

Synthesis of Novel Bis(β -lactam)-1,3-diynes by Copper-Promoted Homo- or Cross-Coupling of Alkynyl-2-azetidinones

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Cu(OAc)₂ in combination with K₂CO₃ (a solid base instead of an amine) was proven to be an extremely effective system for promoting the homocoupling of various (β -lactam)acetylenes to afford C₂-symmetrical bis(β -lactam)-1,3-diynes, whereas these 2-azetidinone-tethered alkynes underwent the Cadiot–Chodkiewicz cross-coupling reaction with different 2-azetidinone bromoalkynes to form a variety of un-

symmetrical bis(β -lactam)diynes in good yields. In addition to their potential biological activity, the resulting enantiopure bis(β -lactam)-1,3-diynes can be converted into bis(β -amino ester)-1,3-diynes, which may find use as macrocyclic cavities, as well as chiral ligands.

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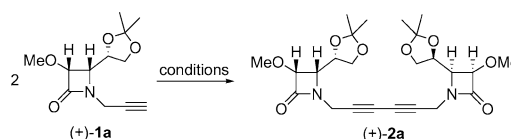
Introduction

Besides the utility of β -lactams as biologically active agents,^[1] they are used as building blocks for α - and β -amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest.^[2] As a small ring, 2-azetidinone provides a structural scaffold of unique bond angles and well-defined configurations of the substituents. Consequently, the development of new approaches to the stereocontrolled synthesis of β -lactam systems is a subject of great interest. On the other hand, diynes are useful building blocks in organic synthesis and a recurring functional group in many natural products and bioactive compounds.^[3] In particular, 1,3-diynes have been utilized as equivalents to various functional groups, as well as valuable intermediates for natural products and pharmaceuticals, and they have been recently recognized as a core functional group in organic molecular materials such as molecular wires and molecular architecture on the nanometer scale.^[4] Glaser oxidative acetylenic coupling,^[5] modified protocols such as the Eglinton^[6] and Hay^[7] variants for homocoupling, and the Cadiot–Chodkiewicz^[8] variant for cross-coupling provide powerful methodologies for 1,3-diyne compounds.^[9] However, bis(β -lactam)-1,3-diynes con-

stitute a new class of compounds not explored as of yet. In view of our interest in the application of metals for the synthesis of β -lactams and other nitrogenated compounds of biological interest,^[10] efforts were directed towards exploring the metal-mediated homo- and heterocoupling of alkynyl-2-azetidinones to access novel racemic and enantiopure C₂-symmetrical and unsymmetrical bis(β -lactam)-1,3-diynes.

Results and Discussion

Our initial goal was to evaluate the effect of metals, bases, and co-oxidants on the metal-promoted homocoupling of alkynyl β -lactams. Starting substrates, isomerically pure alkynyl- β -lactams **1a–j**, were prepared by using our previously described methodologies.^[11] Alkyne (+)-**1a** was chosen as the model compound for the present study (Scheme 1, Table 1). The copper-mediated homocoupling reactions of alkyne (+)-**1a** afforded quantitative yields of bis(β -lactam)-1,3-diyne (+)-**2a** (Table 1, Entries 1–6),^[12] whereas low yields were obtained when homocoupling of alkyne (+)-**1a** was attempted under palladium-catalyzed reaction conditions (Table 1, Entries 7–10). The results in Table 1 indicate that oxidative reagents have no fundamental influence on the reaction. Without any oxidative reagent



Scheme 1. Homocoupling reaction of *N*-alkynyl-2-azetidinone (+)-**1a**.

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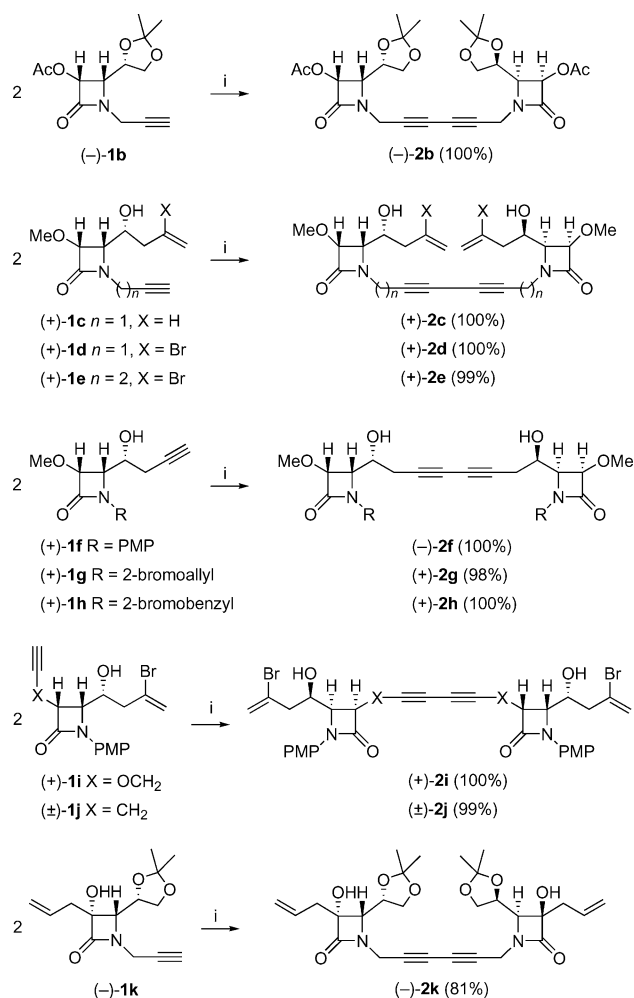
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(Table 1, Entries 2, 4, and 5), the yield of (+)-**2a** did not decrease. The use of either Et₃N or K₂CO₃ as the base gave good results. The reaction proceeded more slowly in the

Table 1. Homocoupling reaction of *N*-alkynyl-2-azetidinone (+)-**1a** under different conditions.

Entry	Metal source ^[a]	Base	Solvent	Gas	<i>t</i> [h]	Yield ^[b] [%]
1	Cu(OAc) ₂	Et ₃ N	MeCN	O ₂	2	100
2	Cu(OAc) ₂	Et ₃ N	MeCN	Ar	2	98
3	Cu(OAc) ₂	K ₂ CO ₃	MeCN	O ₂	4	100
4	Cu(OAc) ₂	K ₂ CO ₃	MeCN	Ar	4	98
5	Cu(OAc) ₂	K ₂ CO ₃	MeCN		4	100
6	Cu(OAc) ₂		MeCN		28	98
7	Cu(OAc) ₂ /Pd(OAc) ₂	K ₂ CO ₃	MeCN	Ar	5	27 ^[c]
8	Cu(OAc) ₂ /Pd(OAc) ₂	K ₂ CO ₃	MeCN	O ₂	4	26 ^[c]
9	Cu(OAc) ₂ /Pd(OAc) ₂	K ₂ CO ₃	DMF	Ar	16	15 ^[c]
10	CuI/PdCl ₂	Et ₃ N ^[d]	MeCN	O ₂	0.5	8 ^[c]

[a] Reactions were conducted by using a metal salt/alkyne molar ratio of 2.1:1. [b] Yield of pure, isolated product (+)-**2a** with correct analytical and spectroscopic data. [c] Disappearance of starting (+)-**1a** was observed in all cases. Unidentified decomposition products were also detected. [d] This experiment was carried out in the additional presence of PPh₃. PMP = 4-MeOC₆H₄.

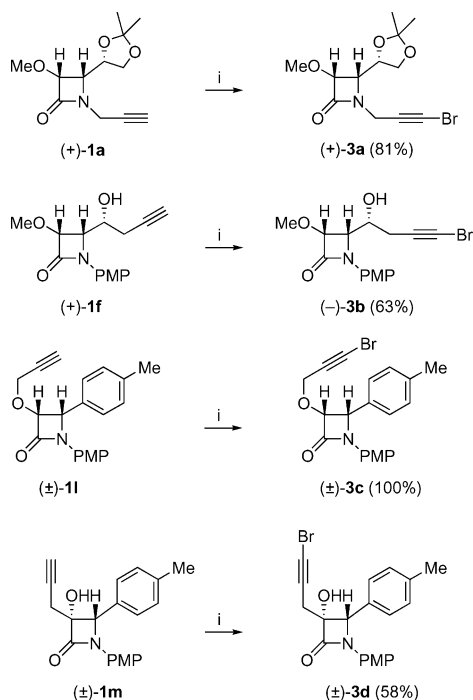


Scheme 2. Copper-promoted preparation of C₂-symmetrical bis(β-lactam)-1,3-diynes **2b–k**. Reagents and conditions: (i) Cu(OAc)₂, K₂CO₃, MeCN, room temp.; **2b**: 5 h; **2c**: 22 h; **2d**: 6 h; **2e**: 2 h; **2f**: 168 h; **2g**: 6 h; **2h**: 20 h; **2i**: 16 h; **2j**: 18 h; **2k**: 24 h.

absence of base, while maintaining an excellent isolated yield (Table 1, Entry 6). Optimization of solvent revealed that acetonitrile was superior to other solvents (THF and DMF, see Table 1, Entry 9).

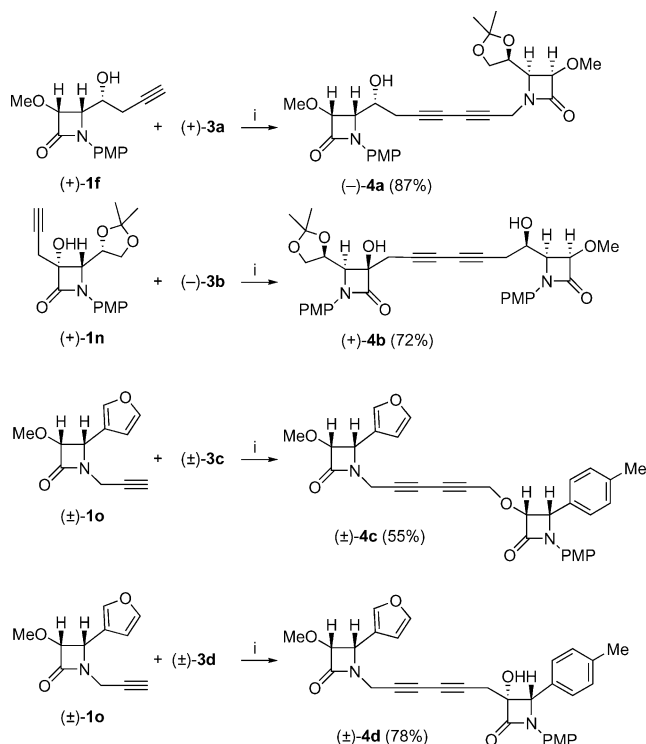
Amines have characteristic foul smells and pungent flavors. For these reasons, the development of an effective procedure for homocoupling of alkynes under amine-free conditions would be desirable. Thus, we chose to use K₂CO₃ (instead of amines as the base) in our copper-promoted homocoupling study of different functionalized 2-azetidinone-tethered alkynes.^[13] Under the optimized reaction conditions, the homocoupling reactions of various other alkynyl-β-lactams **1b–k** were carried out smoothly to afford the corresponding bis(2-azetidinone)-1,3-diynes **2b–k** in excellent-to-quantitative yields, and the results are summarized in Scheme 2. The results show that the copper-mediated homocoupling reaction tolerated a variety of functional groups on the β-lactam ring, such as alkenyl, alkoxy, aryl, bromoaryl, carboxyalkyl, dioxolanyl, hydroxy, and vinyl bromide moieties. It is noteworthy that the dimerization reaction of 2-azetidinones bearing the alkyne tether at any N1, C3, or C4 position occurred with similar efficiency.

Having obtained C₂-symmetrical bis(β-lactam)-1,3-diynes, the next stage was set to carry out selective heterocoupling conditions for the achievement of unsymmetrical bis(β-lactam)-1,3-diynes.^[14] We envisioned that the target unsymmetrical diynes could come from the copper-catalyzed Cadiot–Chodkiewicz cross-coupling reaction of a bromoalkynyl-β-lactam with a terminal alkynyl-β-lactam. Heterocoupling precursors, bromoalkynes **3**, were smoothly prepared from alkynes **1** in excellent yield by reaction with NBS and AgOAc (or AgNO₃) in acetone (Scheme 3).^[15]



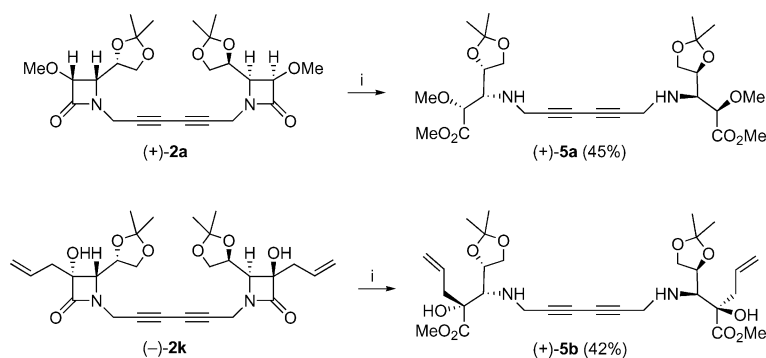
Scheme 3. Preparation of bromoalkynyl-β-lactams **3**. Reagents and conditions: (i) NBS, AgOAc (or AgNO₃), acetone, room temp., darkness; **3a**: 3 h; **3b**: 2.5 h; **3c**: 21 h; **3d**: 4 h.

Cross-coupling by the Cadiot–Chodkiewicz reaction between bromoalkynyl- β -lactams **3** and alkynyl- β -lactams **1** catalyzed by CuCl and $\text{NH}_2\text{OH}\cdot\text{HCl}$ in a 70% ethylamine in water solvent, produced the corresponding unsymmetrical bis(β -lactam)-1,3-diynes **4** in good yields (Scheme 4). The corresponding palladium-catalyzed heterocoupling procedure did afford poor yields of heterodimers **4**.



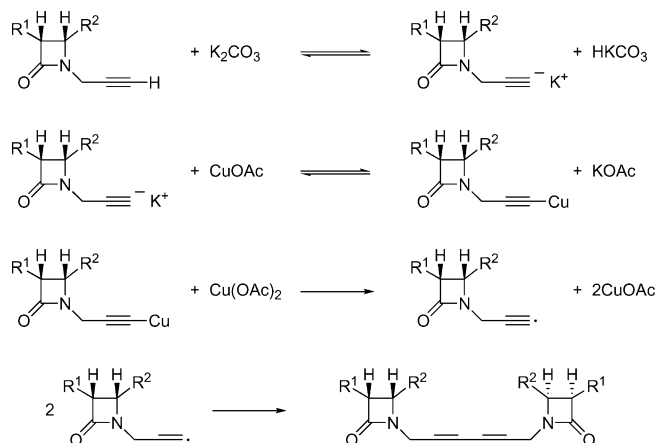
Scheme 4. Copper-promoted preparation of unsymmetrical bis(β -lactam)-1,3-diynes **4a–d**. Reagents and conditions: (i) MeOH/ CH_2Cl_2 , CuCl, $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtNH_2 , 0 °C; **4a**: 3 h; **4b**: 3 h; **4c**: 4 h; **4d**: 2 h.

The application of the alkynyl- β -lactam homo- or cross-coupling strategy followed by selective 2-azetidinone ring opening could afford bis(β -amino ester)s bearing a rigid spacer. Indeed, the sodium methoxide promoted N1–C2 amide bond cleavage in 1,3-diynes (+)-**2a** and (–)-**2k** gave the corresponding bis(β -amino ester)-1,3-diynes (+)-**3a** and (+)-**3b** (Scheme 5).



Scheme 5. Preparation of bis(β -amino ester)-1,3-diynes **5**. Reagents and conditions: (i) MeONa, MeOH, sealed tube, 65 °C; **5a**: 1 h; **5b**: 8 h.

A tentative mechanistic proposal for the copper-promoted homodimerization of alkynyl- β -lactams is depicted in Scheme 6. It may involve the formation of copper(I) acetylides, which are rapidly oxidized by the transfer of a single electron to copper(II) through an acetate ligand bridge. Decomposition of the resultant copper(II) acetylide and recombination of the free radicals would give the homocoupled products.



Scheme 6. Mechanistic explanation for the Cu-promoted homocoupling of alkynyl- β -lactams by using $\text{Cu}(\text{OAc})_2$ and K_2CO_3 in the absence of O_2 .

The structure (by DEPT, HMQC, HMBC, and COSY) and the stereochemistry (by vicinal proton couplings and qualitative homonuclear NOE difference spectra) of bis(β -lactam)-1,3-diynes **2** and **4** were assigned by one- and two-dimensional NMR experiments. The *cis* stereochemistry of the four-membered ring was set during the cyclization step to form the 2-azetidinone ring, and it was transferred unaltered during the further synthetic steps.^[16]

Conclusions

$\text{Cu}(\text{OAc})_2$ in combination with a solid base (K_2CO_3) was proven to be an extremely effective system for promoting the homocoupling of 2-azetidinone-tethered alkynes, whereas the cross-coupling of bromoalkynyl- β -lactams with terminal alkynyl- β -lactams can be easily achieved by a cop-

per-catalyzed Cadiot–Chodkiewicz reaction. These methodologies offer a convenient way for the preparation of both racemic and enantiopure C_2 -symmetrical and unsymmetrical bis(β -lactam)-1,3-diyne hybrids, which in addition to their potential biological activity may find use as macrocyclic cavities, as well as chiral ligands.

Experimental Section

General Methods: ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance-300, Varian VRX-300S, or Bruker AC-200 instrument. NMR spectra were recorded in CDCl_3 solutions, unless otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H , 0.0 ppm), or CDCl_3 (^{13}C , 76.9 ppm). Low- and high-resolution mass spectra were obtained with a HP5989A spectrometer by using the electronic impact (EI) or electrospray modes (ES), unless otherwise stated. Specific rotation $[\alpha]_D$ is given in $10^{-1} \text{ }^\circ\text{cm}^2\text{g}^{-1}$ at 20 $^\circ\text{C}$, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Copper(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes **1 in a Medium Containing K_2CO_3 . General Procedure for the Synthesis of C_2 -Symmetrical Bis(β -lactam)-1,3-diynes **2**:** Copper(II) acetate (1.05 mmol) and potassium carbonate (0.6 mmol) were sequentially added to a well-stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.5 mmol) in acetonitrile (12 mL). The resulting suspension was stirred at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried (MgSO_4), and concentrated under reduced pressure to give analytically pure C_2 -symmetrical bis(β -lactam)-1,3-diynes. Spectroscopic and analytical data for some representative forms of bis(β -lactam)-1,3-diynes **2** follow.

Bis(β -lactam)-1,3-diyne (+)-2a**:** From alkynyl-2-azetidinone (+)-**1a** (54 mg, 0.23 mmol), compound (+)-**2a** (54 mg, 100%) was obtained as a colorless oil. $[\alpha]_D = +26.1$ ($c = 1.3$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): $\delta = 4.46$ (d, $J = 5.1$ Hz, 2 H), 4.43 (d, $J = 16.6$ Hz, 2 H), 4.29 (ddd, $J = 9.1$, 6.5, 4.9 Hz, 2 H), 4.11 (dd, $J = 8.9$, 6.6 Hz, 2 H), 3.97 (d, $J = 17.3$ Hz, 2 H), 3.78 (dd, $J = 9.0$, 5.1 Hz, 2 H), 3.69 (dd, $J = 8.8$, 5.1 Hz, 2 H), 3.53 (s, 6 H), 1.48 and 1.35 (s, each 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 166.5$, 109.6, 83.1, 76.5, 71.8, 67.9, 66.5, 59.4, 59.1, 31.0, 26.8, 25.0 ppm. IR (CHCl_3): $\tilde{\nu} = 1740 \text{ cm}^{-1}$. HRMS (FAB): calcd. for $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_8$ $[\text{M} + \text{H}]^+$ 477.2237; found 477.2259. $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_8$ (477.2): calcd. C 60.49, H 6.77, N 5.88; found C 60.70, H 6.71, N 5.93.

Bis(β -lactam)-1,3-diyne (–)-2b**:** From alkynyl-2-azetidinone (–)-**1b** (112 mg, 0.42 mmol), compound (–)-**2b** (112 mg, 100%) was obtained as a colorless oil. $[\alpha]_D = -26.7$ ($c = 1.0$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): $\delta = 5.79$ (d, $J = 4.9$ Hz, 2 H), 4.49 (d, $J = 17.1$ Hz, 2 H), 4.24 (ddd, $J = 8.8$, 6.5, 5.2 Hz, 2 H), 4.02 (d, $J = 17.6$ Hz, 2 H), 3.97 (dd, $J = 8.9$, 6.5 Hz, 2 H), 3.92 (dd, $J = 8.8$, 4.9 Hz, 2 H), 3.66 (dd, $J = 8.8$, 5.1 Hz, 2 H), 2.13 (s, 6 H), 1.47 and 1.35 (s, each 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 169.1$, 163.6, 110.1, 75.8, 74.4, 71.5, 68.3, 66.3, 59.4, 31.6, 26.7, 25.1, 20.3 ppm. IR (CHCl_3): $\tilde{\nu} = 1740$, 1728 cm^{-1} . MS (ES): m/z (%) = 533 (100) $[\text{M} + \text{H}]^+$, 532 (16) $[\text{M}]^+$. $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_{10}$ (532.5): calcd. C 58.64, H 6.06, N 5.26; found C 58.90, H 5.99, N 5.32.

Bis(β -lactam)-1,3-diyne (+)-2c**:** From alkynyl-2-azetidinone (+)-**1c** (54 mg, 0.26 mmol), compound (+)-**2c** (54 mg, 100%) was obtained as a colorless solid. M.p. 117–118 $^\circ\text{C}$ (hexanes/ethyl acetate). $[\alpha]_D = +14.1$ ($c = 0.7$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): δ

$= 5.85$ (m, 2 H), 5.18 (m, 4 H), 4.48 (d, $J = 4.9$ Hz, 2 H), 4.47 (d, $J = 17.6$ Hz, 2 H), 3.99 (d, $J = 17.8$ Hz, 2 H), 3.92 (m, 2 H), 3.81 (t, $J = 5.0$ Hz, 2 H), 3.59 (s, 6 H), 2.51 (br. s, 2 H), 2.33 (m, 4 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 166.8$, 133.7, 118.5, 83.5, 72.0, 69.8, 68.3, 59.9, 59.4, 38.7, 31.5 ppm. IR (KBr): $\tilde{\nu} = 3424$, 1739 cm^{-1} . MS (ES): m/z (%) = 417 (100) $[\text{M} + \text{H}]^+$, 416 (11) $[\text{M}]^+$. $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_6$ (416.5): calcd. C 63.45, H 6.78, N 6.73; found C 63.69, H 6.85, N 6.79.

Bis(β -lactam)-1,3-diyne (+)-2d**:** From alkynyl-2-azetidinone (+)-**1d** (44 mg, 0.15 mmol), compound (+)-**2d** (44 mg, 100%) was obtained as a colorless oil. $[\alpha]_D = +30.8$ ($c = 0.5$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): $\delta = 5.78$ (s, 2 H), 5.59 (d, $J = 1.5$ Hz, 2 H), 4.52 (d, $J = 5.1$ Hz, 2 H), 4.47 (d, $J = 17.8$ Hz, 2 H), 4.23 (m, 2 H), 4.00 (d, $J = 17.8$ Hz, 2 H), 3.85 (t, $J = 5.0$ Hz, 2 H), 3.62 (s, 6 H), 2.68 (m, 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 166.9$, 129.3, 120.5, 83.7, 72.3, 68.6, 68.5, 59.8, 59.7, 46.0, 31.7 ppm. IR (CHCl_3): $\tilde{\nu} = 3429$, 1743 cm^{-1} . MS (ES): m/z (%) = 577 (44) $[\text{M} + 4 + \text{H}]^+$, 575 (100) $[\text{M} + 2 + \text{H}]^+$, 573 (48) $[\text{M} + \text{H}]^+$. $\text{C}_{22}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_6$ (574.3): calcd. C 46.01, H 4.56, N 4.88; found C 46.25, H 4.62, N 4.81.

Bis(β -lactam)-1,3-diyne (+)-2e**:** From alkynyl-2-azetidinone (+)-**1e** (50 mg, 0.15 mmol), compound (+)-**2e** (49 mg, 99%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:3). $[\alpha]_D = +21.3$ ($c = 0.6$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): $\delta = 5.76$ (s, 2 H), 5.60 (d, $J = 1.7$ Hz, 2 H), 4.55 (d, $J = 5.1$ Hz, 2 H), 4.21 (m, 2 H), 3.83 (t, $J = 5.4$ Hz, 2 H), 3.68 (m, 2 H), 3.62 (s, 6 H), 3.35 (m, 2 H), 2.67 (m, 10 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 167.5$, 129.1, 120.1, 82.9, 74.5, 68.8, 66.6, 60.47, 59.3, 45.6, 40.0, 18.6 ppm. IR (CHCl_3): $\tilde{\nu} = 3431$, 1745 cm^{-1} . MS (ES): m/z (%) = 605 (48) $[\text{M} + 4 + \text{H}]^+$, 603 (100) $[\text{M} + 2 + \text{H}]^+$, 601 (52) $[\text{M} + \text{H}]^+$. $\text{C}_{24}\text{H}_{30}\text{Br}_2\text{N}_2\text{O}_6$ (602.3): calcd. C 47.86, H 5.02, N 4.65; found C 47.64, H 5.09, N 4.71.

Bis(β -lactam)-1,3-diyne (–)-2f**:** From alkynyl-2-azetidinone (+)-**1f** (47 mg, 0.17 mmol), compound (–)-**2f** (47 mg, 100%) was obtained as a colorless oil. $[\alpha]_D = -72.0$ ($c = 1.3$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): $\delta = 7.44$ (d, $J = 9.0$ Hz, 4 H), 6.88 (d, $J = 9.0$ Hz, 4 H), 4.67 (d, $J = 5.4$ Hz, 2 H), 4.55 (dd, $J = 5.2$, 3.5 Hz, 2 H), 4.18 (td, $J = 7.0$, 3.3 Hz, 2 H), 3.69 (s, 6 H), 3.79 (s, 6 H), 2.68 (dd, $J = 17.2$, 6.5 Hz, 2 H), 2.50 (dd, $J = 17.0$, 7.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 164.6$, 156.8, 130.4, 120.1, 114.2, 82.6, 73.7, 69.1, 67.5, 59.7, 58.7, 55.3, 24.7 ppm. IR (CHCl_3): $\tilde{\nu} = 3425$, 1748 cm^{-1} . MS (EI): m/z (%) = 549 (8) $[\text{M} + \text{H}]^+$, 548 (24) $[\text{M}]^+$, 149 (100). $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_8$ (548.6): calcd. C 65.68, H 5.88, N 5.11; found C 65.94, H 5.73, N 5.18.

Bis(β -lactam)-1,3-diyne (+)-2g**:** From alkynyl-2-azetidinone (+)-**1g** (48 mg, 0.17 mmol), compound (+)-**2g** (47 mg, 98%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:2). $[\alpha]_D = +28.1$ ($c = 0.7$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): $\delta = 5.90$ (t, $J = 1.0$ Hz, 2 H), 5.67 (dd, $J = 2.2$, 0.5 Hz, 2 H), 4.58 (d, $J = 5.1$ Hz, 2 H), 4.41 (d, $J = 15.6$ Hz, 2 H), 4.04 (d, $J = 15.6$ Hz, 2 H), 4.03 (m, 2 H), 3.90 (t, $J = 5.4$ Hz, 2 H), 3.62 (s, 6 H), 2.59 (d, $J = 6.1$ Hz, 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 167.6$, 126.9, 120.5, 83.1, 73.4, 69.3, 67.8, 59.6, 59.5, 49.7, 25.0 ppm. IR (CHCl_3): $\tilde{\nu} = 3427$, 1747 cm^{-1} . MS (ES): m/z (%) = 577 (51) $[\text{M} + 4 + \text{H}]^+$, 575 (100) $[\text{M} + 2 + \text{H}]^+$, 573 (54) $[\text{M} + \text{H}]^+$. $\text{C}_{22}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_6$ (574.3): calcd. C 46.01, H 4.56, N 4.88; found C 46.27, H 4.48, N 4.80.

Bis(β -lactam)-1,3-diyne (+)-2h**:** From alkynyl-2-azetidinone (+)-**1h** (47 mg, 0.14 mmol), compound (+)-**2h** (47 mg, 100%) was obtained as a colorless oil. $[\alpha]_D = +34.4$ ($c = 0.7$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): $\delta = 7.55$ (dd, $J = 7.9$, 1.0 Hz, 2 H), 7.38 (dd, $J = 7.6$, 2.0 Hz, 2 H), 7.32 (dd, $J = 7.1$, 1.2 Hz, 2 H), 7.16

(ddd, $J = 7.8, 7.1, 1.9$ Hz, 2 H), 4.79 (d, $J = 15.4$ Hz, 2 H), 4.52 (d, $J = 5.1$ Hz, 2 H), 4.46 (d, $J = 15.6$ Hz, 2 H), 4.00 (td, $J = 6.2, 5.4$ Hz, 2 H), 3.75 (t, $J = 5.2$ Hz, 2 H), 3.62 (s, 6 H), 2.47 (d, $J = 6.3$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 167.7, 134.5, 133.0, 130.6, 129.4, 127.7, 123.3, 83.0, 73.4, 69.3, 67.6, 59.7, 59.5, 46.0, 24.9$ ppm. IR (CHCl_3): $\tilde{\nu} = 3427, 1745\text{ cm}^{-1}$. MS (ES): m/z (%) = 677 (55) $[\text{M} + 4 + \text{H}]^+$, 675 (100) $[\text{M} + 2 + \text{H}]^+$, 673 (50) $[\text{M} + \text{H}]^+$. $\text{C}_{30}\text{H}_{30}\text{Br}_2\text{N}_2\text{O}_6$ (674.4): calcd. C 53.43, H 4.48, N 4.15; found C 53.64, H 4.40, N 4.08.

Bis(β -lactam)-1,3-diyne (+)-2i: From alkynyl-2-azetidinone (+)-1i (53 mg, 0.14 mmol), compound (+)-2i (53 mg, 100%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D = +87.9$ ($c = 1.0$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 7.37$ (d, $J = 9.0$ Hz, 4 H), 6.88 (d, $J = 9.0$ Hz, 4 H), 5.65 (d, $J = 1.7$ Hz, 2 H), 5.57 (d, $J = 1.7$ Hz, 2 H), 5.06 (m, 2 H), 4.99 (d, $J = 5.1$ Hz, 1 H), 4.47 (m, 4 H), 4.36 (dd, $J = 5.1, 3.2$ Hz, 1 H), 3.80 (s, 6 H), 2.70 (m, 4 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 166.9, 157.0, 130.5, 129.1, 120.7, 120.5, 114.4, 77.0, 75.8, 68.8, 68.6, 60.5, 60.4, 55.5, 46.5$ ppm. IR (CHCl_3): $\tilde{\nu} = 3427, 1749\text{ cm}^{-1}$. MS (ES): m/z (%) = 761 (50) $[\text{M} + 4 + \text{H}]^+$, 759 (100) $[\text{M} + 2 + \text{H}]^+$, 757 (52) $[\text{M} + \text{H}]^+$. $\text{C}_{34}\text{H}_{34}\text{Br}_2\text{N}_2\text{O}_8$ (758.5): calcd. C 53.84, H 4.52, N 3.69; found C 53.62, H 4.61, N 3.60.

Bis(β -lactam)-1,3-diyne ($\pm$)-2j: From of alkynyl-2-azetidinone ($\pm$)-1j (55 mg, 0.14 mmol), compound ($\pm$)-2j (54 mg, 99%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 7.36$ (d, $J = 9.0$ Hz, 4 H), 6.88 (d, $J = 9.0$ Hz, 4 H), 5.69 (s, 2 H), 5.59 (d, $J = 1.7$ Hz, 2 H), 4.50 (td, $J = 8.7, 4.5$ Hz, 2 H), 4.30 (dd, $J = 5.5, 4.5$ Hz, 2 H), 3.79 (s, 6 H), 3.58 (dt, $J = 9.5, 5.6$ Hz, 2 H), 2.97 (m, 4 H), 2.79 (dd, $J = 14.5, 3.5$ Hz, 2 H), 2.64 (dd, $J = 14.5, 9.2$ Hz, 2 H), 1.96 (d, $J = 4.6$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 165.7, 157.0, 130.6, 129.0, 121.2, 120.7, 114.3, 74.8, 68.4, 67.0, 58.0, 55.5, 49.9, 47.7, 15.5$ ppm. IR (CHCl_3): $\tilde{\nu} = 3428, 1750\text{ cm}^{-1}$. MS (ES): m/z (%) = 729 (49) $[\text{M} + 4 + \text{H}]^+$, 727 (100) $[\text{M} + 2 + \text{H}]^+$, 725 (52) $[\text{M} + \text{H}]^+$. $\text{C}_{34}\text{H}_{34}\text{Br}_2\text{N}_2\text{O}_6$ (726.5): calcd. C 56.21, H 4.72, N 3.86; found C 53.36, H 4.76, N 3.83.

Bis(β -lactam)-1,3-diyne (–)-2k: From alkynyl-2-azetidinone (–)-1k (32 mg, 0.12 mmol), compound (–)-2k (26 mg, 81%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D = -31.4$ ($c = 0.7$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 5.87$ (ddt, $J = 17.3, 9.8, 7.3$ Hz, 2 H), 5.25 (m, 4 H), 4.49 (d, $J = 17.6$ Hz, 2 H), 4.36 (td, $J = 6.5, 4.5$ Hz, 2 H), 4.17 (dd, $J = 8.9, 7.0$ Hz, 2 H), 3.94 (d, $J = 17.6$ Hz, 2 H), 3.83 (dd, $J = 9.2, 4.5$ Hz, 2 H), 3.64 (d, $J = 6.1$ Hz, 2 H), 2.62 (dd, $J = 13.9, 7.1$ Hz, 2 H), 2.49 (dd, $J = 13.9, 7.6$ Hz, 2 H), 1.46 and 1.35 (s, each 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 170.0, 131.1, 120.3, 110.1, 84.7, 75.3, 71.7, 68.2, 66.5, 64.1, 39.3, 30.9, 26.5, 24.9$ ppm. IR (CHCl_3): $\tilde{\nu} = 3430, 1747\text{ cm}^{-1}$. MS (ES): m/z (%) = 529 (100) $[\text{M} + \text{H}]^+$, 528 (23) $[\text{M}]^+$. $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_8$ (528.6): calcd. C 63.62, H 6.86, N 5.30; found C 63.79, H 6.96, N 5.37.

General Procedure for the Synthesis of Bromoalkynyl- β -lactams 3: To a solution of the appropriate alkynyl-2-azetidinone **1** (0.37 mmol) in acetone (2.5 mL) was added NBS (0.094 g, 0.46 mmol) and silver acetate (0.019 g, 0.11 mmol). The reaction mixture was stirred at room temperature in the dark until disappearance (TLC) of the starting material. The solids were removed by filtration through a Celite pad (washing with ethyl acetate). The combined organic filtrate was washed with water and brine, dried (Na_2SO_4), concentrated under reduced pressure, and then purified by column chromatography (ethyl acetate/hexanes) to give analyti-

cally pure bromoalkynyl- β -lactams **3**. Spectroscopic and analytical data for some representative forms of compounds **3** follow.

Bromoalkynyl- β -lactam (+)-3a: From alkynyl-2-azetidinone (+)-1a (100 mg, 0.42 mmol), compound (+)-3a (108 mg, 81%) was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). $[\alpha]_D = +28.2$ ($c = 0.4$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 4.46$ (d, $J = 5.1$ Hz, 2 H), 4.38 and 3.92 (d, $J = 17.3$ Hz, each 1 H), 4.30 (m, 1 H), 4.11 (dd, $J = 8.8, 6.5$ Hz, 1 H), 3.80 and 3.70 (dd, $J = 9.0, 5.0$ Hz, each 1 H), 3.53 (s, 3 H), 1.48 and 1.35 (s, each 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 166.7, 109.7, 83.1, 76.6, 73.3, 66.7, 59.5, 59.2, 43.7, 31.5, 26.9, 25.1$ ppm. IR (CHCl_3): $\tilde{\nu} = 1742\text{ cm}^{-1}$. MS (EI): m/z (%) = 319 (100) $[\text{M} + 2]^+$, 317 (98) $[\text{M}]^+$. $\text{C}_{12}\text{H}_{16}\text{BrNO}_4$ (318.2): calcd. C 45.30, H 5.07, N 4.40; found C 45.42, H 5.05, N 4.43.

Bromoalkynyl- β -lactam (–)-3b: From alkynyl-2-azetidinone (+)-1f (100 mg, 0.42 mmol), compound (–)-3b (25 mg, 63%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2:1). $[\alpha]_D = -9.0$ ($c = 0.3$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 7.44$ and 6.88 (d, $J = 9.0$ Hz, each 2 H), 4.66 (d, $J = 5.1$ Hz, 1 H), 4.54 (dd, $J = 5.1, 3.7$ Hz, 1 H), 4.16 (m, 1 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 2.81 (d, $J = 3.9$ Hz, 1 H), 2.61 (dd, $J = 17.0, 6.5$ Hz, 1 H), 2.44 (dd, $J = 17.0, 8.0$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 164.8, 156.9, 130.6, 120.3, 114.3, 82.7, 76.1, 69.1, 59.8, 58.8, 55.5, 41.2, 25.2$ ppm. IR (CHCl_3): $\tilde{\nu} = 3310, 1744\text{ cm}^{-1}$. MS (EI): m/z (%) = 353 (100) $[\text{M} + 2]^+$, 355 (98) $[\text{M}]^+$. $\text{C}_{15}\text{H}_{16}\text{BrNO}_4$ (354.2): calcd. C 50.86, H 4.55, N 3.95; found C 50.99, H 4.51, N 3.98.

Bromoalkynyl- β -lactam ($\pm$)-3c: From alkynyl-2-azetidinone ($\pm$)-1l (90 mg, 0.28 mmol), compound ($\pm$)-3c (112 mg, 100%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 4:1). ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 7.26$ and 6.77 (d, $J = 9.0$ Hz, each 2 H), 7.22 (m, 4 H), 5.16 (s, 2 H), 4.14 and 3.91 (d, $J = 15.8$ Hz, each 1 H), 3.73 (s, 3 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 163.2, 156.3, 138.5, 130.5, 130.0, 129.3, 128.0, 118.8, 114.3, 81.5, 74.9, 61.6, 58.5, 55.4, 47.7, 21.2$ ppm. IR (CHCl_3): $\tilde{\nu} = 1742\text{ cm}^{-1}$. MS (EI): m/z (%) = 401 (100) $[\text{M} + 2]^+$, 399 (98) $[\text{M}]^+$. $\text{C}_{20}\text{H}_{18}\text{BrNO}_3$ (399.1): calcd. C 60.01, H 4.53, N 3.50; found C 60.15, H 4.49, N 3.54.

Bromoalkynyl- β -lactam ($\pm$)-3d: From alkynyl-2-azetidinone ($\pm$)-1m (88 mg, 0.26 mmol) compound ($\pm$)-3d (63 mg, 58%) was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 7.28$ and 6.80 (d, $J = 9.0$ Hz, each 2 H), 7.23 (s, 4 H), 5.18 (s, 1 H), 3.75 (s, 3 H), 3.07 (br. s, 1 H), 2.91 (d, $J = 1.5$ Hz, 2 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 165.6, 156.5, 138.9, 130.2, 130.0, 129.9, 127.3, 119.1, 114.4, 84.0, 74.2, 66.6, 55.4, 42.2, 26.7, 21.2$ ppm. IR (CHCl_3): $\tilde{\nu} = 3322, 1743\text{ cm}^{-1}$. MS (EI): m/z (%) = 401 (100) $[\text{M} + 2]^+$, 399 (98) $[\text{M}]^+$. $\text{C}_{20}\text{H}_{18}\text{BrNO}_3$ (399.1): calcd. C 60.01, H 4.53, N 3.50; found C 59.89, H 4.50, N 3.53.

Copper(I) Chloride Promoted Heterocoupling Reaction between 2-Azetidinone-Tethered Alkynes 1 and Bromoalkynyl- β -lactams 3. **General Procedure for the Synthesis of Unsymmetrical Bis(β -lactam)-1,3-diynes 4:** Few crystals of hydroxylamine hydrochloride, EtNH_2 (70% in water, 2.5 mL), and CuCl (0.06 mmol, 0.02 equiv.) were sequentially added at room temperature to a solution of the appropriate alkynyl-2-azetidinone **1** (3.6 mmol) in methanol (18 mL). Then, the corresponding bromoalkynyl- β -lactam **3** (3.6 mmol) in CH_2Cl_2 (50 mL) was added to the above acetylide suspension cooled to 0 °C. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. The reaction mixture

was stirred until disappearance (TLC) of the starting materials. The products were extracted with ethyl acetate (3 × 20 mL), dried with MgSO₄, and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate/hexanes) gave analytically pure unsymmetrical bis(β-lactam)-1,3-diynes. Spectroscopic and analytical data for some representative forms of bis(β-lactam)-1,3-diynes **4** follow.

Bis(β-lactam)-1,3-diyne (–)-4a: From bromoalkynyl-2-azetidinone (+)-**3a** (40 mg, 0.13 mmol), compound (–)-**4a** (58 mg, 87%) was obtained as a pale yellow oil. [α]_D = –27.3 (*c* = 1.4, CHCl₃). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.42 and 6.87 (d, *J* = 9.0 Hz, each 2 H), 4.64 (d, *J* = 5.1 Hz, 1 H), 4.51 (dd, *J* = 5.1, 3.7 Hz, 1 H), 4.45 (d, *J* = 5.1 Hz, 1 H), 4.43 and 3.96 (d, *J* = 18.0 Hz, each H), 4.30 (m, 1 H), 4.10 (dd, *J* = 8.8, 6.6 Hz, 2 H), 3.73 (m, 2 H), 3.79 (s, 3 H), 3.67 (s, 3 H), 3.52 (s, 3 H), 2.91 (br. s, 1 H), 2.66 (dd, *J* = 17.3, 6.3 Hz, 1 H), 2.66 (dd, *J* = 17.3, 7.7 Hz, 1 H), 1.49 and 1.34 (s, each 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 166.7, 164.7, 156.9, 130.5, 120.2, 114.3, 109.7, 83.1, 82.6, 76.6, 75.6, 70.1, 69.1, 68.4, 67.1, 66.5, 60.3, 59.7, 59.5, 58.9, 55.4, 31.1, 26.9, 25.1, 24.8 ppm. IR (CHCl₃): $\tilde{\nu}$ = 3345, 1742 cm^{–1}. MS (ES): *m/z* (%) = 513 (100) [*M* + *H*]⁺, 512 (15) [*M*]⁺. C₂₇H₃₂N₂O₈ (512.6): calcd. C 63.27, H 6.29, N 5.47; found C 63.40, H 6.23, N 5.52.

Bis(β-lactam)-1,3-diyne (+)-4b: From bromoalkynyl-2-azetidinone (–)-**3b** (49 mg, 0.14 mmol), compound (+)-**4b** (61 mg, 72%) was obtained as a colorless oil. [α]_D = +59.4 (*c* = 1.6, CHCl₃). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.57 and 6.86 (d, *J* = 9.0 Hz, each 2 H), 7.38 and 6.82 (d, *J* = 9.0 Hz, each 2 H), 5.07 (br. s, 1 H), 4.63 (d, *J* = 5.1 Hz, 1 H), 4.45 (m, 2 H), 4.31 (dd, *J* = 9.0, 6.8 Hz, 1 H), 4.22 (d, *J* = 7.1 Hz, 1 H), 4.09 (m, 1 H), 3.92 (dd, *J* = 9.0, 6.5 Hz, 2 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.67 (s, 3 H), 2.95 (d, *J* = 3.7 Hz, 1 H), 2.60 (dd, *J* = 17.3, 6.3 Hz, 1 H), 2.41 (dd, *J* = 17.3, 8.0 Hz, 1 H), 1.48 and 1.35 (s, each 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 167.1, 164.9, 156.9, 156.8, 130.5, 130.2, 120.3, 114.3, 114.0, 109.9, 82.6, 74.3, 71.5, 70.1, 69.2, 68.2, 67.4, 66.7, 66.1, 59.7, 58.8, 55.4, 55.3, 26.6, 26.5, 25.0, 24.7 ppm. IR (CHCl₃): $\tilde{\nu}$ = 3340, 1744 cm^{–1}. MS (ES): *m/z* (%) = 605 (100) [*M* + *H*]⁺, 604 (14) [*M*]⁺. C₃₃H₃₆N₂O₉ (604.7): calcd. C 65.55, H 6.00, N 4.63; found C 65.43, H 6.07, N 4.60.

Bis(β-lactam)-1,3-diyne (±)-4c: From bromoalkynyl-2-azetidinone (±)-**3c** (112 mg, 0.28 mmol), compound (±)-**4c** (81 mg, 55%) was obtained as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.55 (m, 1 H), 7.45 (t, *J* = 1.7 Hz, 1 H), 7.23 (m, 4 H), 7.22 and 6.76 (d, *J* = 9.0 Hz, each 2 H), 6.49 (m, 1 H), 5.17 (d, *J* = 4.9 Hz, 1 H), 5.13 (d, *J* = 4.9 Hz, 1 H), 4.84 (d, *J* = 4.6 Hz, 1 H), 4.70 (d, *J* = 4.6 Hz, 1 H), 4.36 and 3.67 (d, *J* = 19.3 Hz, each H), 4.18 and 3.92 (d, *J* = 16.8 Hz, each H), 3.72 (s, 3 H), 3.31 (s, 3 H), 2.34 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 165.8, 163.1, 156.3, 143.6, 142.3, 138.6, 130.4, 129.9, 129.3, 127.9, 118.8, 118.3, 114.3, 110.1, 85.5, 81.4, 73.4, 72.4, 71.4, 68.3, 61.5, 58.5, 57.9, 55.3, 53.4, 29.7, 21.2 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1745 cm^{–1}. MS (ES): *m/z* (%) = 525 (100) [*M* + *H*]⁺, 524 (17) [*M*]⁺. C₃₁H₂₈N₂O₆ (524.6): calcd. C 70.98, H 5.38, N 5.34; found C 71.02, H 5.33, N 5.38.

Bis(β-lactam)-1,3-diyne (±)-4d: From bromoalkynyl-2-azetidinone (±)-**3d** (63 mg, 0.15 mmol), compound (±)-**4d** (62 mg, 78%) was obtained as a pale yellow solid. M.p. 71–73 °C (hexanes/ethyl acetate). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.48 (m, 1 H), 7.42 (m, 1 H), 7.28 and 6.80 (d, *J* = 9.0 Hz, each 2 H), 7.22 (s, 4 H), 6.45 (m, 1 H), 5.16 (s, 1 H), 4.75 (m, 1 H), 4.66 (dd, *J* = 4.6, 3.1 Hz, 1 H), 4.32 and 3.59 (d, *J* = 18.3 Hz, each H), 3.74 (s, 3 H), 3.30 (s, 3 H), 2.97 (s, 2 H), 2.36 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 166.0, 165.5, 156.5, 142.3, 143.6, 138.9, 130.1, 129.9, 127.3, 119.1, 118.3, 114.3, 110.1, 85.4, 84.0, 73.9, 69.4, 68.8, 67.4, 66.6,

60.3, 58.5, 55.4, 53.2, 29.7, 26.3, 21.2 ppm. IR (CHCl₃): $\tilde{\nu}$ = 3348, 1744 cm^{–1}. MS (EI): *m/z* (%) = 524 (40) [*M*]⁺, 226 (100). C₃₁H₂₈N₂O₆ (524.6): calcd. C 70.98, H 5.38, N 5.34; found C 70.85, H 5.34, N 5.29.

Sodium Methoxide Promoted Reaction of Bis(β-lactam)-1,3-diynes 2. General Procedure for the Preparation of Bis(β-amino ester)-1,3-Diynes 5: Sodium methoxide (10.8 mg, 0.2 mmol) was added in portions to a solution of the appropriate bis(β-lactam)-1,3-diyne **2** (0.2 mmol) in methanol (2 mL). The reaction mixture was heated in a sealed tube at 65 °C until disappearance of the starting material (TLC). The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Then, water was added (1 mL), and the aqueous residue was extracted with ethyl acetate (4 × 3 mL). The organic extract was washed with brine, dried with MgSO₄, and the solvent was removed under reduced pressure. Chromatography of the residue (ethyl acetate/hexanes) gave analytically pure compounds **5**. Spectroscopic and analytical data for some representative forms of bis(β-amino ester)-1,3-diynes **3** follow.

Bis(β-amino ester)-1,3-diyne (+)-5a: From bis(β-lactam)-1,3-diyne (+)-**2a** (41 mg, 0.08 mmol), compound (+)-**5a** (21 mg, 45%) was obtained as a pale brown oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). [α]_D = +31.2 (*c* = 1.2, CHCl₃). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 4.16 (m, 2 H), 4.04 (dd, *J* = 8.3, 6.5 Hz, 2 H), 3.91 (d, *J* = 3.6 Hz, 2 H), 3.90 (dd, *J* = 8.3, 6.7 Hz, 2 H), 3.79 (s, 6 H), 3.67 (d, *J* = 9.1 Hz, 4 H), 3.42 (s, 6 H), 3.21 (dd, *J* = 6.2, 3.6 Hz, 2 H), 1.43 and 1.34 (s, each 6 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.3, 109.2, 79.6, 76.1, 75.8, 68.1, 66.7, 59.7, 58.7, 52.1, 37.6, 26.5, 25.2 ppm. IR (CHCl₃): $\tilde{\nu}$ = 3420, 1720 cm^{–1}. MS (EI): *m/z* (%) = 540 (11) [*M*]⁺, 43 (100). C₂₆H₄₀N₂O₁₀ (540.6): calcd. C 57.76, H 7.46, N 5.18; found C 57.60, H 7.37, N 5.10.

Bis(β-amino ester)-1,3-diyne (+)-5b: From bis(β-lactam)-1,3-diyne (–)-**2j** (26 mg, 0.05 mmol), compound (+)-**5b** (12 mg, 42%) was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). [α]_D = +5.9 (*c* = 0.5, CHCl₃). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 5.76 (m, 2 H), 5.16 (m, 4 H), 4.34 (m, 2 H), 4.14 (dd, *J* = 8.3, 6.6 Hz, 2 H), 3.88 (dd, *J* = 8.4, 7.0 Hz, 2 H), 3.81 (s, 6 H), 3.80 (m, 4 H), 3.18 (d, *J* = 4.6 Hz, 2 H), 2.52 (m, 4 H), 1.46 and 1.36 (s, each 6 H) ppm. IR (CHCl₃): $\tilde{\nu}$ = 3430, 3420, 1722 cm^{–1}. MS (ES): *m/z* (%) = 593 (100) [*M* + *H*]⁺, 592 (35) [*M*]⁺. C₃₀H₄₄N₂O₁₀ (592.7): calcd. C 60.80, H 7.48, N 4.73; found C 60.96, H 7.40, N 4.79.

Supporting Information (see also the footnote on the first page of this article): Full spectroscopic and analytical data for previously unreported compounds not included in the Experimental Section. Compound characterization data and experimental procedures for the dimerization reaction of *N*-alkynyl-2-azetidinones under different conditions.

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