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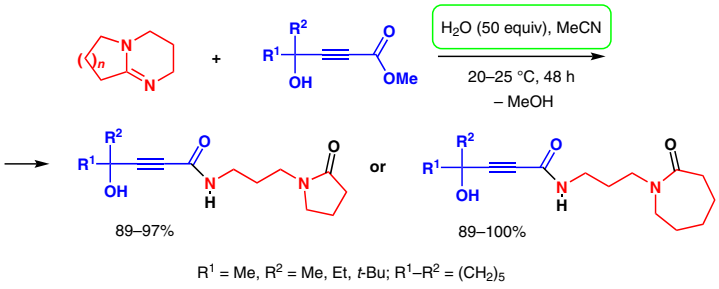
Synthesis of Acetylenic Amides with Propyllactam Moieties by In Situ DBU or DBN Ring-Opening Rearrangement in the Presence of Acetylenic Esters

Olesya A. Shemyakina
Ol'ga G. Volostnykh
Anton V. Stepanov
Anastasiya G. Mal'kina
Igor' A. Ushakov
Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., 664033, Irkutsk, Russian Federation
boris_trofimov@irioch.irk.ru



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Abstract DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) react with methyl esters of acetylenic acids and excess water (the reactant molar ratio 1:1, in aqueous MeCN, at 20–25 °C, for 48 h) to afford acetylenic amides with pyrrolidone and caprolactam moieties in 89–100% yields. The synthesis involves amines formed in situ from the cyclic amidines, which further react with acetylenic esters.

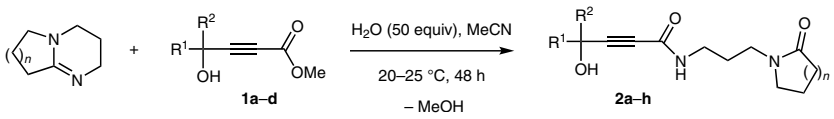
Key words DBN (1,5-diazabicyclo[4.3.0]non-5-ene), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), acetylenic acid esters, acetylenic amides, lactam

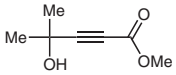
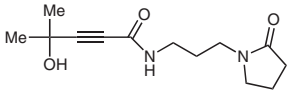
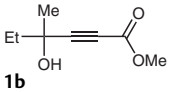
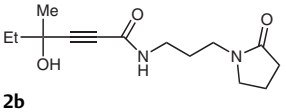
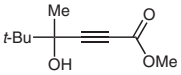
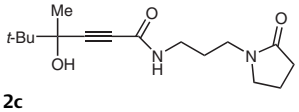
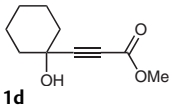
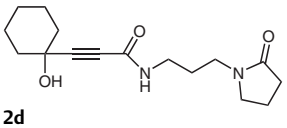
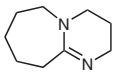
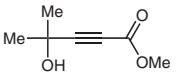
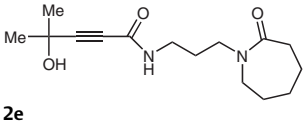
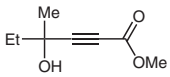
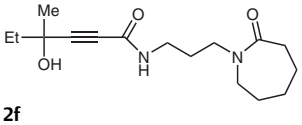
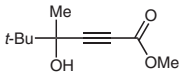
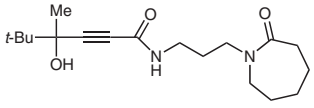
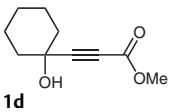
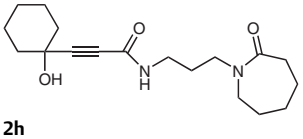
Bicyclic amidines, DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which are non-nucleophilic organic superbases, are widely used in organic synthesis as catalysts.[1] However, transformations of these amidines as nucleophiles are less common although this is currently attracting increasing attention.[2] Among them, there are rare reactions of DBN and DBU with acetylenic compounds, mostly alkynoates.[3] DBU was shown to be capable of annulating with dimethyl acetylenedicarboxylate, resulting in the formation of diazabenzoazulene.[3a] DBN and DBU annulation with methyl perfluoro-2-alkynoates[3b,c] and methyl propiolate[3d] led to diazaacenaphthalenes and diazacycloheptanaphthalenes.[3b–d] *p*-Nitrophenyl carbonates of 1-ethynylcyclohexanol and homopropargylic alcohol exclusively afforded the caprolactam and pyrrolidone products, 2-propynyl and 3-butynyl *N*-[3-(2-oxo-1-pyrrolidinyl/azepanyl)propyl]carbamates, when 2 equivalents of DBN and DBU were used.[3e] Recently, it was found[3f] that DBN and DBU annulated with electron-deficient acetylenic alcohols bearing CN, C(O)Ph, or CO_2Me electron-withdrawing functions to give condensed tricyclic derivatives – functionalized oxazolopyrrolohexahydropyrimidines and oxazolohexahydropyrimidoazepines. Notably, in the reaction of DBN with methyl esters of acetylenic acids, the participation of trace water in the ring opening of the pyrimidine moiety of the amidine was observed. This resulted in formation of complex molecules containing pyrrolidone and 2(5*H*)-furanone structures linked with the 1,3-diaminopropane chain.[3f] Thereby, the aim of the present work was to study the reaction of DBN and DBU with available[4] methyl esters of acetylenic acids in the presence of water in order to develop a general, efficient approach to the synthesis of the above pharmaceutically attractive compounds. Indeed, pyrrolidone and caprolactam are of high medicinal value. These structures are frequently met in natural products[5] (cotinine,[5a] mycobactin,[5b] cononusine,[5c] hygrocin,[5d] ervaluteine,[5c] pestalactams A–C,[5e] silvaticamide[5f] and the like), in some common drugs (e.g., benazepril, pecilocin, pyrrolidone-type nootropics as aniracetam, piracetam, pramiracetam, and others) and pharmacologically important compounds exhibiting antitumor,[6] anti-inflammatory,[7] and antimicrobial[8] activities. Some lactam derivatives are effective against Alzheimer's disease[9] and osteoporosis[10] as well as delivery carriers for therapeutic agents[11] and transdermal permeation enhancers[12] (trademark Azone and analogues).

Our experiments revealed that the reaction of DBN and DBU with methyl esters of acetylenic acids **1a–d** (a molar ratio amidines/**1**, 1:1, MeCN, 20–25 °C, 48 h) in the presence of excess water (1 mL, 50 equiv) proceeded chemoselectively (at the ester function only) and completed with formation of acetylenic amides **2a–h** tethered with pyrrolidone or caprolactam moiety, with yields ranging from 89 to 100% (Table 1).

The progress of the reaction was monitored by ^1H NMR spectroscopy following the disappearance of the MeO-group signal of starting acetylene **1** at δ = 3.77–3.74 ppm.

Table 1 Synthesis of Acetylenic Amides **2a–h**

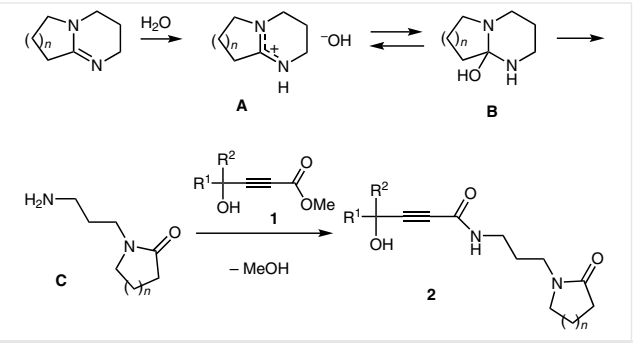


Amidine	Methyl ester of acetylenic acid **1**	Product **2**	Isolated yield (%)
	 **1a**	 **2a**	96
	 **1b**	 **2b**	89
	 **1c**	 **2c**	97
	 **1d**	 **2d**	97
	 **1a**	 **2e**	100
	 **1b**	 **2f**	93
	 **1c**	 **2g**	89
	 **1d**	 **2h**	98

The structures of amides **2a–h** have been proven by ^{1}H, ^{13}C, ^{15}N and 2D (NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C and ^{1}H-^{15}N HMBC) NMR techniques, as well as IR spectra. In the ^{1}H NMR spectra, the alkyl protons signals of lactam and alcohol moieties are present. In the ^{13}C NMR spectra of compounds **2a–h** the carbonyl carbons resonate in the region of 159.1–161.4 and 164.5–167.4 ppm, the signals of the C≡C carbons appear at 80.2–82.3 and 81.8–84.5 ppm. In the IR spectra of the products **2a–h**, the C≡C, C=O (lactam), and C=O (amide) absorption bands are observed at 2213–2225, 1644–1689, and 1576–1593 cm^{-1}, respectively.

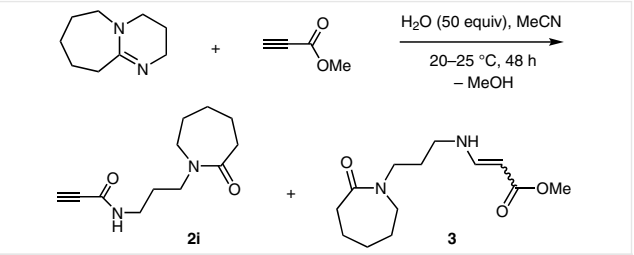
Notably, in contrast to the expectations, the reaction takes quite another direction as compared with the previous results.[3f] Indeed, the electron-deficient triple bond avoids the nucleophilic attack from the site of amidine nitrogen. Apparently, in excess water this nitrogen undergoes competitive protonation by a water molecule to give

ammonium hydroxide intermediate **A** (Scheme 1). In other words, the amidines behave in this case as typical bases rather than as nucleophiles. Furthermore, the covalent form of intermediate **A**, intermediate **B**, is subjected to rearrangement with the ring opening delivering 3-aminopropyllactams **C**. Their reaction with the methyl ester of acetylenic acid **1** leads to the final products, acetylenic amides **2** tethered to lactam cycles by 1,3-diaminopropane linkers. Such a rationalization is supported by reports[13] that DBU in water is protonated to form ammonium hydroxide (Scheme 1, intermediate **A**). Further support for the mechanism presented in Scheme 1 is the report[14] that DBN and DBU undergo ring opening in water (85 °C, 12 h) to afford aminopropyllactams in high yields (Scheme 1, intermediate **C**).



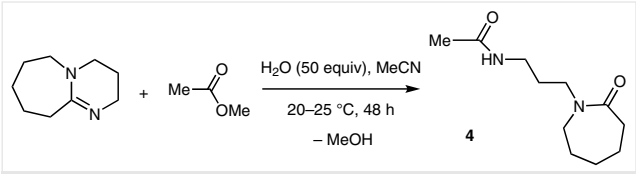
Scheme 1 Plausible mechanism

We have carried out the reaction of DBU with water without acetylenic substrate under the same conditions (1 mL H_2O, MeCN, 20–25 °C, 48 h) and observed by ^1H NMR spectroscopic analysis the formation of the expected amine **C** in ca. 85% yield. Since the yields of acetylenic amides **2a–h** are higher (89–100%, Table 1) it may be suggested that the presence of an acetylenic substrate facilitates the amidation, probably through formation of the corresponding zwitterion.[3f] When the reaction was conducted with methyl propiolate (with DBU), instead of acetylenic alcohols **1a–d**, the expected acetylenic amide **2i** is isolated in 84% yield along with adduct **3** of intermediate **C** to the triple bond of methyl propiolate (Scheme 2). Notably, such an addition has not been detectable for acetylenic alcohols, which is a specific feature of the latter.



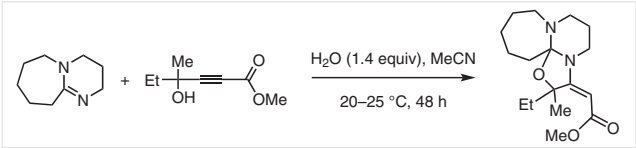
Scheme 2 Reaction of DBU and methyl propiolate

An additional support for the above mechanism is formation of acetamide **4** when DBU is allowed to react with methyl acetate under the same conditions (Scheme 3). This reaction may have a general value for organic synthesis if it is systematically developed.



Scheme 3 Reaction of DBU and methyl acetate

The excess water appeared to be crucial to determine the reaction chemoselectivity. In fact, in the presence of just 1.4 equivalents of water (relative to the reactant), acetylenic amide **2e** was not obtained. Instead, the DBU annulation with methyl ester of acetylenic acid **1b** took place to afford [1,3]oxazolo[3′,2′:3,4]hexahydropyrimido[1,2-*a*]azepine[3f] in 85% yield (Scheme 4).



Scheme 4 The DBU annulation with methyl ester of acetylenic acid **1b**

In conclusion, a crucial effect of the excess water on the reaction of DBN and DBU with methyl esters of acetylenic acids has been established. Unlike the previously described reactions[3f] carried out under anhydrous or water-limited conditions that result in the synthesis of oxazolopyrrolohexahydropyrimidines and oxazolohexahydropyrimidoazepines, the excess water (50 equiv in MeCN, 20–25 °C) completely redirects the interaction to the formation of acetylenic amides having pyrrolidone and caprolactam moieties in high yields (89–100%). The novel family of densely functionalized acetylenes represents a rewarding field for research towards the synthesis of drug precursors and building blocks for the design of pharmaceutically important molecules.

^1H and ^{13}C NMR spectra were recorded with a Bruker DPX-400 spectrometer (400.1 and 100.6 MHz, respectively) in $CDCl_3$ or CD_3OD using hexamethyldisiloxane as internal reference at 20–25 °C. IR spectra were measured with a Bruker Vertex-70 instrument in thin films or KBr pellets. Microanalyses were performed with a Flash 2000 elemental analyzer. Melting points were determined with a Kofler micro hot-stage.

The solvent was MeCN (spectroscopic grade) from Scientific Production Company 'Cryochrom' (St. Petersburg, Russia). DBN, DBU, methyl propiolate are commercial reagents (Merck). Methyl esters of acety-

lenic acids **1a–d** were prepared according to a published method.[4] Commercially available starting materials were used without further purification.

Synthesized acetylenic amides **2a–h** are hygroscopic.

4-Hydroxy-4-methyl-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-2-pentynamide (2a); Typical Procedure

To a stirred solution of DBN (124 mg, 1 mmol) in MeCN (4 mL), a solution of methyl 4-hydroxy-4-methyl-2-pentynoate (**1a**; 142 mg, 1 mmol) in MeCN (3 mL) and H_2O (1 mL) was added dropwise over 10 min. The reaction mixture was stirred at 20–25 °C for 48 h. Solvent was evaporated in vacuo and the residue was washed with a mixture of hexane–acetone (1:1) to give the desired product **2a**.

Yield: 242 mg (96%); snow-white solid; mp 131–135 °C.

IR (KBr): 3405, 3248, 3105, 3054, 2974, 2929, 2884, 2773, 2219 (–C≡C–), 1683, 1577 (C=O), 1460, 1340, 1211, 1173, 1142, 1067, 988, 946, 883, 849, 784, 734, 686, 559, 523, 464 cm^{-1}.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 3.64 (t, *J* = 7.1 Hz, 2 H, CH_2-5′), 3.48 (t, *J* = 5.5 Hz, 2 H, CH_2-3), 3.42 (t, *J* = 5.6 Hz, 2 H, CH_2-1), 3.07 (t, *J* = 7.9 Hz, 2 H, CH_2-3′), 2.16 (m, 2 H, CH_2-4′), 2.05 (m, 2 H, CH_2-2), 1.49 (s, 6 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.5 (C-2′), 159.1 (C=O), 83.1 (–C≡), 80.2 (≡C–), 64.3 (C–OH), 53.2 (C-5′), 42.5 (C-3), 38.0 (C-1), 31.2 (CH_3), 29.9 (C-3′), 18.8 (C-2), 18.7 (C-4′).

Anal. Calcd for $C_{13}H_{20}N_2O_3$ (252.31): C, 61.88; H, 7.99; N; 11.10. Found: C, 61.70; H, 7.92; N, 10.91.

4-Hydroxy-4-methyl-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-2-hexynamide (2b)

The residue was washed with a mixture of hexane–acetone (1:2) to give the desired product **2b**.

Yield: 236 mg (89%); snow-white solid; mp 104–108 °C.

IR (KBr): 3360, 3292, 3105, 3051, 2971, 2934, 2882, 2781, 2628, 2213 (–C≡C–), 1686, 1586 (C=O), 1461, 1399, 1337, 1286, 1190, 1134, 1061, 1023, 965, 917, 886, 852, 783, 718, 689, 598, 524, 467 cm^{-1}.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 3.63 (t, *J* = 7.2 Hz, 2 H, CH_2-5′), 3.48 (t, *J* = 5.7 Hz, 2 H, CH_2-3), 3.40 (t, *J* = 5.8 Hz, 2 H, CH_2-1), 3.08 (t, *J* = 8.0 Hz, 2 H, CH_2-3′), 2.15 (m, 2 H, CH_2-4′), 2.03 (m, 2 H, CH_2-2), 1.68 (m, 2 H, CH_3CH_2), 1.45 (s, 3 H, CH_3), 1.01 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.5 (C-2′), 159.1 (C=O), 82.0 (–C≡), 81.5 (≡C–), 67.9 (C–OH), 53.1 (C-5′), 42.5 (C-3), 38.0 (C-1), 36.2 (CH_3CH_2), 29.9 (CH_3), 28.9 (C-3′), 18.8 (C-2), 18.7 (C-4′), 8.9 (CH_3CH_2).

Anal. Calcd for $C_{13}H_{20}N_2O_3$ (266.34): C, 63.13; H, 8.33; N, 10.52. Found: C, 62.89; H, 8.31; N, 10.12.

4-Hydroxy-4,5,5-trimethyl-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-2-hexynamide (2c)

The residue was washed with a mixture of hexane–acetone (1:2) to give the desired product **2c**.

Yield: 284 mg (97%); snow-white solid; mp 138–143 °C.

IR (KBr): 3408, 3294, 3104, 3051, 2967, 2881, 2777, 2616, 2214 (–C≡C–), 1681, 1576 (C=O), 1460, 1418, 1341, 1212, 1155, 1114, 1069, 1015, 970, 915, 856, 790, 734, 685, 590, 556, 462 cm^{-1}.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 3.62 (t, *J* = 7.1 Hz, 2 H, CH_2-5′), 3.47 (t, *J* = 5.7 Hz, 2 H, CH_2-3), 3.40 (t, *J* = 5.7 Hz, 2 H, CH_2-1), 3.08 (t, *J* = 8.0 Hz, 2 H, CH_2-3′), 2.15 (m, 2 H, CH_2-4′), 2.03 (m, 2 H, CH_2-2), 1.42 (s, 3 H, CH_3), 1.03 (s, 9 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.5 (C-2′), 159.3 (C=O), 82.5 (–C≡), 82.1 (≡C–), 73.4 (C–OH), 53.1 (C-5′), 42.5 (C-3), 38.1 [*C*$(CH_3)_3$], 38.0 (C-1), 29.9 (C-3′), 25.2 [$(CH_3)_3$], 24.6 (CH_3), 18.8 (C-2), 18.7 (C-4′).

Anal. Calcd for $C_{16}H_{26}N_2O_3$ (294.39): C, 65.28; H, 8.90; N, 9.52. Found: C, 65.04; H, 8.52; N, 9.16.

3-(1-Hydroxycyclohexyl)-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-2-propynamide (2d)

The residue was washed with a mixture of hexane–acetone (1:2) to give the desired product **2d**.

Yield: 282 mg (97%); snow-white solid; mp 138–144 °C.

IR (KBr): 3393, 3098, 3048, 2935, 2889, 2858, 2738, 2679, 2623, 2207 (–C≡C–), 1689, 1581 (C=O), 1448, 1335, 1282, 1259, 1218, 1167, 1132, 1075, 994, 966, 894, 851, 781, 749, 711, 626, 522 cm^{-1}.

^1H NMR (400.1 MHz, CD_3OD): δ = 3.72 (t, *J* = 7.2 Hz, 2 H, CH_2-5′), 3.47 (t, *J* = 5.7 Hz, 2 H, CH_2-3), 3.42 (t, *J* = 5.6 Hz, 2 H, CH_2-1), 2.91 (t, *J* = 7.9 Hz, 2 H, CH_2-3′), 2.18 (m, 2 H, CH_2-4′), 2.06 (m, 2 H, CH_2-2), 1.88 (m, 2 H, CH_2), 1.70–1.49 (m, 7 H, CH_2), 1.29 (m, 1 H, CH_2).

^{13}C NMR (100.6 MHz, CD_3OD): δ = 165.8 (C-2′), 161.4 (C=O), 84.5 (–C≡), 82.2 (≡C–), 68.8 (C-cHex), 54.7 (C-5′), 43.8 (C-3), 40.5 (C-cHex), 39.3 (C-1), 31.1 (C-3′), 26.3, 24.0 (C-cHex), 19.6 (C-2), 19.5 (C-4′).

^{15}N NMR (40.56 MHz, CD_3OD): δ = –257.5 (N-1′), –280.4 (NH).

Anal. Calcd for $C_{16}H_{24}N_2O_3$ (292.37): C, 65.73; H, 8.27; N, 9.58. Found: C, 65.78; H, 8.46; N, 9.96.

4-Hydroxy-4-methyl-*N*-[3-(2-oxo-1-azepanyl)propyl]-2-pentynamide (2e)

The residue was washed with diethyl ether to give the desired product **2e**.

Yield: 280 mg (100%); snow-white solid; mp 94–98 °C.

IR (KBr): 3410, 3221, 3137, 3043, 2971, 2925, 2866, 2806, 2701, 2225 (–C≡C–), 1648, 1582 (C=O), 1469, 1413, 1346, 1202, 1164, 1111, 987, 949, 923, 891, 846, 787, 729, 608, 557, 529 cm^{-1}.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 3.50–3.44 (m, 6 H, CH_2-1,3,7′), 2.85 (m, 2 H, CH_2-3′), 2.02 (m, 2 H, CH_2-2), 1.75, 1.67 (m, 6 H, CH_2-4′,5′,6′), 1.50 (s, 6 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.1 (C-2′), 159.3 (C=O), 82.7 (–C≡), 80.5 (≡C–), 64.7 (C–OH), 54.2 (C-7′), 48.6 (C-3), 38.1 (C-1), 32.1 (C-3′), 31.2 (CH_3), 29.1 (C-5′), 27.0 (C-6′), 24.1 (C-4′), 19.7 (C-2).

Anal. Calcd for $C_{15}H_{24}N_2O_3$ (280.36): C, 64.26; H, 8.63; N, 9.99. Found: C, 64.58; H, 8.61; N, 9.92.

4-Hydroxy-4-methyl-*N*-[3-(2-oxo-1-azepanyl)propyl]-2-hexynamide (2f)

The residue was washed with a mixture of hexane–acetone (2:1) to give the desired product **2f**.

Yield: 274 mg (93%); snow-white solid; mp 105–108 °C.

IR (KBr): 3379, 3261, 3107, 3039, 2974, 2929, 2882, 2785, 2733, 2680, 2636, 2217 (–C≡C–), 1644, 1583 (C=O), 1471, 1345, 1321, 1286, 1204, 1163, 1104, 1038, 972, 921, 855, 783, 724, 692, 639, 599, 563, 509 cm^{-1}.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 3.50–3.44 (m, 6 H, CH_2-1,3,7′), 2.86 (m, 2 H, CH_2-3′), 2.02 (m, 2 H, CH_2-2), 1.75, 1.67 (m, 6 H, CH_2-4′,5′,6′), 1.66 (m, 2 H, CH_3CH_2), 1.45 (s, 3 H, CH_3), 1.01 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.1 (C-2′), 159.3 (C=O), 81.8 (–C≡), 81.6 (≡C–), 68.3 (C–OH), 54.2 (C-7′), 48.6 (C-3), 38.0 (C-1), 36.3 (CH_3CH_2), 32.1 (C-3′), 29.1 (CH_3), 29.0 (C-5′), 27.0 (C-6′), 24.1 (C-4′), 19.7 (C-2), 9.0 (CH_3CH_2).

Anal. Calcd for $C_{16}H_{26}N_2O_3$ (294.39): C, 65.28; H, 8.90; N, 9.52. Found: C, 65.08; H, 8.82; N, 9.20.

4-Hydroxy-4,5,5-trimethyl-*N*-[3-(2-oxo-1-azepanyl)propyl]-2-hexynamide (2g)

The residue was washed with a mixture of hexane–acetone (1:2) to give the desired product **2g**.

Yield: 285 mg (89%); snow-white solid; mp 139–144 °C.

IR (KBr): 3408, 3236, 3055, 2974, 2929, 2864, 2794, 2757, 2705, 2214 (–C≡C–), 1650, 1593 (C=O), 1474, 1454, 1384, 1337, 1234, 1206, 1161, 1108, 1008, 975, 915, 867, 801, 781, 730, 693, 606, 585, 558, 510 cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.50–3.44 (m, 6 H, CH_2-1,3,7′), 2.86 (m, 2 H, CH_2-3′), 2.02 (m, 2 H, CH_2-2), 1.75, 1.67 (m, 6 H, CH_2-4′,5′,6′), 1.43 (s, 3 H, CH_3), 1.03 (s, 9 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.1 (C-2′), 159.3 (C=O), 82.7 (–C≡), 81.5 (≡C–),73.6 (C–OH), 54.2 (C-7′), 48.6 (C-3), 38.2 [$C(CH_3)_3$], 38.0 (C-1), 32.0 (C-3′), 29.0 (C-5′), 27.0 (C-6′), 25.2 [$(CH_3)_3$], 24.6 (CH_3), 24.1 (C-4′), 19.6 (C-2).

Anal. Calcd for $C_{18}H_{30}N_2O_3$ (322.44): C, 67.05; H, 9.38; N, 8.69. Found: C, 66.81; H, 9.40; N, 8.82.

3-(1-Hydroxycyclohexyl)-*N*-[3-(2-oxo-1-azepanyl)propyl]-2-propynamide (2h)

The residue was washed with acetone to give the desired product **2h**.

Yield: 314 mg (98%); snow-white solid; mp 135–140 °C.

IR (KBr): 3297, 3231, 3043, 2981, 2930, 2857, 2803, 2693, 2202 (–C≡C–), 1652, 1578 (C=O), 1465, 1450, 1339, 1266, 1204, 1174, 1166, 1082, 989, 970, 890, 845, 813, 784, 714, 682, 542 cm^{-1}.

^{1}H NMR (400.1 MHz, CD_3OD): δ = 3.62 (m, 2 H, CH_2-7′), 3.57 (m, 2 H, CH_2-3), 3.37 (m, 2 H, CH_2-1), 2.71 (m, 2 H, CH_2-3′), 2.05 (m, 2 H, CH_2-2), 1.89 (m, 2 H, CH_2), 1.79 (m, 2 H, CH_2-5′), 1.76 (m, 2 H, CH_2-4′), 1.72 (m, 2 H, CH_2-6′), 1.65, 1.59, 1.56, 1.54 (m, 7 H, CH_2), 1.27 (m, 1 H, CH_2).

^{13}C NMR (100.6 MHz, CD_3OD): δ = 167.4 (C-2′), 161.3 (C=O), 84.5 (–C≡), 82.3 (≡C–), 68.8 (C-cHex), 55.3 (C-7′), 49.5 (C-3), 40.5 (C-cHex), 39.3 (C-1), 33.7 (C-3′), 29.9 (C-5′), 27.4 (C-6′), 26.3 (C-cHex), 24.9 (C-4′), 24.0 (C-cHex), 20.4 (C-2).

^{15}N NMR (40.56 MHz, CD_3OD): δ = –259.7 (N-1′), –268.6 (NH).

Anal. Calcd for $C_{18}H_{28}N_2O_3$ (320.43): C, 67.47; H, 8.81; N, 8.74. Found: C, 67.13; H, 8.78; N, 8.81.

***N*-(3-(2-Oxo-1-azepanyl)propyl)propiolamide (2i) and Methyl 3-((3-(2-Oxo-1-azepanyl)propyl)amino)acrylate (3)**

The residue was washed with diethyl ether to give **2i** (186 mg, 84%), solvent was removed from the diethyl ether fraction to obtain **3** (36 mg, 14%).

***N*-(3-(2-Oxo-1-azepanyl)propyl)propiolamide (2i)**

Yellow oil.

IR (film): 3403, 3232, 3113, 3043, 2928, 2863, 2811, 2702, 2076, 1643, 1603, 1448, 1328, 1206, 1153, 1105, 987, 872, 791, 744, 693, 578, 506 cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.53 (m, 4 H, CH_2-7′,3), 3.42 (m, 2 H, CH_2-1), 2.80 (m, 2 H, CH_2-3′), 2.49 (s, 1 H, ≡CH), 2.03 (m, 2 H, CH_2-2), 1.77–1.66 (m, 6 H, CH_2-4′,5′,6′).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.9 (C-2′), 157.8 (C=O), 81.8 (≡C–), 65.88 (≡CH), 54.1 (C-7′), 48.4 (C-3), 37.9 (C-1), 32.0 (C-3′), 28.8 (C-5′), 26.6 (C-6′), 23.8 (C-4′), 19.3 (C-2).

^{15}N NMR (40.56 MHz, $CDCl_3$): δ = –263.9 (N-1′), –261.4 (NH).

Anal. Calcd for $C_{12}H_{18}N_2O_2$ (222.29): C, 64.84; H, 8.16; N, 12.60. Found: C, 64.58; H, 8.41; N, 12.65.

Methyl 3-((3-(2-Oxo-1-azepanyl)propyl)amino)acrylate (3)

Light-yellow oil; *E*/*Z* ~ 80/20.

IR (film): 3314, 3054, 2929, 2857, 1675, 1618, 1537, 1485, 1439, 1367, 1304, 1240, 1189, 1147, 1081, 1050, 983, 938, 546, 791, 718, 576 cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ (*E*-isomer) = 7.49 [m, 1 H, =*CH*(NH)], 5.73 (br s, 1 H, NH), 4.71 [d, *J* = 13.0 Hz, 1 H, =*CH*(CO_2Me)], 3.60 (s, 3 H, OMe), 3.41 (m, 2 H, CH_2-3), 3.32 (m, 2 H, CH_2-7′), 3.02 (m, 2 H, CH_2-1), 2.51 (m, 2 H, CH_2-3′), 1.77–1.60 (m, 8 H, CH_2-2,4′,5′,6′); δ (*Z*-isomer) = 7.96 (br s, 1 H, NH), 6.62 [dd, *J* = 8.1 Hz, 1 H, =*CH*(NH)], 4.45 [d, *J* = 8.1 Hz, 1 H, =*CH*(CO_2Me)], 3.60 (s, 3 H, OMe), 3.41 (m, 2 H, CH_2-3), 3.32 (m, 2 H, CH_2-7′), 3.16 (m, 2 H, CH_2-1), 2.51 (m, 2 H, CH_2-3′), 1.77–1.60 (m, 8 H, CH_2-2,4′,5′,6′).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ (*E*-isomer) = 176.7 (C=O), 170.1 (OCO), 149.7 [=CH(NH)], 84.5 [=*C*H(CO_2Me)], 50.4 (OMe), 49.7 (C-7′), 45.1 (C-3), 40.0 (br, C-1), 37.1 (C-3′), 29.9 (C-5′), 28.5 (C-6′), 26.8 (br, C-2), 23.4 (C-4′); δ (*Z*-isomer) = 176.0 (C=O), 171.0 (OCO), 152.2 [=CH(NH)], 81.5 [=*C*H(CO_2Me)], 50.1 (OMe), 49.6 (C-7′), 46.2 (C-1), 45.4 (C-3), 26.8 (C-2), 37.1 (C-3′), 29.9 (C-5′), 28.7 (C-6′), 23.4 (C-4′).

Anal. Calcd for $C_{13}H_{22}N_2O_3$ (254.33): C, 61.39; H, 8.72; N, 11.01. Found: C, 61.41; H, 8.52; N, 11.05.

***N*-[3-(2-Oxo-1-azepanyl)propyl]acetamide (4)**

The residue was washed with diethyl ether to give the desired product **4**.

Yield: 180 mg (85%); light-yellow oil.

IR (film): 3390, 3253, 3096, 3035, 2929, 2863, 2810, 2698, 1644, 1574, 1442, 1397, 1325, 1205, 1157, 1108, 1009, 989, 916, 842, 748, 692, 647, 527, 506, 470 cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 4.96 (br s, 1 H, NH), 3.44 (m, 6 H, CH_2-1,3,7′), 2.87 (m, 2 H, CH_2-3′), 1.99 (m, 2 H, CH_2-2), 1.96 (s, 3 H, CH_3), 1.76, 1.67 (m, 6 H, CH_2-4′,5,6′).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.9 (C-2′), 165.6 (C=O), 53.8 (C-7′), 48.3 (C-3), 37.8 (C-1), 31.8 (C-3′), 28.8 (C-5′), 26.7 (C-6′), 24.5 (CH_3), 23.9 (C-4′), 19.4 (C-2).

^{15}N NMR (40.56 MHz, $CDCl_3$): δ = –255.1 (N-1′), –266.8 (NH).

Anal. Calcd for $C_{11}H_{20}N_2O_2$ (212.15): C, 62.24; H, 9.50; N, 13.20. Found: C, 62.13; H, 9.63; N, 13.29.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591852.

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