2 (80 mL) and the mixture was stirred overnight. Then, a white solid (urea) was filtered and the solvent was evaporated at reduced pressure. The residue was purified by column chromatography (MeOH) to afford **7a** as a white solid that was triturated in cold ether (93%): mp 60–61 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.37–7.26 (m, 5H), 6.32 (br s, 1H), 5.34 (br s, 1H), 5.09 (s, 2H), 3.33–3.20 (m, 4H), 2.54–2.49 (m, 2H), 2.41–2.36 (m, 2H), 1.99 (s, 1H), 1.66–1.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.6, 128.5, 128.0, 82.9, 69.3, 37.6, 36.0, 35.4, 30.0, 15.0; IR ν (cm^{-1}) 3300, 2926, 1700, 1648; MS [M+1] *m*/*z*: 289 (55), 245 (46), 197 (20), 181 (100), 153 (16), 136 (18), 111 (20); HRMS calcd for $C_{16}H_{20}N_2O_3\cdot H^+$: 289.1552, found: 289.1551.

*4.3.2. Synthesis of N-(2-aminobenzyl)-4-pentynamide (**17**).* According to the typical procedure amide **17** was prepared from amine **11** and purified as a white solid in 82% yield by column chromatography (hexanes/EtOAc, 1/1) followed by crystallization from Et_2O: mp 76–77 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.10–6.99 (m, 2H), 6.67–6.60 (m, 2H), 6.48 (br s, 1H), 4.30 (d, *J*=6.1, 2H), 4.11 (br s, 2H), 2.48–2.43 (m, 2H), 2.36–2.31 (m, 2H), 1.947(s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.6, 145.5, 130.6, 129.2, 121.9, 117.8, 115.8, 83.0, 69.5, 40.8, 35.1, 14.9; IR ν (cm^{-1}) 3292, 3059, 1643; MS [M+1] *m*/*z*: 203 (35), 202 (100), 134 (10), 121 (31), 106 (81); HRMS calcd for $C_{12}H_{14}N_2O_3\cdot H^+$: 203.1184, found: 203.1186.

*4.3.3. N-(2-Nitromethylphenyl)-4-pentynamide (**23**).* According to the typical procedure amide **23** was prepared from benzylamine **22** as a yellowish solid in a 65% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration of the resultant solid in hexanes: mp 62–63 °C (hexanes); ^1H NMR ($CDCl_3$) δ (ppm) 7.96 (d, *J*=8.1, 1H), 7.58–7.50 (m, 2H), 7.40–7.34 (m, 1H), 7-01–6.97 (m, 1H), 4.62 (d, *J*=6.3, 2H), 2.43–2.36 (m, 4H), 1.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.6, 148.1, 133.7, 133.9, 131.5, 128.5, 125.0, 82.7, 69.5, 41.1, 35.0, 14.8; IR ν (cm^{-1}) 3296, 1653, 1524; MS [M+1] *m*/*z*: 233 (100), 225 (16), 186 (30), 153 (26), 136 (43), 135 (12); HRMS calcd for $C_{12}H_{12}N_2O_3\cdot H^+$: 233.0926, found: 233.0936.

4.4. Typical procedure for the acylation of amines. Method 2

*4.4.1. Synthesis of N-(3-N′-benzyloxycarbonylamino-2,2-dimethyl-propyl)-4-pentynamide (**7b**).* A solution of 4-pentynoic acid (640 mg, 6.5 mmol) in 5 mL of CH_2Cl_2 was added to a magnetically stirred solution of EDC·HCl (1.9 g, 9.9 mmol) and HOBt (1.35 g,

9.9 mmol) in 20 mL of the same solvent followed by the addition of the monoprotected diamine **6b** (2.35 g, 9.9 mmol) dissolved in 5 mL of CH_2Cl_2. The mixture was cooled to 0 °C and Et_3N (1.4 mL, 9.9 mmol) was added dropwise, and was left to react at room temperature overnight. Then, the reaction was diluted with CH_2Cl_2, water (25 mL) was added, the mixture was decanted, and the organic layer was consecutively washed with 20 mL of HCl (5% aq), 20 mL of a saturated solution of aqueous $NaHCO_3$, and 20 mL of a saturated solution of NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant chromatographically pure colorless oil was identified as amide **7b** (87%) and used without any further purification: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.26–7.18 (m, 5H), 6.23 (br s, 1H), 5.02 (s, 2H), 2.94 (d, J=6.6, 2H), 2.87 (d, J=6.6, 2H), 2.46–2.40 (m, 2H), 2.36–2.32 (m, 2H), 1.94 (s, 1H), 0.78 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.0, 157.6, 136.7, 128.4, 128.0, 127.9, 83.0, 69.5, 66.5, 47.5, 45.8, 36.4, 23.5, 15.2; IR ν (cm^{-1}) 3296, 1702, 1649; MS [M+1] m/z: 317 (12), 273 (37), 209 (100), 153 (17), 129 (27), 110 (17); HRMS calcd for $C_{18}H_{24}N_2O_3\cdot H^+$ 317.1865, found: 317.1858.

*4.4.2. N-[(2-N′-Benzyloxycarbonylaminomethyl)phenyl]-4-pentyamide (**13**).* According to the typical procedure amide **13** was prepared from monoprotected amine **12** as a white solid in 80% yield. It was purified by crystallization from Et_2O: mp 121–122 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 9.31 (br s, 1H), 8.06–8.04 (m, 1H), 7.34–7.06 (m, 8H), 5.54 (br s, 1H), 5.12 (s, 2H), 4.30 (d, J=6.7, 2H), 2.66–2.58 (m, 4H), 2.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.2, 157.8, 136.4, 136.0, 116.1, 130.4, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 124.6, 123.3, 83.1, 69.1, 67.5, 42.0, 35.9, 14.8; IR ν (cm^{-1}) 3295, 3024, 1686, 1653; MS [M+1] m/z: 337 (8), 276 (20), 201 (12), 185 (28), 149 (25), 108 (100), 107 (76); HRMS calcd for $C_{20}H_{20}N_2O_3\cdot H^+$: 337.1552, found: 337.1598.

4.5. Typical procedure for the Sonogashira coupling reaction

*4.5.1. Synthesis of N-(3-N′-benzyloxycarbonylaminopropyl)-5-(4-methoxyphenyl)-4-pentynamide (**8a**).* A solution of *para*-iodoanisole (1.4 g, 6.0 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), and carbamate **7a** (2.35 g, 6.0 mmol) in Et_3N (15 mL) was stirred at 80 °C for 24 h. When cooled, water (3 mL) was added, the mixture was extracted with EtOAc (3×25 mL), and the combined organic extracts were dried over Na_2SO_4 (anhyd). Once the solvent was evaporated under vacuum, the whole crude was purified by column chromatography (hexanes/EtOAc, 1/1) to afford amide **8a** as a white solid that was triturated in hexanes (60%): mp 114–116 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.35–7.29 (m, 7H), 6.80 (d, J=8.8, 2H), 6.20 (br s, 1H), 5.25 (br s, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 3.36–3.30 (m, 2H), 3.25–3.20 (m, 2H), 2.72 (t, J=7.2, 2H), 2.46 (t, J=7.2, 2H), 1.65–1.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.8, 159.3, 136.0, 115.5, 132.9, 128.5, 128.1, 128.0, 113.9, 86.8, 81.3, 66.7, 55.2, 37.5, 36.6, 35.9, 30.1, 16.1; IR ν (cm^{-1}) 3325, 2950, 1678, 1643; MS [M+1] m/z: 288 (M+1−Cbz), 287 (79), 245 (40), 189 (70), 188 (73), 159 (48), 147 (63), 135 (80), 101 (100); HRMS calcd for [$C_{23}H_{26}N_2O_4\cdot H^+$−Cbz] 288.1474, found: 288.1487.

*4.5.2. N-(3-N′-Benzyloxycarbonylamino-2,2-dimethylpropyl)-5-(4-methoxyphenyl)-4-pentynamide (**8b**).* According to the typical procedure amide **8b** was prepared from carbamate **7b** in 66% yield as a yellowish oil. It was purified by column chromatography (hexanes/EtOAc, 1/1): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.46–7.26 (m, 7H), 6.78 (d, J=8.9, 2H), 6.62–6.60 (m, 1H), 5.64–5.62 (m, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 3.05 (d, J=6.8, 2H), 2.93 (d, J=6.8, 2H), 2.72 (t, J=7.1, 2H), 2.48 (t, J=7.1, 2H), 0.85 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.0, 157.5, 159.2, 132.9, 128.5, 128.1, 128.0, 113.8, 86.8, 66.8, 55.2, 47.5, 45.7, 36.4, 36.1, 23.3, 16.2; IR ν (cm^{-1}) 3323, 2960, 1704, 1657; MS [M+1] m/z: 423 (17), 315 (100), 313 (14), 273 (37), 216 (10); HRMS calcd for $C_{25}H_{30}N_2O_4\cdot H^+$: 423.2284, found: 423.2287.

*4.5.3. N-[(2-N′-Benzyloxycarbonylaminomethyl)phenyl]-5-(4-methoxyphenyl)-4-pentyamide (**14**).* According to the typical procedure amide **14** was prepared from carbamate **13** in 64% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 1/1) followed by trituration of the resultant solid in hexanes: mp 125–126 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 9.32 (s, 1H), 8.08 (d, J=8.1, 1H), 7.33–7.07 (m, 10H), 6.79 (d, J=8.6, 2H), 5.44–5.42 (m, 1H), 5.11 (s, 2H), 4.28 (d, J=6.7, 2H), 3.78 (s, 3H), 2.87–2.80 (m, 2H), 2.73–2.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.5, 159.1, 157.7, 136.0, 133.0, 129.0, 128.6, 128.3, 128.1, 124.6, 123.4, 115.9, 113.8, 87.1, 81.1, 67.5, 55.2, 41.9, 36.5, 16.0; IR ν (cm^{-1}) 3295, 3054, 1689; MS [M+1] m/z: 443 (19), 335 (49), 293 (40), 187 (61), 149 (100), 147 (50), 135 (14), 108 (41), 107 (25); HRMS calcd for $C_{27}H_{26}N_2O_4\cdot H^+$: 443.1971, found: 443.1953.

*4.5.4. N-[(2-N-Benzyloxycarbonylamino)benzyl]-5-(4-methoxyphenyl)-4-pentyamide (**19**).* According to the typical procedure amide **19** was prepared from carbamate **18** in 54% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 109–110 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 9.03 (s, 1H), 7.88 (d, J=8.0, 1H), 7.43–7.21 (m, 11H), 6.75 (d, J=8.6, 1H), 6.64 (br s, 1H), 5.22 (s, 2H), 4.34 (d, J=6.4, 2H), 3.78 (s, 3H), 2.66 (t, J=7.1, 2H), 2.40 (t, J=7.1, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.4, 154.6, 136.8, 136.7, 132.9, 128.5, 127.6, 123.8, 123.7, 122.3, 115.3, 86.4, 81.6, 72.9, 66.6, 55.3, 40.5, 35.5, 15.9; IR ν (cm^{-1}) 3300, 3073, 1727, 1646; MS [M+1] m/z: 336 (23, M+1−Cbz), 335 (100), 293 (98), 199 (14), 188 (52), 160 (26), 147 (35); HRMS calcd for [$C_{27}H_{26}N_2O_4\cdot H^+$−Cbz] 336.1474, found: 336.1440.

*4.5.5. 5-(4-Methoxyphenyl)-N-(2-nitrobenzyl)-4-pentynamide (**24a**).* According to the typical procedure amide **24a** was prepared from amide **23** in 62% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 98–99 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.92 (d, J=8.1, 1H), 7.61 (d, J=7.6, 1H), 7.39–7.17 (m, 4H), 6.91–6.89 (m, 1H), 6.73 (d, J=8.7, 2H), 4.65 (d, J=6.3, 2H), 3.74 (s, 3H), 2.70–2.65 (m, 2H), 2.49–2.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.7, 159.2, 148.1, 133.8, 115.4, 134.0, 132.9, 131.5, 128.4, 124.9, 113.8, 86.6, 81.4, 55.2, 41.1, 35.6, 15.9; IR ν (cm^{-1}) 3290, 1653, 1509; MS [M+1] m/z: 339 (100), 297 (28), 291 (10), 203 (53), 158 (10), 136 (27); HRMS calcd for $C_{19}H_{18}N_2O_4\cdot H^+$: 339.1345, found: 339.1346.

*4.5.6. N-(2-Nitrobenzyl)-5-phenyl-4-pentynamide (**24b**).* According to the typical procedure amide **24b** was prepared from amide **23b** in 52% yield as a yellowish solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 82–83 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.97 (d, J=8.0, 1H), 7.68 (d, J=7.6, 1H), 7.50 (t, J=7.5, 1H), 7.39 (t, J=7.7, 1H), 7.31–7.23 (m, 5H), 6.58–6.56 (m, 1H), 4.71 (d, J=6.4, 2H), 2.74 (t, J=7.1, 2H), 2.50 (t, J=7.2, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.3, 148.3, 134.1, 133.6, 132.4, 131.5, 128.6, 128.2, 127.8, 125.0, 123.3, 88.0, 81.7, 41.2, 35.7, 15.9; IR ν (cm^{-1}) 3294, 1653, 1523; MS [M+1] m/z: 309 (100), 291 (10), 172 (8), 136 (17), 115 (12); HRMS calcd for $C_{18}H_{16}N_2O_3\cdot H^+$: 309.1239, found: 309.1231.

*4.5.7. 5-(4-Chlorophenyl)-N-(2-nitrobenzyl)-4-pentynamide (**24c**).* According to the typical procedure amide **24c** was prepared from amide **23c** in 80% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 101–102 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.99 (d, J=8.1, 1H), 7.68 (d, J=6.5, 1H), 7.54 (t, J=7.5, 1H), 7.41 (t, J=7.7, 1H),

7.25–7.18 (m, 4H), 6.54–6.52 (m, 1H), 4.70 (d, J=6.4, 2H), 2.73 (t, J=7.1, 2H), 2.49 (t, J=7.0, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.1, 148.3, 134.1, 133.5, 132.8, 132.6, 128.7, 128.5, 125.0, 89.1, 80.6, 41.3, 35.5, 15.8; IR ν (cm^{-1}) 3290, 1648, 1523; MS [M+1] m/z: 345 (34), 343 (100), 325 (11), 301 (11), 295 (22); HRMS calcd for $C_{18}H_{15}{}^{35}ClN_2O_3\cdot H^+$: 343.0849, found: 343.0851.

4.6. Typical procedure for the PIFA-mediated heterocyclization

*4.6.1. N-(3-N′-Benzyloxycarbonylaminopropyl)-5-(4′-methoxybenzoyl)-2-pyrrolidinone (**9a**).* A solution of alkynylamide **8a** (315 mg, 0.8 mmol) in CF_3CH_2OH (12 mL) was stirred at 0 °C and a solution of PIFA (526.8 mg, 1.2 mmol) in 6 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 2 h. For the work up, aqueous Na_2CO_3 (10%) was added and the mixture extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave the desired product **9a** as a chromatographically pure yellowish oil (70%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.93 (d, J=8.8, 2H), 7.33–7.26 (m, 5H), 6.97 (d, J=8.8, 2H), 5.61 (m, 1H), 5.15–5.02 (m, 3H), 3.89 (s, 3H), 3.71–3.56 (m, 1H), 3.41–3.27 (m, 1H), 3.16–3.02 (m, 2H), 2.52–2.34 (m, 3H), 2.02–1.98 (m, 1H), 1.70–1.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.4, 176.4, 164.3, 136.7, 130.7, 128.4, 128.0, 127.81, 114.3, 66.4, 61.8, 55.6, 39.3, 37.9, 29.5, 27.4, 23.8; IR ν (cm^{-1}) 3332, 2938, 1685, 1599, 1512; MS [M+1] m/z: 304 (12, M+1−Cbz), 303 (79), 260 (28), 167 (100), 135 (17); HRMS calcd for [$C_{23}H_{26}N_2O_5\cdot H^+$−Cbz] 304.1423, found: 304.1390.

*4.6.2. N-(3-N′-Benzyloxycarbonylamino-2,2-dimethylpropyl)-5-(4′-methoxybenzoyl)-2-pyrrolidi-none (**9b**).* According to the typical procedure pyrrolidinone **9b** was obtained from **8b** in 89% yield. It was purified by column chromatography (EtOAc) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.93 (d, J=8.8, 2H), 7.35–7.28 (m, 5H), 6.99 (d, J=8.8, 2H), 6.49–6.47 (m, 1H), 5.27 (d, J=9.1, 1H), 5.11 (d, J=12.3, 1H), 5.04 (d, J=12.3, 1H), 3.89 (s, 3H), 3.76 (d, J=14.8, 1H), 3.26–3.24 (m, 1H), 2.74–2.70 (m, 1H), 2.49–2.36 (m, 3H), 2.26 (d, J=14.8, 1H), 2.06–1.99 (m, 1H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.1, 177.7, 164.3, 157.2, 137.0, 130.7, 128.4, 127.9, 127.8, 127.0, 114.3, 66.3, 64.3, 55.6, 50.3, 47.7, 37.2, 28.9, 24.7, 23.6; IR ν (cm^{-1}) 3338, 2962, 1682, 1600; MS [M+1] m/z: 439 (1), 359 (10), 331 (100), 303 (11), 195 (47); HRMS calcd for $C_{25}H_{30}N_2O_5\cdot H^+$: 439.2233, found: 439.2249.

*4.6.3. N-[(2-N′-Benzyloxycarbonylaminomethyl)phenyl]-5-(4′-methoxybenzoyl)-2-pyrrolidinone (**15**).* According to the typical procedure pyrrolidinone **15** was obtained from **14** in 39% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a pale brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.87 (d, J=8.6, 2H), 7.49 (br s, 1H), 7.37–7.22 (m, 8H), 6.91 (d, J=8.8, 2H), 5.69–5.65 (m, 1H), 5.13 (s, 2H), 4.56–4.54 (m, 2H), 3.84 (s, 3H), 2.52–2.23 (m, 3H), 2.15–2.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.1, 164.3, 156.8, 136.8, 136.1, 127.0, 130.8, 128.5, 128.3, 128.1, 128.0, 114.2, 66.6, 64.9, 55.6, 41.4, 30.1, 24.5; IR ν (cm^{-1}) 3354, 1693, 1599; MS [M+1] m/z: 459 (6), 351 (17), 323 (20), 308 (100), 215 (63), 135 (11); HRMS calcd for $C_{27}H_{26}N_2O_5\cdot H^+$: 459.1920, found: 459.1900.

*4.6.4. N-[(2-N′-Benzyloxycarbonylamino)benzyl]-5-(4′-methoxybenzoyl)-2-pyrrolidinone (**20**).* According to the typical procedure pyrrolidinone **20** was obtained from **19** in 65% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 8.90 (s, 1H), 8.02 (d, J=8.1, 1H), 7.86 (d, J=8.7, 2H), 7.46–7.26 (m, 6H), 6.97–6.89 (m, 4H), 5.22 (s, 2H), 5.03–4.98 (m, 3H), 3.87 (s, 3H), 2.52–2.28 (m, 3H), 2.02–1.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 194.8, 176.4, 164.4, 154.3, 137.4, 136.8, 124.9, 130.7, 129.3, 128.5, 128.0, 127.9, 123.1, 121.7, 114.3, 66.5, 60.6, 55.6, 42.8, 29.2, 23.5; IR ν (cm^{-1}) 3251, 1732, 1679, 1597; MS [M+1] m/z: 352 (22, M+1−Cbz), 351 (100), 215 (84), 132 (33); HRMS calcd for [$C_{27}H_{26}N_2O_5\cdot H^+$−Cbz] 352.1323, found: 352.1387.

*4.6.5. 5-(4-Methoxybenzoyl)-N-(2-nitrobenzyl)-2-pyrrolidinone (**25a**).* According to the typical procedure pyrrolidinone **25a** was obtained from **24a** in 69% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a yellowish solid that was triturated in hexanes: mp 55–58 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.88–7.82 (m, 3H), 7.59–7.57 (m, 2H), 7.48–7.38 (m, 1H), 6.92 (d, J=8.8, 2H), 5.19–5.10 (m, 2H), 4.30 (d, J=16.0, 1H), 3.84 (s, 3H), 2.52–2.33 (m, 3H), 2.09–1.97 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.0, 176.2, 164.2, 148.7, 133.5, 132.0, 131.3, 130.7, 128.6, 126.9, 124.6, 114.2, 61.7, 55.6, 42.8, 29.0, 23.6; IR ν (cm^{-1}) 1690, 1600, 1524; MS [M+1] m/z: 355 (100), 219 (62), 135 (13); HRMS calcd for $C_{19}H_{18}N_2O_5\cdot H^+$: 355.1294, found: 355.1302.

*4.6.6. 5-Benzoyl-N-(2-nitrobenzyl)-2-pyrrolidinone (**25b**).* According to the typical procedure pyrrolidinone **25b** was obtained from **24b** in 81% yield. It was purified as a yellowish oil by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.91–7.88 (m, 3H), 7.66–7.56 (m, 3H), 7.49–7.40 (m, 3H), 5.22–5.15 (m, 2H), 4.41 (d, J=15.8, 1H), 2.50–2.43 (m, 3H), 2.05–2.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 196.5, 176.2, 148.7, 133.9, 131.8, 134.0, 133.6, 131.3, 129.0, 128.6, 128.3, 124.7, 62.0, 42.7, 28.9, 23.4; IR ν (cm^{-1}) 1696, 1525; MS [M+1] m/z: 326 (20), 325 (100), 219 (86), 136 (18); HRMS calcd for $C_{18}H_{16}N_2O_4\cdot H^+$: 325.1188, found: 325.1185.

*4.6.7. 5-(4-Chlorobenzoyl)-N-(2-nitrobenzyl)-2-pyrrolidinone (**25c**).* According to the typical procedure pyrrolidinone **25a** was obtained from **24a** in 57% yield. It was purified as a colorless oil by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.88–7.80 (m, 3H), 7.66–7.56 (m, 2H), 7.43 (d, J=8.6, 3H), 5.16–5.11 (m, 2H), 4.37 (d, J=15.6, 1H), 2.45–2.41 (m, 3H), 2.00–1.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.4, 175.9, 171.1, 148.8, 132.3, 131.8, 133.6, 131.9, 129.7, 129.3, 128.7, 124.6, 61.9, 42.5, 28.9, 23.3; IR ν (cm^{-1}) 1697, 1524; MS [M+1] m/z: 361 (23), 360 (14), 359 (70), 219 (100), 136 (22); HRMS calcd for $C_{18}H_{15}{}^{35}ClN_2O_4\cdot H^+$: 359.0799, found: 359.0798.

4.7. Typical procedure for the reductive amination (method 1)

*4.7.1. Synthesis of 1-(4-methoxyphenyl)-octahydro-pyrrolo[1,2-a][1,4]diazepin-7-one (**10a**).* A solution of pyrrolidinone **9a** (246 mg, 0.6 mmol) in 6 mL of MeOH and 0.5 mL of HCl (1 M) was hydrogenated (70 psi) in the presence of Pd/C overnight. The catalyst was filtered through Celite and the solution treated with 15 mL of an aqueous solution of Na_2CO_3 (20%). The mixture was extracted with CH_2Cl_2 (3×15 mL), the combined organic extracts were dried with Na_2SO_4, and the solvent evaporated under vacuum. The resulting oil was purified by column chromatography (MeOH) to afford diazepinone **10a** as a colorless oil (48%) as an inseparable mixture of both diastereoisomers. Reported data is given for the both of them: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.27 (d, J=8.8, 2H), 7.21 (d, J=8.5, 2H), 6.88–6.82 (m, 4H), 5.08 (br s, 1H), 4.60 (d, J=6.7, 1H), 3.84–3.79 (m, 1H), 3.82–3.79 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73–3.69 (m, 1H), 3.63–3,56 (m, 1H), 3.48–3.35 (m, 2H), 2.93–2.87 (m, 1H), 2.84–2.79 (m, 1H), 2.77–2.70 (m, 2H), 2.39–2.32 (m, 2H), 2.18–2.10 (m, 2H), 2.10–2.00 (m, 1H), 1.99–1.85 (m, 3H), 1.82–1.73 (m, 1H), 1.71–1.64 (m, 1H), 1.63–1.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.6, 176.1, 158.8, 158.5, 133.1, 133.8, 127.7, 127.0, 114.0, 113.7, 75.6, 71.2, 65.7, 63.6, 55.2, 40.6, 39.9, 39.2, 38.3, 30.5, 30.1, 29.5, 21.0, 17.7;

IR ν (cm^{-1}) 3349, 1663; HRMS calcd for $C_{15}H_{20}N_2O_2 \cdot H^+$: 261.1603, found: 261.1615.

*4.7.2. 4,4-Dimethyl-1-(4-methoxyphenyl)-octahydro-pyrrolo[1,2-a][1,4]diazepin-7-one (**10b**).* According to the typical procedure diazepinone **10b** was obtained from pyrrolidinone **9b** in 43% yield. It was purified by column chromatography (MeOH) as a pale brown oil as an inseparable mixture of both isomers. Reported data is given for the both of them: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.29 (d, J=8.4, 2H), 7.25 (d, J=8.0, 2H), 6.86–6.80 (m, 4H), 5.12 (br s, 1H), 4.80 (d, J=5.7, 1H), 4.03–4.00 (m, 1H), 3.96–3.91 (m, 1H), 3.89–3.85 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.65–3.62 (m, 1H), 3.44–3.42 (m, 1H), 3.25–3.20 (m, 1H), 3.08–2.79 (m, 4H), 2.56–2.54 (m, 1H), 2.15–2.10 (m, 1H), 2.05–1.99 (m, 3H), 1.82–1.72 (m, 3H), 1.13 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.4, 176.8, 127.6, 159.2, 158.8, 127.1, 113.9, 113.5, 74.7, 72.9, 71.5, 69.0, 55.4, 55.3, 52.7, 49.5, 49.3, 47.9, 29.6, 24.8, 24.7, 24.3, 24.0, 23.9, 20.9, 19.1; IR ν (cm^{-1}) 3285, 2955, 1673; HRMS calcd for $C_{17}H_{24}N_2O_2 \cdot H^+$: 289.1916, found: 289.1925.

*4.7.3. 4-(4-Methoxyphenyl)-2,3,3a,4,5,6-hexahydro-benzo[f]pyrrolo[1,2-a][1,4]diazepin-1-one (**16**).* According to the typical procedure diazepinone **16** was obtained from pyrrolidinone **15** in 51% yield. It was purified by column chromatography (MeOH) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.23–6.76 (m, 8H), 5.00–4.98 (m, 1H), 4.67 (d, J=17.0, 1H), 4.55 (d, J=17.0, 1H), 4.47–4.45 (m, 1H), 3.79 (s, 3H), 2.42–2.33 (m, 1H), 2.09–1.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 160.6, 159.3, 137.5, 132.3, 119.3, 127.7, 127.4, 126.1, 123.2, 113.6, 111.3, 72.3, 62.7, 55.2, 48.7, 29.1, 21.1; IR ν (cm^{-1}) 3310, 1670; MS [M+1] m/z: 309 (30), 291 (13), 172 (28), 171 (100); HRMS calcd for $C_{19}H_{20}N_2O_2 \cdot H^+$: 309.1603, found: 309.1615.

*4.7.4. 11-(4-Methoxyphenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21a**).* According to the typical procedure diazepinone **21a** was obtained from pyrrolidinone **20** in 15% yield. It was purified as a yellowish oil by column chromatography (MeOH) as an inseparable mixture of both isomers.

4.8. Typical procedure for the reductive amination (method 2)

*4.8.1. Synthesis of 11-(4-methoxyphenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21a**).* A solution of pyrrolidinone **25a** (500 mg, 1.4 mmol) in 10 mL of MeOH was hydrogenated (70 psi) in the presence of PtO_2 (50 mg) overnight. The catalyst was filtered through Celite and the solution was evaporated under vacuum. The resulting chromatographically pure white solid was identified as a diastereoisomeric mixture of diazepinone **21a** in a combined 92% yield. Both diastereoisomers could be partially purified by column chromatography (Et_2O) followed by triturating in the same solvent. Reported data is given for the isolated major (*syn*) stereoisomer: mp (Et_2O) 68–70 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.22–7.08 (m, 4H), 6.88–6.83 (m, 2H), 6.67–6.62 (m, 2H), 4.92 (d, J=6.0, 1H), 4.79 (d, J=14.6, 1H), 4.38–4.27 (m, 2H), 3.79–3.75 (m, 4H), 2.06–2.00 (m, 1H), 1.90–1.83 (m, 1H), 1.76–1.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.5, 159.5, 145.9, 132.7, 120.1, 131.8, 129.2, 127.6, 117.4, 115.6, 113.9, 75.0, 61.7, 55.3, 43.0, 29.7, 21.0; IR ν (cm^{-1}) 3358, 2931, 1655; MS [M+1] m/z: 309 (24), 204 (11), 190 (64), 189 (27), 106 (100); HRMS calcd for $C_{19}H_{20}N_2O_2 \cdot H^+$: 309.1603, found: 309.1609.

*4.8.2. 11-Phenyl-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21b**).* According to the typical procedure diazepinone **21b** was obtained from pyrrolidinone **25b** in combined 95% yield as a mixture of diastereoisomers that could be partially purified by column chromatography (Et_2O). Reported data is given for the isolated major (*syn*) stereoisomer: mp (Et_2O) 131–132 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.37–7.28 (m, 5H), 7.12–7.05 (m, 2H), 6.68–6.63 (m, 2H), 4.93 (d, J=14.6, 1H), 4.86 (d, J=5.7, 1H), 4.25 (d, J=14.6, 1H), 3.82–3.80 (m, 1H), 2.08–2.02 (m, 1H), 1.99–1.75 (m, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.5, 145.8, 140.7, 120.0, 131.8, 129.2, 128.6, 128.3, 126.4, 117.4, 115.6, 75.6, 61.7, 43.1, 29.7, 21.2; IR ν (cm^{-1}) 3357, 1651; MS [M+1] m/z: 279 (9), 204 (13), 190 (11), 189 (53), 106 (100); HRMS calcd for $C_{18}H_{18}N_2O \cdot H^+$: 279.1497, found: 279.1511.

*4.8.3. 11-(4-Chlorophenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21c**).* According to the typical procedure diazepinone **21c** was obtained from pyrrolidinone **25c** in 49% yield as a 71/29 mixture of *syn*/*anti* diastereoisomers that could be partially purified by column chromatography (Et_2O). Reported data is given for the major (*syn*) stereoisomer: mp (Et_2O) 239–240 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.29–7.26 (m, 2H), 7.22–7.19 (m, 3H), 7.11–7.06 (m, 1H), 6.79–6.76 (m, 1H), 6.55–6.53 (m, 1H), 4.99 (m, 1H), 4.67 (d, J=17.0, 1H), 4.55 (d, J=17.0, 1H), 4.47–4.45 (m, 1H), 3.79 (br s, 1H), 2.42–2.33 (m, 1H), 2.09–1.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.5, 146.2, 136.4, 134.1, 124.6, 129.9, 129.0, 128.7, 128.2, 121.1, 119.4, 63.5, 62.1, 44.8, 30.2, 20.2; IR ν (cm^{-1}) 3327, 1678; MS [M+1] m/z: 315 (33), 313 (100), 279 (7), 229 (45), 227 (54); HRMS calcd for $C_{18}H_{17}{}^{35}ClN_2O \cdot H^+$: 313.1108, found: 313.1111.

*4.8.4. Synthesis of N-(2′-aminobenzyl)-5-(4-methoxybenzoyl)-2-pyrrolidinone (**26a**).* A solution of pyrrolidinone **25a** (500 mg, 1.4 mmol) in 10 mL of MeOH was hydrogenated (70 psi) in the presence of PtO_2 (25 mg) overnight. The catalyst was filtered through Celite and the solution was evaporated under vacuum. The resulting chromatographically pure white solid (98% yield) was triturated in MeOH and identified as pyrrolidinone **26a**: mp 136–137 °C (MeOH); ^{1}H NMR (CD_3COCD_3) δ (ppm) 7.96 (d, J=8.9, 2H), 7.04 (d, J=8.9, 2H), 6.96 (t, J=7.6, 1H), 6.75 (d, J=7.0, 1H), 6.67 (d, J=8.0, 1H), 6.40 (d, J=7.3, 1H), 5.06–5.03 (m, 1H), 4.92 (d, J=14.7, 1H), 4.85–4.83 (m, 2H), 3.80 (s, 3H), 3.76 (d, J=14.7, 1H), 2.52–2.30 (m, 3H), 1.93–1.84 (m, 1H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 195.5, 175.9, 164.2, 145.9, 131.3, 130.7, 129.4, 127.2, 118.8, 117.3, 115.5, 114.2, 60.0, 55.6, 42.7, 29.6, 23.3; IR ν (cm^{-1}) 3359, 2931, 1679, 1599; MS [M+1] m/z: 325 (16), 324 (30), 307 (70), 306 (100), 223 (19), 189 (40), 106 (90); HRMS calcd for $C_{19}H_{20}N_2O_3 \cdot H^+$: 324.1474, found: 324.1481.

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Supplementary data

Supplementary data for this article can be found in the online version, at doi:10.1016/j.tet.2010.05.080. These data include MOL files and InChIKeys of the most important compounds described in this article.

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