The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo301113g • Publication Date (Web): 19 Jul 2012

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Regio- and Diastereoselective Synthesis of β-Lactam-Triazole Hybrids *via* Passerini/CuAAC Sequence

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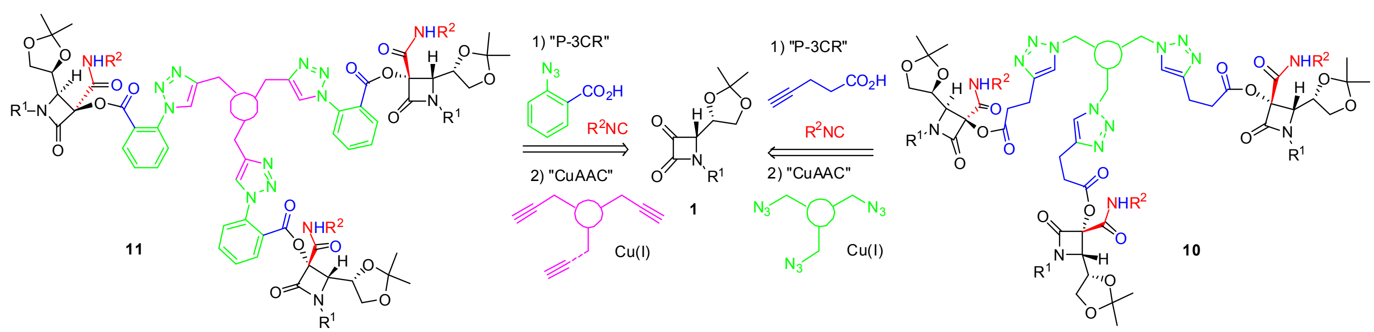
ABSTRACT

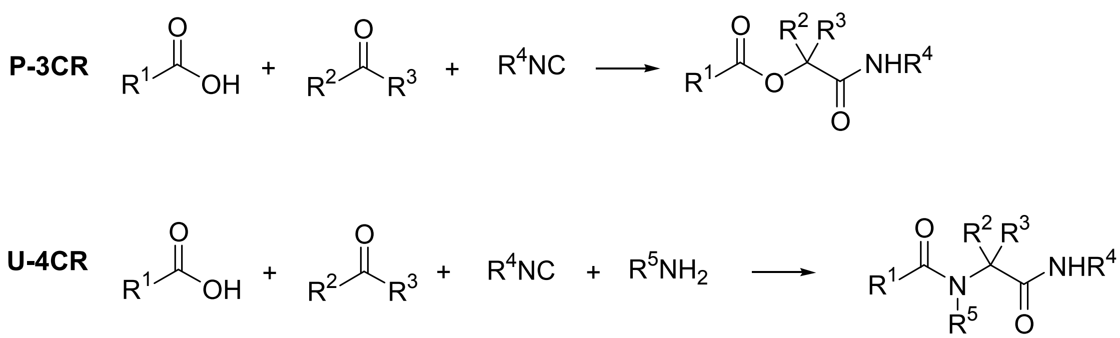


Passerini (P-3CR) and Passerini-Smiles reactions were investigated in azetidine-2,3-diones, affording the corresponding 3,3-disubstituted-β-lactams with complete diastereoselectivity in high yields. The study has been carried out using different isocyanides, carboxylic acids and phenols showing the scope of both reactions. In addition, the regioselective synthesis of highly functionalized β-lactam-triazole hybrids has been developed *via* a Passerini/CuAAC sequence. Interestingly, the use of dialkynes/diazides or trialkynes/triazides as linkers in the CuAAC step has allowed the synthesis of C_2 and C_3 symmetric β-lactam-triazole hybrids respectively.

INTRODUCTION

Multicomponent reactions (MCRs) are very powerful synthetic processes, which allow achieving both complexity and diversity in a single and simple experimental step with high efficiency and atom economy.[1] The applicability of MCRs has been widely demonstrated in the synthesis of natural products,[2] and medicinal chemistry.[3] In particular, isocyanide based MCRs (IMCRs) are specially interesting due to the versatility of isocyanides in terms of functional group tolerance and the high levels of chemo-, regio-, and stereoselectivity obtained.[4] In particular, the impact of IMCRs is remarkable in target-oriented and diversity-oriented synthetic (TOS and DOS, respectively) strategies.[5] Among them, the Passerini three-component reaction (P-3CR) and the Ugi four-component reaction (U-4CR) are the most classic and successful ones (Scheme 1). In the classical Passerini reaction, an isocyanide, a carboxylic acid and either an aldehyde or a ketone react to yield an α-acyloxy carboxamide.[6,7] This methodology has been applied to the synthesis of potentially bioactive molecules.[8] Particular attention has been focused on the combination of the P-3CR with other synthetic reactions for the construction of cyclic or more complex structures.[1c]

Scheme 1. General Passerini (P-3CR) and Ugi (U-4CR) Reactions



On the other hand, the concept of "click chemistry" coined by Sharpless and co-workers in 2001 embraces the synthetic approach to use practical and reliable chemical transformations.[9] The application of "click chemistry" in many areas has been widely documented in the bibliography.[10] The copper(I) catalyzed Huisgen organic azides and terminal alkynes 1,3-dipolar cycloaddition (CuAAC), to give 1,4-

disubstituted 1,2,3-triazoles regioselectively, is undoubtedly on the top of click chemistry reactions. This valuable transformation is playing an outstanding role in nearly all areas of contemporary chemistry from drug discovery to material science.[11] In addition, although the 1,2,3-triazole moiety is not found in nature, there are synthetic molecules containing this unit with different interesting biological activities.[12] Besides, due to the stereoelectronic similarity between the 1,2,3-triazole core and the amide bond, this heterocycle represents an isostere of the peptide bond with the advantage of being stable to hydrolytic and proteolytic cleavage.[13]

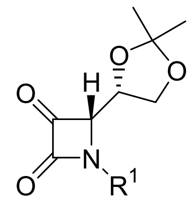
In connection with our ongoing project aimed at the asymmetric synthesis of nitrogenated compounds,[14] we became interested in the study of the P-3CR and the subsequent CuAAC in azetidine-2,3-diones in order to obtain β-lactam-triazole hybrids[15] with C_2 and C_3 symmetry.

RESULTS AND DISCUSSION

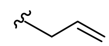
Passerini three-component reaction in azetidine-2,3-diones

The starting materials, optically pure azetidine-2,3-diones **1a–c** (Figure 1) were synthesized from aromatic or aliphatic (*R*)-2,3-*O*-isopropylideneglyceraldehyde derived imines by Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation, as previously reported.[16]

Figure 1. Starting Materials for the Passerini Reaction



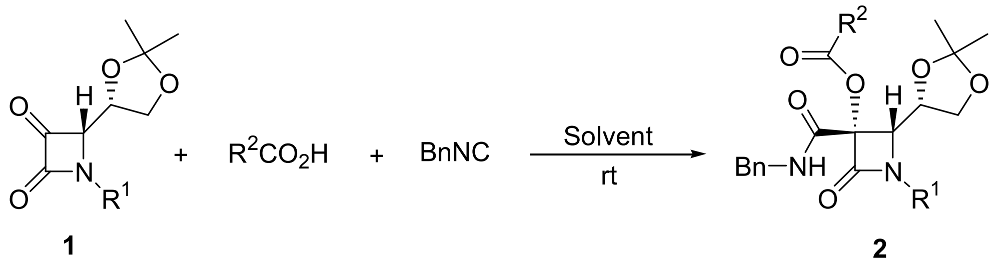
(+)-**1a** R^1 = 4-MeOC_6H_4

(–)-**1b** R^1 = 

(–)-**1c** R^1 = Bn

The initial survey was conducted with azetidine-2,3-dione (+)-**1a**, benzoic acid, and benzyl isocyanide in dichloromethane at room temperature, affording α-acyloxy carboxamide (+)-**2a** as single isomer in 92 % yield after 21h (entry 1, Table 1). Taking into account that Passerini reactions have been shown to exhibit rate accelerations in more environmentally friendly solvents, such as water, compared to organic solvents,[17] we decided to test the above reaction in water and in a mixture of acetonitrile/water (1:1). However, only conversions up to 85% were observed in both experiments by ^{1}H-NMR after long reaction times (entries 2 and 3, Table 1). Thus, the scope of the P-3CR was explored in dichloromethane using benzyl isocyanide, azetidine-2,3-diones (–)-**1b** and (–)-**1c**, and carboxylic acids. α-Acyloxy carboxamides **2b–h** were obtained with complete *syn*-diastereoselectivity (with cis configuration between the β-lactamic H4 and the amide group on C3) and the and moderate to excellent yields in almost all cases (entries 4–10, Table 1). 2-Iodo and 2-azido benzoic acids required longer reaction times (22h and 16h, respectively), but diastereoselectivity values and yields were not affected (entries 7 and 8, Table 1).

Table 1. Survey of the Passerini Reaction of Azetidine-2,3-diones 1a–c, Benzyl isocyanide, and Carboxylic Acids[a]

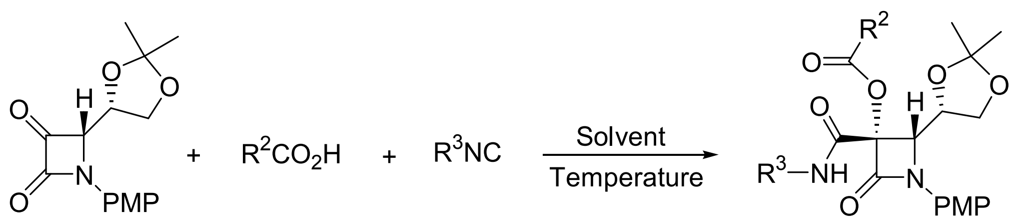


Entry	Substrate	R[1]	R[2]	Solvent	t (h)[d]	Product	Conversion (%)[e]	syn/anti[e]	yield (%)[f]
1	(+)-**1a**	PMP[b]	Ph	CH_2Cl_2	21	(+)-**2a**	100	100:0	92
2	(+)-**1a**	PMP[b]	Ph	H_2O	48	(+)-**2a**	85	100:0	*g*
3	(+)-**1a**	PMP[b]	Ph	MeCN, H_2O (1:1)	24	(+)-**2a**	85	100:0	*g*
4	(–)-**1b**	2-propenyl	Ph	CH_2Cl_2	4	(–)-**2b**	100	100:0	71
5	(+)-**1a**	PMP[b]	Me	CH_2Cl_2	4	(+)-**2c**	100	100:0	95+
6	(+)-**1a**	PMP[b]	3-butynyl	CH_2Cl_2	6	(+)-**2d**	100	100:0	95+
7	(+)-**1a**	PMP[b]	2-I-C_6H_4	CH_2Cl_2	22	(–)-**2e**	100	100:0	89
8	(+)-**1a**	PMP[b]	2-N_3-C_6H_4	CH_2Cl_2	16	(–)-**2f**	100	100:0	90
9	(+)-**1a**	PMP[b]	$PhtCH_2$[c]	CH_2Cl_2	3	(–)-**2g**	100	100:0	91
10	(–)-**1c**	Bn	3-butynyl	CH_2Cl_2	3	(–)-**2h**	100	100:0	53

[a]All reactions were performed by using an azetidin-2,3-dione/carboxilic acid/isocyanide ratio of 1.00:1.05:1.10 mmol. [b]PMP = 4-$MeOC_6H_4$. [c]Pht = Phtalimidoyl. [d]Reaction progress was followed by TLC. [e]The conversion and the *syn/anti* ratio were determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [f]Yield of pure *syn* isomer after flash chromatography. [g]The crude reaction was not purified.

Analogous results were observed when benzyl isocyanide was replaced by *t*-butyl isocyanide and *p*-toluenesulfonyl methyl isocyanide (TosMIC), affording compounds (+)-**2i** and (+)-**2j** in 1 and 72h, respectively, as single isomers in excellent yields (entries 1 and 2, Table 2). In order to minimize the reaction time to obtain compound (+)-**2j**, we decided to carry out the reaction at 50 °C in a sealed tube. However, the desired reduction of time was not observed (entry 3, Table 2). Then, we decided to use acetonitrile as solvent. However, we did not get better results, in fact only a conversion of 85% was observed after 72 h (entry 4, Table 2). Fortunately, when the reaction was studied in acetonitrile at reflux temperature, compound (+)-**2j** was obtained in 89% yield after 3h (entry 5, Table 2). Similar results were observed when the reaction was carried out with acetic acid and 4-pentynoic acid, affording compounds (+)-**2k** and (+)-**2l** in 34% and 62 % yields respectively (entries 6 and 7, Table 2). Probably, the 2,2-dimethyl-1,3-dioxolan-4-yl group placed at C4 position of the β-lactam ring is affected under the acidic conditions at reflux temperature, giving decomposition products from a complex crude reaction (checked by TLC), causing the lower yield obtained in adduct (+)-**2k**. Analogously, compound (+)-**2m** was isolated in 74% yield when the reaction was carried out in acetonitrile at reflux temperature (entry 8, Table 2).

Table 2. Passerini Reaction of Azetidine-2,3-dione (+)-1a, Carboxylic acids and other Isocyanides[a]



(+)-**1a** **2**

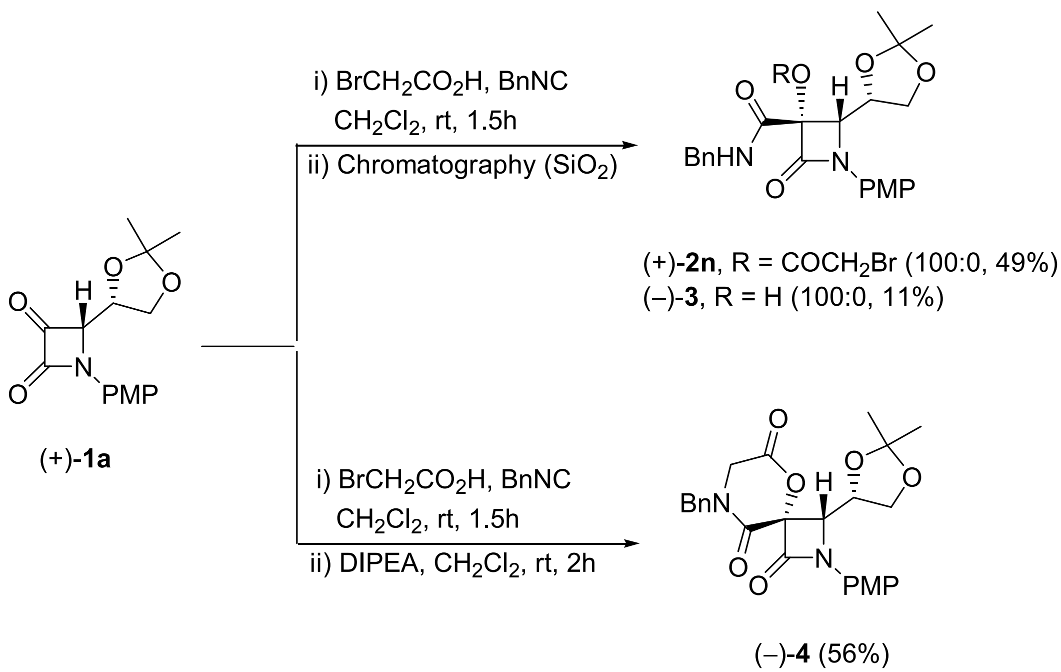
Entry	R^2	R^3	Solvent/T (°C)	t (h)[e]	Product	Conversion (%)[f]	syn/anti[f]	Yield (%)[g]
1	3-butynyl	*t*Bu	CH_2Cl_2/rt	1	(+)-**2i**	100	100:0	88
2	Ph	$TsCH_2$	CH_2Cl_2/rt	72	(+)-**2j**	100	100:0	95+
3	Ph	$TsCH_2$	CH_2Cl_2/50[c]	72	(+)-**2j**	100	100:0	97
4	Ph	$TsCH_2$	CH_3CN/rt	72	(+)-**2j**	85	100:0	*h*
5	Ph	$TsCH_2$	CH_3CN/reflux	3	(+)-**2j**	100	100:0	89
6	Me	$TsCH_2$	CH_3CN/reflux	22	(+)-**2k**	100	100:0	34
7	3-butynyl	$TsCH_2$	CH_3CN/reflux	3	(+)-**2l**	100	100:0	62
8	Ph	PMP[b]	CH_3CN/reflux[d]	46	(+)-**2m**	100	100:0	74

[a]All reactions were performed by using an azetidin-2,3-dione/carboxilic acid/isocyanide ratio of 1.00:1.05:1.10 mmol. [b]PMP = 4-$MeOC_6H_4$. [c]Reaction was carried out in a sealed tube. [d]A second equivalent of *p*-methoxyphenyl isocyanide was added after 12h. [e]Reaction progress was followed by TLC. [f]The conversion and the *syn/anti* ratio were determined by integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [g]Yield of pure *syn* isomer after flash chromatography. [h]The crude reaction was not purified.

When the P3CR was studied with azetidine-2,3-dione (+)-**1a**, bromoacetic acid, and benzyl isocyanide, the corresponding Passerini adduct (+)-**2n** and 3-hydroxy-β-lactam (−)-**3** were isolated

(49% and 11% yields, respectively) after flash chromatography. Probably, compound (+)-**2n** is unstable under the acidic conditions of the chromatography and gives its *O*-deprotected derivative (–)-**3**. Taking advantage of the high reactivity of compound (+)-**2n**, we decided to carry out the Passerini reaction followed by addition of non nucleophilic base N,N´-diisopropylethylamine (DIPEA), affording spirocyclic β-lactam derivative (–)-**4** in 56% yield (Scheme 2).

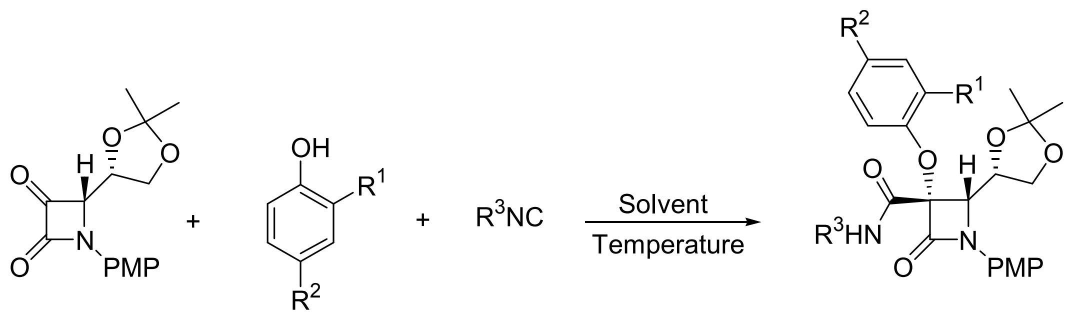
Scheme 2. Passerini Reaction of Azetidine-2,3-dione (+)-1a, Bromoacetic Acid, and Benzyl Isocyanide. Synthesis of Spirocycle (–)-4



Passerini-Smiles three-component reaction in azetidine-2,3-diones

The use of phenols instead of carboxylic acids is known as Passerini-Smiles reaction,[18] which involves an irreversible Smiles rearrangement in place of the traditional Mumm acyl transfer of the classical Passerini reaction, affording α-aryloxy amides. Knowing that Passerini reactions usually require stronger acidic conditions than Ugi couplings, we decided to test the reaction of azetidine-2,3-dione (+)-**1a** and benzyl isocyanide with an electron-deficient phenol as acidic partner, such as *p*-nitrophenol (entry 1, Table 3). Thus, the corresponding α-aryloxy amide (+)-**5a** was obtained in high yield and good diastereoselectivity. Analogous results were observed when the reaction was studied with *t*-butyl isocyanide (entry 2, Table 3), and when 4-nitrophenol was replaced by 2-halo-4-nitrophenols (entries 3-5, Table 3), affording compounds **5b–e** in good yields. Next, we examined the reaction of azetidine-2,3-dione (+)-**1a** and benzyl isocyanide with *o*-nitrophenol, showing longer reaction time and a complex reaction crude, probably due to steric hindrance (entry 6, Table 3). Nevertheless, performing the reaction at 80 °C in a sealed tube allowed 100% conversion and 63% isolated yield (entry 7, Table 3). However, these results were not improved by changing dichloromethane by acetonitrile as solvent at reflux temperature or in a sealed tube at 80 °C (see entries 8 and 9, Table 3).

Table 3. Passerini-Smiles Reaction of Azetidine-2,3-dione (+)-1a[a,b]



(+)-**1a** **5**

Entry	R^1	R^2	R^3	Solvent/T (°C)	Time (h)[d]	Product	syn/anti[e]	Conversion (%)	Yield (%)[f]
1	H	NO_2	Bn	CH_2Cl_2/rt	53	(+)-**5a**	>95:5	100	79
2	H	NO_2	*t*-Bu	CH_2Cl_2/rt	46	(+)-**5b**	>95:5	100	63
3	Br	NO_2	Bn	CH_2Cl_2/rt	24	(+)-**5c**	95:5	100	94
4	Br	NO_2	*t*-Bu	CH_2Cl_2/rt	24	(+)-**5d**	95:5	100	89
5	I	NO_2	Bn	CH_2Cl_2/rt	21	(+)-**5e**	95:5	100	73
6	NO_2	H	Bn	CH_2Cl_2/rt	168	(+)-**5f**	95:5	50	*g*
7	NO_2	H	Bn	CH_2Cl_2/80[c]	168	(+)-**5f**	95:5	100	63
8	NO_2	H	Bn	CH_3CN/reflux	26	(+)-**5f**	95:5	100	24

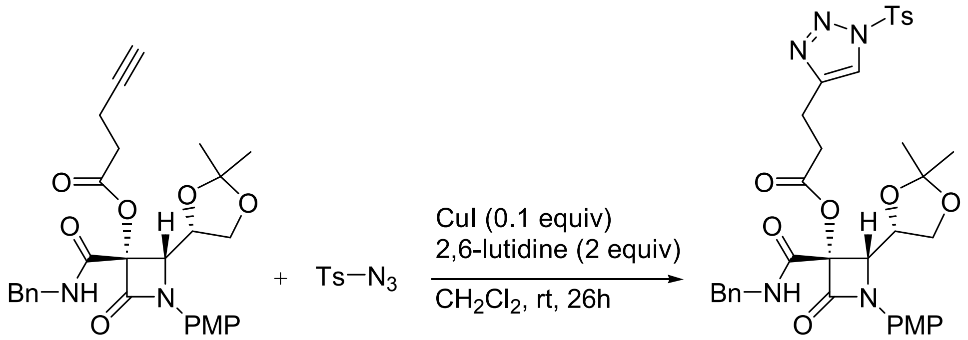
9	NO_2	H	Bn	CH_3CN/80[c]	240	(+)-**5f**	95:5	100	25

[a]All reactions were performed by using an azetidin-2,3-dione/phenol/isocyanide ratio of 1.00:1.05:1.10 mmol. [b]PMP = 4-MeOC_6H_4. [c]Reaction was carried out in a sealed tube. [d]Reaction progress was followed by TLC. [e]The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [f]Yield of pure *syn* isomer.[g]The crude of reaction was not purified.

CuAAC of Passerini Aducts

The combination of the β-lactam skeleton and the triazole ring is present in the cephalosporin antibiotic cefatrizine,[19] and in the β-lactamase inhibitor tazobactam.[20] In addition, in the last few years the synthesis of several 1,2,3-triazole linked β-lactams with interesting pharmacological activities has been developed.[15] Taking into account the appealing properties of β-lactam-triazole hybrids, we were interested in the study of the CuAAC methodology to our Passerini products. Although the most common conditions of CuAAC use $CuSO_4$ with sodium ascorbate (AscNa) as a reducing agent in aqueous conditions, we were particularly interested in carrying out the CuAAC reaction in the same solvent used for the Passerini reaction, in order to study both reactions in a one pot procedure. Thus, we decided to use Cu(I) salts in anhydrous conditions to achieve our goal. First, we focused our attention in the sequential synthesis of the desired triazole compound from the isolated Passerini adduct **2**. Thus, treatment of compound (+)-**2d** with tosylazide, CuI, and 2,6-lutidine in dichloromethane at room temperature afforded the corresponding β-lactam triazole hybrid (−)-**6a** in moderate yield (50%) and total regioselectivity (Scheme 3).

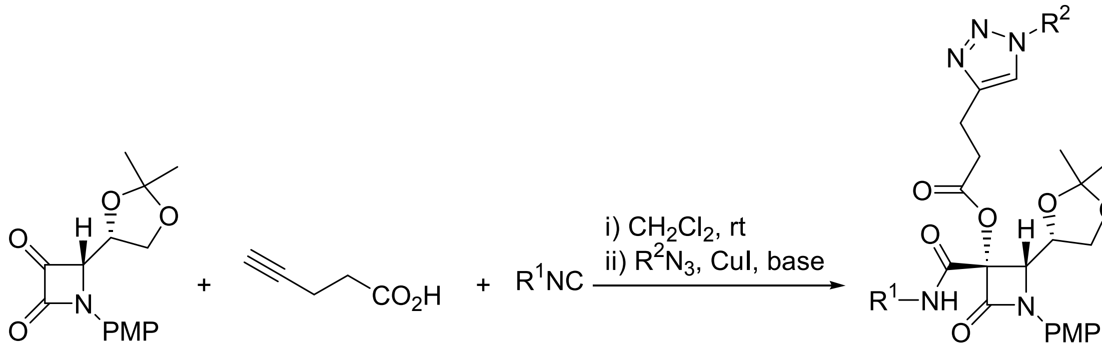
Scheme 3. CuAAC of Passerini Adduct (+)-2d



(+)-**2d** (–)-**6a** (50%)

The next step was to study a tandem reaction of azetidine-2,3-dione (+)-**1a**, 4-pentynoic acid, benzyl isocyanide, and tosyl azide in presence of CuI and 2,6-lutidine. However, under the reaction conditions tested, β-lactam-triazole hybrid (–)-**6a** was isolated after chromatography from a complex reaction mixture in only 15% yield. Then, we decided to turn our attention to the study of the one-pot reaction, treating the crude Passerini adduct (total consumption of the starting azetidine-2,3-dione **1** as checked by TLC) with tosyl azide, CuI, and 2,6-lutidine. In the event, compound (–)-**6a** was isolated in 80% yield (entry 1, Table 4). The use of other bases, such as Et_3N, DIPEA, and K_2CO_3 did not improve the yield of compound (–)-**6a** (entries 2-4, Table 4). Next, the one-pot Passerini-CuAAC was studied with *t*-butyl and benzyl isocyanide under the optimal reaction conditions, affording β-lactam-triazole hybrids (+)-**6b** and (+)-**6c** in 85% and 91% yield, respectively (entries 5 and 6, Table 4). However, the best result for the synthesis of the β-lactam-triazole hybrid (+)-**6d** was achieved using the optimized conditions for its Passerini adduct (+)-**2l** (acetonitrile at reflux temperature) followed by removal of the acetonitrile before carrying out the CuAAC step in dichloromethane (entry 7, Table 4).

Table 4. Synthesis of β-Lactam-Triazole Hybrids 6 via One-Pot Passerini/CuAAC Reactions of Azetidine-2,3-dione (+)-1a[a,b]



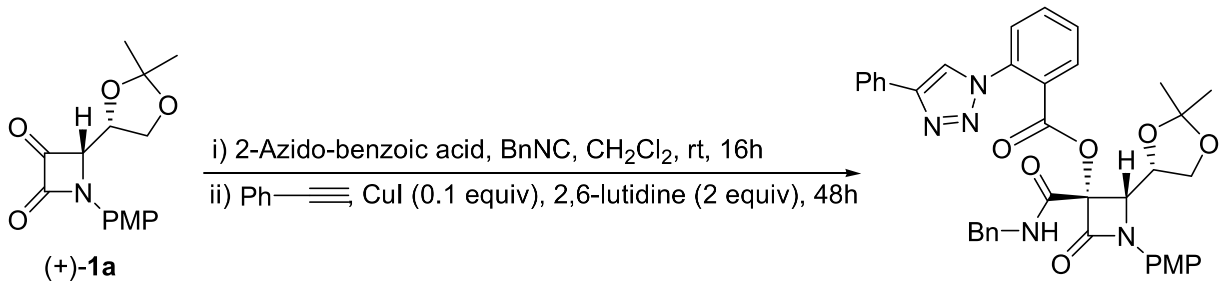
(+)-**1a** **6**

Entry	R^1	R^2	Base	t (h)[e]	Product	yield (%)[f]
1	Bn	Ts	2,6-lutidine	6+4	(–)-**6a**	80
2	Bn	Ts	Et_3N	6+17	(–)-**6a**	20
3	Bn	Ts	DIPEA[c]	6+22	(–)-**6a**	14
4	Bn	Ts	K_2CO_3	6+20	(–)-**6a**	10
5	*t*-Bu	Ts	2,6-lutidine	1+4	(+)-**6b**	85
6	Bn	Bn	2,6-lutidine	6+17	(+)-**6c**	91
7	$TsCH_2$	Bn	2,6-lutidine[d]	3+13	(+)-**6d**	74

[a]All P-3CR/CuAAC reactions were catalyzed by CuI (10 mol%) and performed by using an azetidin-2,3-dione/carboxilic acid/isocyanide/azide/base molar ratio of 1.00:1.05:1.10:2.00:2.00. [b]PMP = 4-$MeOC_6H_4$. [c]DIPEA = N,N′-diisopropylethylamine. [d]P-3CR was carried out in MeCN while the CuAAC was performed in dichloromethane. [e]Reaction time of the Passerini and the CuAAC steps. Reaction progress was followed by TLC. [f]Yield of pure isolated compound.

When the optimum reaction conditions were applied to the reaction of azetidine-2,3-dione (+)-**1a**, 3-azidobenzoic acid, benzyl isocyanide, and phenylacetylene, β-lactam-triazole hybrid (+)-**7** was obtained in good yield (75%, Scheme 4).

Scheme 4. Synthesis of β-Lactam-Triazole Hybrid (+)-7 via One-Pot Passerini/CuAAC Reactions of Azetidine-2,3-dione (+)-1a

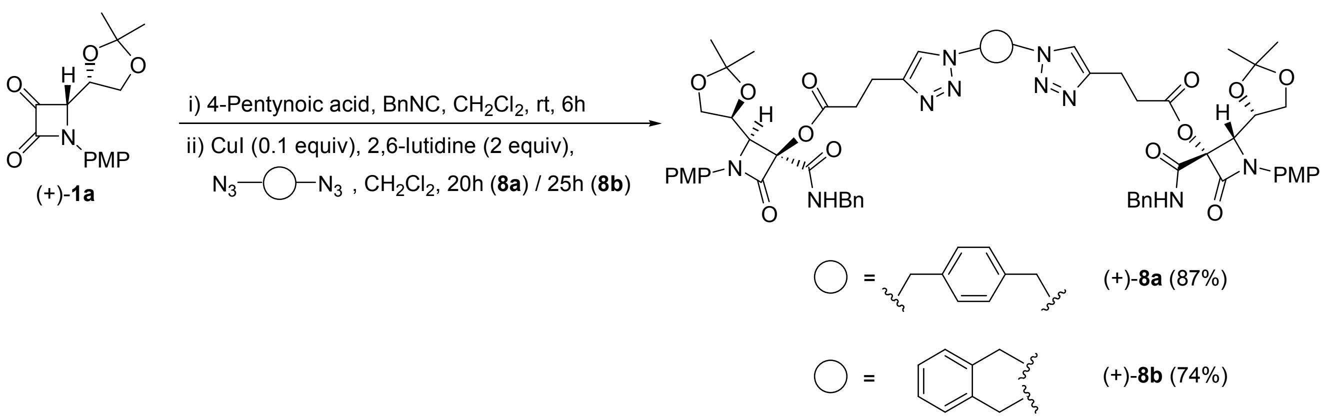


(+)-**1a**

(+)-**7** (75%)

Taking into account that dimers have superior biological activity in comparison to their monomers,[21] we were interested in synthesizing dimeric structures[22] via the designed Passerini/CuAAC sequence using diazides or dialkynes. We examined the one-pot reaction of azetidine-2,3-dione (+)-**1a** in presence of 4-pentynoic acid and benzyl isocyanide, followed by addition of the corresponding bis-azide, affording C_2 symmetric bis(β-lactam triazole) hybrids (+)-**8a** and (+)-**8b** in good yields (87% and 74%, respectively, Scheme 5). Due to the high polarity of (+)-**8a** and (+)-**8b**, these compounds were isolated by precipitation using cool hexanes followed by filtration.

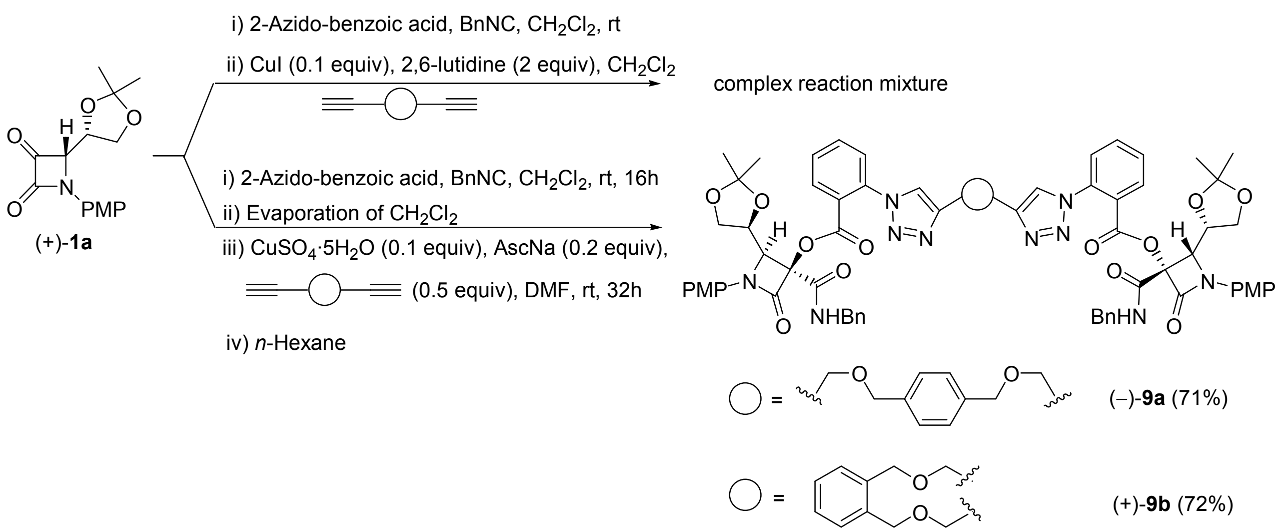
Scheme 5. Synthesis of C_2 Symmetric Bis(β-Lactam-Triazole) Hybrids (+)-8a and (+)-8b via One-Pot Passerini/CuAAC Reactions of Azetidine-2,3-dione (+)-1a



(+)-**1a**

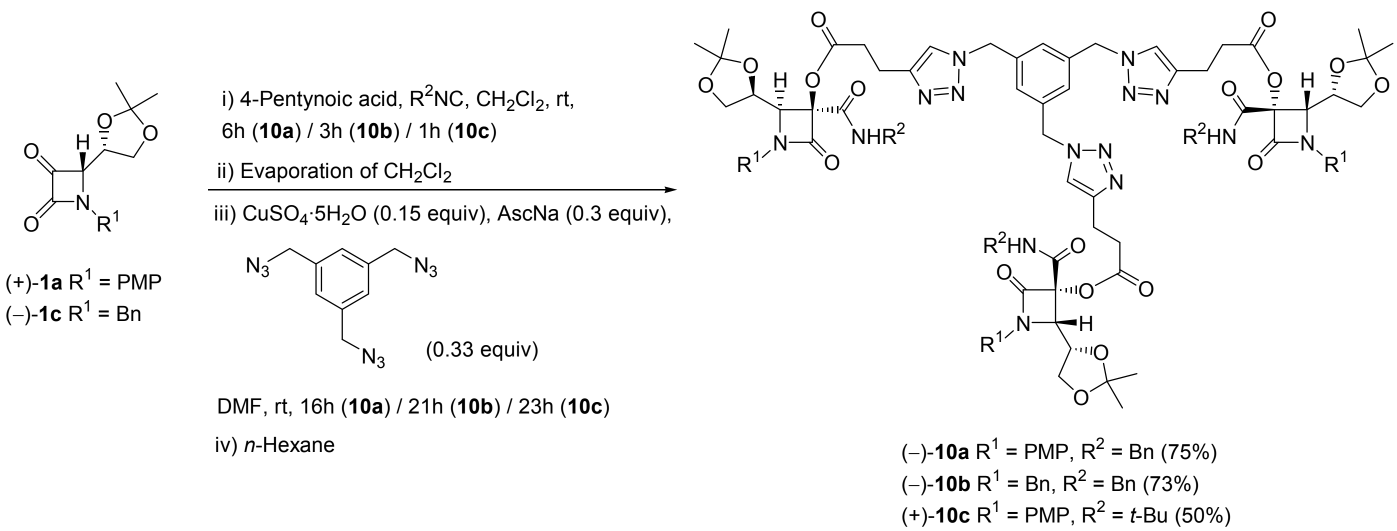
Next, we were interested in studying the reaction by using dialkynes as linkers. However, when we tested the reaction of azetidine-2,3-dione (+)-**1a** with 2-azido-benzoic acid and benzyl isocyanide, followed by addition of CuI/2,6-lutidine and the corresponding dialkyne, a complex reaction mixture was observed. Fortunately, C_2 symmetric bis(β-lactam-triazole) derivatives (–)-**9a** and (+)-**9b** were obtained by previous formation of the Passerini adduct and evaporation of the solvent, followed by CuAAC (using the $CuSO_4 \cdot 5H_2O$/AscNa system in dimethylformamide as solvent) (Scheme 6). Thus, compounds (–)-**9a** and (+)-**9b** were isolated in 71% and 72% yields respectively, after precipitation using cool hexanes.

Scheme 6. Synthesis of C_2 Symmetric Bis(β-Lactam-Triazole) Hybrids (–)-9a and (+)-9b via Passerini/CuAAC Sequence Using a Dialkyne as Linker

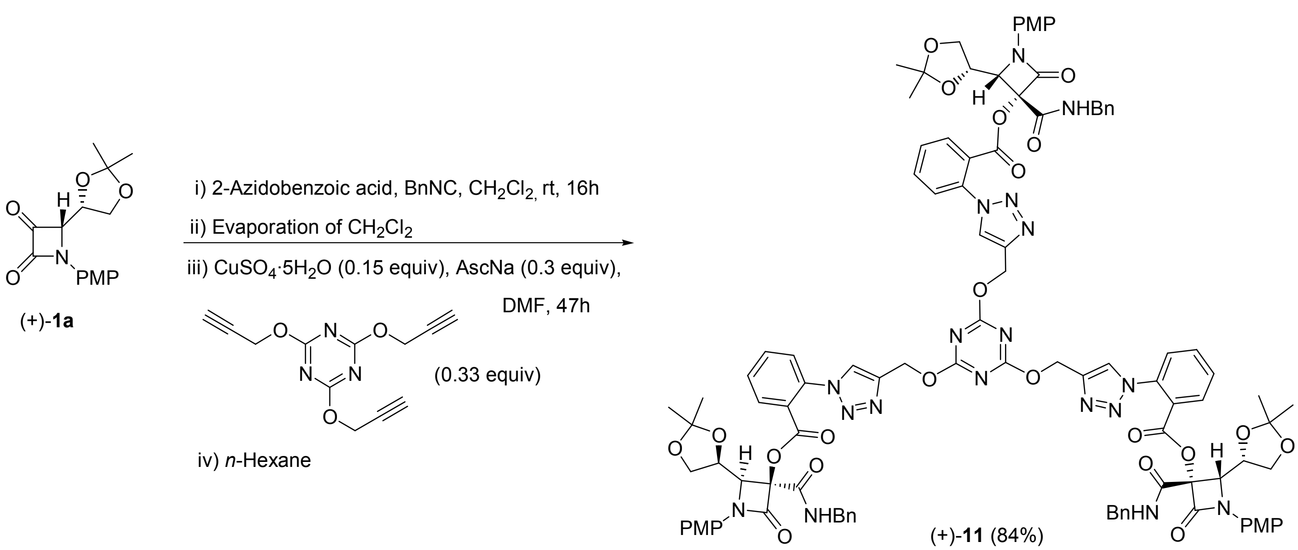


Due to the importance of C_3-symmetric derivatives containing the triazole ring in their structures,[23] we decided to apply this protocol to the synthesis of tris(β-lactam-triazole) derivatives, by using either the corresponding triazides or trialkynes. However, the one-pot reaction of azetidine-2,3-dione (+)-**1a**, 4-pentynoic acid, and benzyl isocyanide, followed by addition of CuI, 2,6-lutidine, and 1,3,5-tris(azidomethyl)benzene after formation of the Passerini adduct, gave a complex reaction mixture. Once again, the problem was solved evaporating the dichloromethane after completion of the Passerini reaction followed by CuAAC using the system Cu(II)/AscNa in dimethylformamide (Scheme 7). Then, C_3 symmetric tris(β-lactam-triazole) hybrids **10a–c** were obtained in moderate to good yields after precipitation in cool hexanes. Analogously, when 2,4,6-tris(prop-2-ynyloxy)-1,3,5-triazine was used as linker in the CuAAC, the expected C_3 symmetric tris(β-lactam-triazole) derivative (+)-**11** was obtained in excellent yield under similar reaction conditions (Scheme 8).

Scheme 7. Synthesis of C_3 Symmetric Tris(β-Lactam-Triazole) Hybrids 10a–c via Passerini/CuAAC Sequence Using a Triazide as Linker



Scheme 8. Synthesis of C_3-Symmetric Tris(β-Lactam-Triazole) Hybrid (+)-11 via Passerini/CuAAC Sequence Using a Trialkyne as Linker



The diastereoselectivity in the Passerini reaction with azetidine-2,3-diones **1** is explained by the presence of a bulky chiral auxiliary at C-4, in which one face of the carbonyl group is blocked preferentially. Thus, the nucleophilic addition takes place to the less hindered face of the carbonyl group affording Passerini adducts as single isomers.[24] On the other hand, the simplicity of the proton and carbon NMR spectra of bis- and tris(β-lactam-triazole) hybrids pointed to C_2- and C_3 symmetrical structures. In addition, 1,4-disubstituted 1,2,3-triazoles were obtained regioselectively,[25] which was confirmed unequivocally by single crystal X-ray analysis of compound (+)-**6b**.[26]

CONCLUSIONS

In conclusion, the present work demonstrates the diastereoselective synthesis of various 3,3-disubstituted β-lactams via Passerini and Passerini-Smiles reactions, with stereocontroled formation of a new quaternary stereogenic centre in excellent optical purity and generally high yields. The Passerini reaction was coupled with CuAAC using the corresponding alkynes or azides to afford a family of mono- bis- and tris(β-lactam-triazole) hybrids regioselectively. This Passerini/CuAAC synthetic sequence represents a practical and efficient opportunity to obtain highly functionalized and complex β-lactam-triazole structures, which combine the interesting biological features of the β-lactam skeleton and the 1,2,3-triazole moiety.

EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. NMR were recorded in $CDCl_3$ or $C_2D_2Cl_4$ solutions. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), $CDCl_3$ (^{13}C, 77.0 ppm) or $C_2D_2Cl_4$ (^{1}H, 5.94 ppm; ^{13}C, 75.5 ppm). NMR spectra of compounds **8–11** were recorded at high temperature (120-130°C) to resolve the multiplicity of the signals. High resolution mass spectra were performed on a QTOF LC/MS spectrometer under electrospray mode (ESI) technique unless otherwise stated. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in grams per 100 mL. All commercially available compounds were used without further purification. Flash S-2 chromatography was performed by using silica gel 60 (230−400 mesh). Products were identified by TLC (Kieselgel 60F-254). UV light (λ = 254nm) and a solution of phosphomolibdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL EtOH) was used to develop the plates.

General Procedure for the Passerini Reaction. Synthesis of Compounds 2. Method A. To a solution of azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (5 mL), the corresponding carboxylic acid (1.05 mmol) and the appropriate isocyanide (1.10 mmol) were sequentially added at room temperature and under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the mixture was diluted with CH_2Cl_2 (2 mL) and $NaHCO_3$ aq. sat. (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/ethyl acetate mixtures. **Method B**. To a solution of azetidine-2,3-dione **1** (1 mmol) in anhydrous acetonitrile (5 mL), the corresponding carboxylic acid (1.05 mmol) and TosMIC (1.10 mmol) were sequentially added at room temperature and under argon atmosphere. The reaction mixture was stirred at reflux temperature until complete disappearance of the starting material (TLC). Then, the mixture was diluted with CH_2Cl_2 (10 mL) and $NaHCO_3$ aq. sat. (4 mL) was added. The resulting reaction mixture was worked-up as indicated above (Method A). **Method C**. To a solution of azetidine-2,3-dione **1** (1 mmol) in anhydrous acetonitrile (5 mL), the corresponding carboxylic acid (1.05 mmol) and *p*-methoxyphenyl isocyanide (PMPNC) (1.10 mmol) were sequentially added, at room temperature and under argon atmosphere. The reaction mixture was stirred at reflux temperature for 12 h. Then, a second equivalent of PMPNC was added and the resulting mixture was stirred at reflux temperature until complete disappearance of the starting material (TLC). After that, the resulting reaction mixture was worked-up as indicated above (Method B).

Passerini Adduct (+)-2a. **Method A**. From 50 mg (0.17 mmol) of azetidine-2,3-dione (+)-**1a**, 84 mg (92%) of compound (+)-**2a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 28.7 (*c* 0.2, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.04-8.01 (m, 2H), 7.66 (m, 2H), 7.61-7.67 (m, 1H), 7.51-7.46 (m, 2H), 7.22-7.32 (m, 5H), 6.89 (m, 2H), 6.70 (t, *J* = 5.6 Hz, 1H), 4.92 (d, *J* = 7.5 Hz, 1H), 4.61 (dd, *J* = 15.0, 6.1 Hz 1H), 4.50 (q, *J* = 7.1 Hz, 1H), 4.44 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.14 (dd, *J* = 8.8, 6.6 Hz, 1H), 4.03 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.81 (s, 3H), 1.46 and 1.26 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.4, 164.3, 160.0, 157.2, 137.0, 134.3, 130.2, 130.1, 128.8, 128.7, 127.9, 127.6, 127.5, 120.7, 114.1, 110.2, 86.4, 75.2, 66.8, 64.1, 55.4, 43.9, 26.4, 25.1; IR ($CHCl_3$, cm^{-1}): υ 3337, 1763, 1734, 1682; HRMS (ESI): for $C_{30}H_{31}N_2O_7^+$ $(M+H)^+$ calcd 531.2126, found 531.2123.

Passerini Adduct (–)-2b. **Method A**. From 64 mg (0.28 mmol) of azetidine-2,3-dione (–)-**1b**, 94 mg (71%) of compound (–)-**2b** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = – 50.8 (*c* 1.6, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.03-8.00 (m, 2H), 7.63 (bt, *J* = 7.5 Hz, 1H), 7.47 (bt, *J* = 7.7 Hz, 2H), 7.22-7.29 (m, 5H), 6.52 (t, *J* = 5.6 Hz, 1H), 5.82 (dddd, *J* = 17.2, 10.2, 7.0, 4.8 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 4.46 (d, *J* = 7.6 Hz, 1H), 4.56 (dd, *J* = 15.1, 5.8 Hz, 1H), 4.44 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.35 (q, *J* = 6.7 Hz, 1H), 4.28 (dd, *J* = 15.7, 4.8 Hz, 1H), 4.05 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.95 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.85 (dd, *J* = 15.6, 7.2 Hz, 1H), 1.43 and 1.28 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.5, 164.5, 162.4, 137.2, 134.2, 130.7, 130.1, 128.73, 128.66, 127.9, 127.5, 127.4, 119.1, 110.0, 87.0, 75.1, 67.0, 62.0, 44.5, 43.8, 26.6, 25.0; IR ($CHCl_3$, cm^{-1}): υ 3333, 1770, 1732, 1683; HRMS (ESI) for $C_{26}H_{29}N_2O_6^+$ $(M+H)^+$ calcd 465.2020, found 465.2038.

Passerini Adduct (+)-2c. **Method A**. From 36 mg (0.12 mmol) of azetidine-2,3-dione (+)-**1a**, 54 mg (100%) of compound (+)-**2c** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 44.2 (*c* 1.7, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.60

(m, 2H), 7.37-7.25 (m, 5H), 6.88 (m, 2H), 6.83 (t, *J* = 5.8 Hz, 1H), 4.73 (d, *J* = 7.3 Hz, 1H), 4.59 (dd, *J* = 14.9, 6.2 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 1H), 4.36 (dd, *J* = 14.9, 5.0 Hz, 1H), 4.16 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.97 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.80 (s, 3H), 2.19 (s, 3H), 1.48 and 1.35 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 168.5, 164.4, 160.0, 157.2, 137.0, 130.1, 128.7, 127.6, 127.6, 120.5, 114.1, 110.2, 86.0, 75.3, 66.6, 64.3, 55.4, 43.9, 26.4, 25.1, 20.6; IR ($CHCl_3$, cm^{-1}) υ 3332, 1754, 1677; HRMS (ESI) for $C_{25}H_{29}N_2O_7^+$ $(M+H)^+$ calcd 469.1969, found 469.1976.

Passerini Adduct (+)-2d. **Method A**. From 221 mg (0.76 mmol) of azetidine-2,3-dione (+)-**1a**, 384 mg (100%) of compound (+)-**2d** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 15.5 (*c* 0.6, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.59 (m, 2H), 7.34-7.24 (m, 5H), 6.92 (t, *J* = 5.7 Hz, 1H), 6.88 (m, 2H), 4.82 (d, *J* = 7.2 Hz, 1H), 4.57 (dd, *J* = 14.8, 6.2 Hz, 1H), 4.41 (q, *J* = 6.9 Hz, 1H), 4.37 (dd, *J* = 14.9, 5.4 Hz, 1H), 4.16 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.92 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.80 (s, 3H), 2.72-2.67 (m, 2H), 2.56-2.51 (m, 2H), 1.89 (t, *J* = 2.6 Hz, 1H), 1.47 and 1.33 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 169.5, 164.1, 159.7, 157.2, 137.0, 130.1, 128.7, 127.7, 127.6, 120.6, 114.0, 110.2, 86.3, 81.8, 75.0, 69.8, 66.7, 64.1, 55.4, 43.9, 33.0, 26.4, 25.1, 14.2; IR ($CHCl_3$, cm^{-1}) υ 3295, 1758, 1678; HRMS (ESI) for $C_{28}H_{31}N_2O_7^+$ $(M+H)^+$ calcd 507.2126, found 507.2124.

Passerini adduct (–)-2e. **Method A**. From 42 mg (0.14 mmol) of azetidine-2,3-dione (+)-**1a**, 84 mg (89%) of compound (–)-**2e** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = – 1.3 (*c* 0.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.02 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.61 (m, 2H), 7.56 (td, *J* = 7.6, 1.1 Hz, 1H,), 7.37-7.28 (m, 5H), 7.23 (td, *J* = 7.7, 1.8 Hz, 1H), 6.90 (m, 2H), 6.76 (t, *J* = 5.8 Hz, 1H), 5.00 (d, *J* = 6.6 Hz, 1H), 4.66 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.53 (q, *J* = 6.8 Hz, 1H), 4.43 (dd, *J* = 14.9, 5.4 Hz, 1H), 4.12 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.99 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.81 (s, 3H), 1.45 and 1.28 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.3, 164.0, 159.6, 157.3, 141.7, 137.0, 133.7, 132.9, 131.7, 130.1, 128.8, 128.1, 127.8, 127.7, 120.8, 114.1, 110.2, 94.4, 86.9, 74.9, 66.8, 63.8, 55.5, 44.1, 26.4, 25.2, IR ($CHCl_3$, cm^{-1}) υ 3333, 1764, 1680; HRMS (ESI) for $C_{30}H_{30}IN_2O_7^+$ $(M+H)^+$ calcd 657.1092, found 657.1094.

Passerini Adduct (–)-2f. **Method A**. From 33 mg (0.11 mmol) of azetidine-2,3-dione (+)-**1a**, 58 mg (90%) of compound (–)-**2f** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D = -17.1$ (*c* 1.5, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.95 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.69 (m, 2H), 7.61 (td, *J* = 8.2, 1.6 Hz, 1H), 7.55 (t, *J* = 5.3 Hz, 1H), 7.38-7.29 (m, 5H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H,), 6.91 (m, 2H), 4.91 (d, *J* = 7.8 Hz, 1H), 4.63 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.55 (q, *J* = 7.2 Hz, 1H), 4.51 (dd, *J* = 14.8, 5.1 Hz, 1H), 4.02 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.83 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.82 (s, 3H), 1.31 and 1.48 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.2, 163.1, 159.4, 157.0, 140.1, 136.9, 134.7, 133.2, 130.4, 128.9, 127.85, 127.75, 125.0, 120.5, 119.9, 119.4, 114.1, 110.2, 86.9, 75.1, 66.6, 65.3, 55.4, 44.2, 26.5, 25.2; IR ($CHCl_3$, cm^{-1}) υ 3354, 2123, 1766, 1735, 1683; HRMS (ESI) for $C_{30}H_{30}N_5O_7^+$ $(M+H)^+$ calcd 572.2140; found 572.2143.

Passerini Adduct (–)-2g. **Method A**. From 40 mg (0.14 mmol) of azetidine-2,3-dione (+)-**1a**, 76 mg (91%) of compound (–)-**2g** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D = -13.2$ (*c* 3.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.86 (AA'BB', 2H), 7.76 (AA'BB', 2H), 7.52 (m, 2H), 7.32-7.23 (m, 5H), 7.07 (bs, 1H), 6.86 (m, 2H), 5.00 (d, *J* = 6.4 Hz, 1H), 4.57 (s, 2H), 4.56 (dd, *J* = 14.8, 6.2 Hz, 1H), 4.41 (dd, *J* = 14.0, 6.3 Hz, 1H), 4.39 (q, *J* = 6.6 Hz, 1H), 4.12 (dd, *J* = 8.6, 6.9 Hz, 1H), 3.82 (dd, *J* = 9.0, 6.8 Hz, 1H), 3.79 (s, 3H), 1.43 and 1.37 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 167.1, 165.6, 163.2, 159.1, 157.3, 137.0, 134.5, 131.7, 129.9, 128.6, 127.6, 127.5, 123.8, 121.0, 114.1, 110.2, 87.2, 74.4, 66.5, 63.4, 55.4, 44.0, 38.8, 26.3, 24.9; IR ($CHCl_3$, cm^{-1}) υ 3342, 1764, 1722, 1683; HRMS (ESI) for $C_{33}H_{32}N_3O_9^+$ $(M+H)^+$ calcd 614.2133, found 614.2132.

Passerini Adduct (–)-2h. **Method A**. From 46 mg (0.17 mmol) of azetidine-2,3-dione (–)-**1c**, 44 mg (53%) of compound (–)-**2h** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = – 59.8 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.37-7.21 (m, 10H), 6.55 (t, *J* = 5.6 Hz, 1H), 4.94 (d, *J* = 14.9 Hz, 1H), 4.48 (d, *J* = 5.7, 2H), 4.36-4.27 (m, 1H), 4.26 (d, *J* = 14.9 Hz, 1H), 4.10 (d, *J* = 7.4 Hz, 1H), 4.05 (dd, *J* = 9.0, 6.9 Hz, 1H), 3.76 (dd, *J* = 9.1, 5.4 Hz, 1H), 2.67-2.61 (m, 2H), 2.54-2.48 (m, 2H), 1.84 (t, *J* = 2.6 Hz, 1H), 1.33 and 1.32 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 169.6, 164.3, 162.4, 137.1, 134.4, 128.7, 128.7, 128.4, 127.9, 127.64, 127.61, 110.1, 86.8, 81.8, 74.7, 69.8, 66.6, 61.7, 45.7, 43.8, 32.9, 26.4, 24.9, 14.1; IR ($CHCl_3$, cm^{-1}) υ 3299, 1762, 1680; HRMS (ESI) for $C_{28}H_{31}N_2O_6^+$ $(M+H)^+$ calcd 491.2177, found 491.2174.

Passerini Adduct (+)-2i. **Method A**. From 40 mg (0.14 mmol) of azetidine-2,3-dione (+)-**1a**, 58 mg (88%) of compound (+)-**2i** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 53.3 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.63 (m, 2H), 6.89 (m, 2H), 6.17 (bs, 1H), 4.62 (d, *J* = 7.6 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 1H), 4.19 and 3.99 (dd, *J* = 8.8, 6.8 Hz, each 1H), 3.81 (s, 3H), 2.73-2.68 (m, 2H), 2.59-2.53 (m, 2H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.49 (s, 3H), 1.36 (s, 9H), 1.33 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 169.3, 163.2, 160.1, 157.1, 130.2, 120.4, 114.0, 110.1, 86.4, 81.6, 75.3, 69.8, 66.7, 64.2, 55.4, 52.2, 33.0, 28.4, 26.4, 25.0, 14.1; IR ($CHCl_3$, cm^{-1}) υ 3304, 1755, 1684; HRMS (ESI) for $C_{25}H_{33}N_2O_7^+$ $(M+H)^+$ calcd 473.2282; found 473.2303.

Passerini Adduct (+)-2j. **Method A**. From 48 mg (0.16 mmol) of azetidine-2,3-dione (+)-**1a**, 100 mg (100%) of compound (+)-**2j** was obtained as a yellowish solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). **Method B**. From 28 mg (0.10 mmol) of azetidine-2,3-dione (+)-**1a**, 52 mg (89%) of pure compound (+)-**2j** was obtained. Mp: 208–210 °C; $[\alpha]_D$ = + 31.0 (*c* 1.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.07-8.01 (m, 2H), 7.68 (m, 2H), 7.67-7.60 (m, 1H), 7.59 (m, 2H), 7.49 (m, 2H), 7.33 (t, *J* = 6.7 Hz, 1H), 7.11 (2H, m), 6.91 (m, 2H), 4.85 (dd, *J* = 14.2, 7.4 Hz, 1H), 4.59 (dd, *J* = 14.0, 6.8 Hz, 1H), 4.57 (d, *J* = 7.3 Hz, 1H), 4.38 (q, *J* = 6.9 Hz, 1H), 4.04 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.83 (s, 3H), 3.79 (dd, *J* = 8.7, 6.8 Hz, 1H), 2.28 (s, 3H), 1.43 and 1.24 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.3, 164.0, 158.9, 157.2, 145.3, 134.5, 133.4, 130.2, 130.1, 129.9, 129.0, 128.9, 127.5, 120.5, 114.1, 110.2, 86.0, 75.0, 66.7, 63.7, 60.1, 55.5, 26.4, 25.0, 21.5; IR (KBr, cm^{-1}) υ 3328, 1766, 1737, 1701; HRMS (ES) for $C_{31}H_{33}N_2O_9S^+$ $(M+H)^+$ calcd 609.1901, found 609.1894.

Passerini Adduct (+)-2k. **Method B**. From 39 mg (0.13 mmol) of azetidine-2,3-dione (+)-**1a**, 24 mg (34%) of compound (+)-**2k** was obtained as a white solid after purification by flash chromatography (hexanes/ethyl acetate, 2:1). Mp: 197−198 °C; $[\alpha]_D$ = + 45.6 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.70 (m, 2H), 7.56 (m, 2H), 7.49 (t, 1H, *J* = 6.7 Hz), 7.16 (m, 2H), 6.90 (m, 2H), 4.86 (dd, *J* = 14.2, 7.5 Hz, 1H), 4.60 (dd, *J* = 14.1, 6.2 Hz, 1H), 4.40 (d, *J* = 7.4 Hz, 1H), 4.31 (q, *J* = 6.9 Hz, 1H), 4.05 (dd, *J* = 8.8, 6.6 Hz, 1H), 3.82 (s, 3H), 3.71 (dd, *J* = 8.8, 6.8 Hz, 1H), 2.20 (s, 3H), 2.31(s, 3H), 1.32 and 1.45 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): δ 168.6, 164.2, 158.9, 157.2, 145.4, 133.5, 130.0, 129.9, 128.9, 120.4, 114.1, 110.2, 85.7, 74.9, 66.5, 63.9, 60.2, 55.5, 26.4, 25.0, 21.6, 20.5; IR (KBr, cm^{-1}) υ 3324, 1761, 1699; HRMS (ESI) for $C_{26}H_{30}N_2NaO_9S^+$ $(M+Na)^+$ calcd 569.1564, found 569.1553.

Passerini Adduct (+)-2l. **Method B**. From 49 mg (0.17 mmol) of azetidine-2,3-dione (+)-**1a**, 60 mg (62%) of compound (+)-**2l** was obtained as a yellowish oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 22.4 (*c* 2.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.71 (m, 2H), 7.56 (m, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.18 (m, 2H), 6.91 (m, 2H), 4.84 (dd, *J* = 14.2, 7.6 Hz, 1H), 4.53 (dd, *J* = 14.2, 6.1 Hz, 1H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.32 (q, *J* = 6.8 Hz, 1H), 4.09 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.83 (s, 3H), 3.71 (dd, *J* = 8.8, 6.3 Hz, 1H), 2.72 (t, *J* = 6.7 Hz, 2H), 2.60-2.55 (m, 2H), 2.32 (s, 3H), 2.14 (t, *J* = 2.6 Hz, 1H), 1.45 and 1.31 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ

169.6, 163.9, 158.6, 157.2, 145.4, 133.3, 130.0, 129.0, 120.5, 114.0, 110.2, 85.9, 81.8, 74.7, 70.1, 66.5, 63.8, 60.1, 55.5, 32.9, 26.4, 25.0, 21.6, 14.2; IR ($CHCl_3$, cm^{-1}) υ 3300, 1761, 1698; HRMS (ESI) for $C_{29}H_{33}N_2O_9S^+$ $(M+H)^+$ calcd 585.1901, found 585.1910.

Passerini Adduct (+)-2m. **Method C**. From 45 mg (0.15 mmol) of azetidine-2,3-dione (+)-**1a**, 61 mg (74%) of compound (+)-**2m** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D = +25.6$ (*c* 0.3, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.16 (bs, 1H), 8.09-8.06 (m, 2H), 7.64 (m, 2H), 7.67-7.63 (m, 1H), 7.54-7.49 (m, 2H), 7.44 (m, 2H), 6.93 (m, 2H), 6.84 (m, 2H), 4.94 (d, *J* = 7.8 Hz, 1H), 4.55 (q, *J* = 7.8 Hz, 1H), 4.20 (dd, *J* = 8.9, 6.7 Hz, 1H), 4.11 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.82 and 3.78 (s, each 3H), 1.50 and 1.31 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.5, 162.0, 160.2, 157.2, 157.1, 134.3, 130.2, 130.1, 129.8, 128.8, 127.9, 122.1, 120.6, 114.2, 114.1, 110.3, 86.5, 75.4, 66.9, 64.4, 55.5, 55.4, 26.5, 25.2; IR ($CHCl_3$, cm^{-1}) υ 3309, 1753, 1687; HRMS (ESI) for $C_{30}H_{31}N_2O_8^+$ $(M+H)^+$ calcd 547.2075, found 547.2097.

P-3CR of Azetidine-2,3-dione (+)-1a with Benzyl Isocyanide and Bromoacetic Acid. **Method A**. From 50 mg (0.17 mmol) of azetidine-2,3-dione (+)-**1a**, 46 mg (49%) of Passerini adduct (+)-**2n** and 8 mg (11%) of 3-hydroxy-β-lactam (–)-**3** were obtained after purification by flash chromatography (hexanes/ethyl acetate, 1:1).

Passerini Adduct (+)-2n. Colorless oil. $[\alpha]_D = +26.4$ (*c* 1.8, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.60 (m, 2H), 7.36-7.24 (m, 5H), 6.89 (m, 2H), 6.90-6.85 (m, 1H), 4.77 (d, *J* = 7.3 Hz, 1H), 4.59 (dd, *J* = 14.3, 6.9 Hz, 1H), 4.42 (q, *J* = 6.7 Hz, 1H), 4.37 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.24 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.97 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.93 (s, 2H), 3.81 (s, 3H), 1.35 and 1.48 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.9, 163.6, 159.1, 157.4, 136.8, 129.8, 128.8, 127.72, 127.69, 120.7, 114.1, 110.4, 86.7, 75.0, 66.7, 64.2, 55.5, 44.0, 26.4, 25.0, 24.3; IR ($CHCl_3$, cm^{-1}) υ 3336, 1758, 1673; HRMS (ESI) for $C_{25}H_{28}BrN_2O_7^+$ $(M+H)^+$ calcd 547.1074, found: 547.1079.

3-Hydroxy-β-Lactam (–)-3. White solid. Mp: 184–186 °C; $[\alpha]_D = -6.8$ (*c* 0.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.54 (m, 2H), 7.36-7.20 (m, 5H), 7.01 (t, J = 5.8 Hz, 1H), 6.85 (m, 2H), 5.98 (bs, 1H), 4.61 (d, J = 6.1 Hz, 1H), 4.50 (dd, J = 15.6, 6.7 Hz, 1H), 4.45 (q, J = 6.7 Hz, 1H), 4.29-4.22 (m, 2H), 3.79 (s, 3H), 3.77 (dd, J = 8.6, 6.1 Hz, 1H), 1.45 and 1.37 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 167.1, 164.4, 157.2, 137.4, 130.0, 128.7, 127.7, 127.6, 120.7, 114.1, 110.2, 84.6, 75.9, 66.5, 65.5, 55.4, 43.4, 26.4, 25.2; IR (KBr, cm^{-1}) υ 3302, 1755, 1655; HRMS (ESI) for $C_{23}H_{27}N_2O_6^+$ $(M+H)^+$ calcd 427.1864, found: 427.1861.

P-3CR-Base Promoted Cyclization Sequence. Synthesis of Spiro Compound (–)-4. To a solution of azetidine-2,3-dione (+)-**1a** (58 mg, 0.20 mmol) in anhydrous dichloromethane (1 mL), bromoacetic acid (29 mg, 0.21 mmol) and benzyl isocyanide (27 μL, 0.22 mmol) were successively added, at room temperature under argon. The reaction mixture was stirred at room temperature for 1.5h. Then, DIPEA was added (36 μL, 0.21 mmol) and the resulting mixture was stirred at room temperature for 2h. Then, the mixture was diluted with CH_2Cl_2 (1 mL) and H_2O (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/ethyl acetate (3:1) affording 52 mg (56%) of compound (–)-**4** as a colorless oil. $[\alpha]_D = -2.5$ (*c* 0.5, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.63 (m, 2H), 7.34-7.28 (m, 5H), 6.89 (m, 2H), 5.16 (d, J = 16.5 Hz, 1H), 5.03 (s, 2H), 4.77 (d, J = 8.9 Hz, 1H), 4.61 (d, J = 16.7 Hz, 1H), 4.42 (dt, J = 8.7, 6.6 Hz, 1H), 4.20 (dd, J = 9.1, 6.9 Hz, 1H), 3.81 (s, 3H), 3.58 (dd, J = 9.1, 6.3 Hz, 1H), 1.53 and 1.34 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 167.5, 165.4, 159.2, 157.2, 135.5, 129.9, 128.7, 128.3, 127.9, 120.3, 114.0, 110.4, 86.3, 75.9, 66.8, 66.3, 63.7, 55.4, 43.0, 26.5, 24.8; IR ($CHCl_3$, cm^{-1}) υ 1755, 1692; HRMS (ESI) for $C_{25}H_{27}N_2O_7^+$ $(M+H)^+$ calcd 467.1813, found 467.1808.

General Procedure for the Passerini-Smiles Reaction. Synthesis of compounds 5. Method A. To a solution of azetidine-2,3-dione (+)-**1a** (1 mmol) in anhydrous dichloromethane (5 mL), the corresponding phenol (1.05 mmol) and the appropriate isocyanide (1.10 mmol) were sequentially added, at room temperature and under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the mixture was diluted with CH_2Cl_2 (2 mL) and $NaHCO_3$ aq. sat. (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The organic extract was washed with $NaHCO_3$ aq. sat. (3 x 2 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with mixtures of hexanes/ethyl acetate. **Method B.** To a solution of azetidine-2,3-dione (+)-**1a** (1 mmol) in anhydrous dichloromethane (5 mL), the appropriate phenol (1.05 mmol) and the corresponding isocyanide (1.10 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was heated in a sealed tube at 80 °C until complete disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (2 mL) and, then $NaHCO_3$ aq. sat. (1 mL) was added. The resulting reaction mixture was worked-up as indicated above (Method A).

Passerini-Smiles Adduct (+)-5a. **Method A**. From 35 mg (0.12 mmol) of azetidine-2,3-dione (+)-**1a**, 52 mg (79%) of compound (+)-**5a** was obtained as a yellow solid after purification by flash chromatography (hexanes/ethyl acetate, 3:2). Mp: 164–166 °C; $[\alpha]_D$ = + 167.0 (*c* 0.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.12 (m, 2H), 7.68 (m, 2H), 7.34 (m, 2H), 7.27-7.20 (m, 3H), 7.04-7.02 (m, 2H), 6.92 (m, 2H), 6.48 (t, 1H, J = 5.9 Hz), 4.59-4.50 (m, 2H), 4.46-4.41 (m, 1H), 4.28 (dd, J = 14.6, 5.4 Hz, 1H), 4.12 (dd, J = 8.9, 5.7 Hz, 1H), 3.85-3.81 (m, 1H), 3.83 (s, 3H), 1.54 and 1.37 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.4, 160.2, 159.3, 157.4, 143.6, 136.5, 129.8, 128.7, 128.0, 127.7, 125.7, 120.5, 118.3, 114.1, 110.4, 88.7, 76.0, 66.9, 65.7, 55.5, 43.8, 26.5, 24.8; IR (KBr, cm^{-1}) υ 3351, 1756, 1676; HRMS (ESI) for $C_{29}H_{30}N_3O_8^+$ $(M+H)^+$ calcd 548.2027, found 548.2030.

Passerini-Smiles Adduct (+)-5b. **Method A**. From 35 mg (0.12 mmol) of azetidine-2,3-dione (+)-**1a**, 39 mg (63%) of compound (+)-**5b** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 142.0 (*c* 0.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.24 (m, 2H), 7.69 (m, 2H), 7.40 (m, 2H), 6.92 (m, 2H), 5.95 (bs, 1H), 4.57-4.50 (m, 1H), 4.46 (d, *J* = 8.0 Hz, 1H), 4.42 (dd, *J* = 8.7, 6.6 Hz, 1H), 4.10 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.83 (s, 3H), 1.54 and 1.37 (s, each 3H), 1.24 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 163.4, 160.7, 159.6, 157.4, 143.7, 130.0, 125.6, 120.5, 118.5, 114.1, 110.4, 89.0, 76.0, 66.9, 65.7, 55.5, 52.6, 28.4, 26.5, 24.8; IR ($CHCl_3$, cm^{-1}) υ 3394, 1758, 1684; HRMS (ESI) for $C_{26}H_{32}N_3O_8^+$ $(M+H)^+$ calcd 514.2184, found 514.2191.

Passerini-Smiles Adduct (+)-5c. **Method A**. From 101 mg (0.35 mmol) of azetidine-2,3-dione (+)-**1a**, 205 mg (94%) of compound (+)-**5c** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 153.4 (*c* 2.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.41 (d, *J* = 2.8 Hz, 1H), 8.01 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.68 (m, 2H), 7.33-7.24 (m, 3H), 7.10-7.06 (m, 2H), 6.91 (m, 2H), 6.39 (t, *J* = 5.9 Hz, 1H), 4.71-4.64 (m, 2H), 4.50 (dd, *J* = 14.5, 6.1 Hz, 1H), 4.46 (d, *J* = 7.0 Hz, 1H), 4.39 (dd, *J* = 14.6, 5.8 Hz, 1H), 4.17-4.10 (m, 1H), 3.83 (s, 3H), 1.57 and 1.38 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.2, 159.4, 157.5, 156.4, 143.3, 136.6, 129.6, 129.1, 128.8, 128.0, 127.7, 124.3, 120.8, 117.4, 114.0, 112.3, 110.6, 89.3, 76.1, 67.4, 66.0, 55.4, 43.9, 26.7, 24.7; IR ($CHCl_3$, cm^{-1}) υ 3347, 1757, 1680; HRMS (ESI) for $C_{29}H_{29}BrN_3O_8^+$ $(M+H)^+$ calcd 626.1133, found: 626.1137.

Passerini-Smiles Adduct (+)-5d. **Method A**. From 101 mg (0.35 mmol) of azetidine-2,3-dione (+)-**1a**, 183 mg (89%) of compound (+)-**5d** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 158.3 (*c* 3.2, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.50 (d, *J* = 2.8 Hz, 1H), 8.21 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.70 (m, 2H), 6.92 (m, 2H), 5.84 (bs, 1H), 4.70-4.63 (m, 2H), 4.42-4.36 (m, 1H), 4.13-4.07 (m, 1H), 3.83 (s, 3H), 1.58 and 1.38 (s, each 3H), 1.28 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 163.3, 159.8, 157.5, 156.6, 143.4, 129.8, 129.2, 124.2, 120.8, 117.5, 114.1, 112.4, 110.5, 89.6, 76.0, 67.4, 66.1, 55.5, 52.8, 28.4, 26.6, 24.7; IR ($CHCl_3$, cm^{-1}) υ 3405, 1758, 1689; HRMS (ESI) for $C_{26}H_{31}BrN_3O_8^+$ $(M+H)^+$ calcd 592.1289, found: 592.1285.

Passerini-Smiles Adduct (+)-5e. **Method A**. From 103 mg (0.35 mmol) of azetidine-2,3-dione (+)-**1a**, 174 mg (73%) of compound (+)-**5e** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 132.3 (*c* 0.8, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.61 (d, *J* = 2.6 Hz, 1H), 8.04 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.66 (m, 2H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.28-7.26 (m, 3H), 7.11-7.08 (m, 2H), 6.91 (m, 2H), 6.35 (t, *J* = 5.7 Hz, 1H), 4.77-4.69 (m, 2H), 4.50 (dd, *J* = 14.6, 6.1 Hz, 1H), 4.46 (d, *J* = 8.2 Hz, 1H), 4.40 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.15-4.09 (m, 1H), 3.83 (s, 3H), 1.38 and 1.55 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 164.3, 159.3, 158.8, 157.5, 143.4, 136.6, 135.2, 129.6, 128.8, 128.0, 127.7, 125.2, 121.0, 116.2, 114.0, 110.6, 89.5, 85.0, 75.8, 67.9, 65.9, 55.4, 43.9, 26.7, 24.8; IR ($CHCl_3$, cm^{-1}) υ 3361, 1759, 1680; HRMS (ESI) for $C_{29}H_{29}IN_3O_8^+$ $(M+H)^+$ calcd 674.0994, found 674.1007.

Passerini-Smiles Adduct (+)-5f. **Method B**. From 32 mg (0.11 mmol) of azetidine-2,3-dione (+)-**1a**, 38 mg (63%) of compound (+)-**5f** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 66.1 (*c* 0.6, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.17 (d, *J* = 8.5 Hz, 1H), 7.71 (td, *J* = 8.8, 1.6 Hz, 1H), 7.70 (m, 2H), 7.53 (td, *J* = 8.0, 1.7 Hz, 1H), 7.23-7.07 (m, 4H), 7.09 (t, *J* = 5.6 Hz, 1H), 6.94-6.87 (m, 2H), 6.90 (m, 2H), 4.58-4.51 (m, 2H), 4.42 (d, *J* = 8.9 Hz, 1H), 4.34-4.28 (m, 1H), 4.32 (dd, *J* = 9.4, 6.6 Hz, 1H), 3.97 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.82 (s, 3H), 1.55 and 1.34 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 165.1, 159.5, 157.3, 147.7, 140.1, 136.7, 134.6, 129.8, 128.7, 127.6, 127.4, 125.3, 123.6, 120.9, 119.7, 113.9, 110.4, 89.9, 76.1, 66.9, 65.9, 55.4, 43.7, 26.6, 24.6; IR ($CHCl_3$, cm^{-1}) υ 3602, 1759, 1679; HRMS (ESI) for $C_{29}H_{29}N_3NaO_8^+$ $(M+Na)^+$ calcd 570.1847, found 570.1857.

General Procedure for the CuAAC. Synthesis of β-Lactam-Triazole Hybrids 6. Method A. To a solution of the appropriate Passerini adduct **2** (1 mmol) in anhydrous dichloromethane (3.2 mL), CuI (0.10 mmol), 2,6-lutidine (2 mmol) and tosylazide (2 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearance of the starting material (TLC). Then, the mixture was diluted with CH_2Cl_2 (6.4 mL) and NH_4Cl aq. sat. (3.2 mL) and stirred at room temperature for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 6 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with mixtures of hexanes/ethyl acetate.

General Procedure for the Passerini/CuAAC Sequence. Synthesis one-pot of β-Lactam Triazole Hybrids 6–11. Method B. To a solution of the appropriate azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (5 mL), the appropriate carboxylic acid (1.05 mmol) and the corresponding isocyanide (1.10 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred at the same temperature until complete disappearances of the azetidine-2,3-dione **1** (TLC). Then, CuI (0.10 mmol), 2,6-lutidine (2 mmol) and the corresponding azide (2 mmol) were sequentially added. The resulting mixture was stirred at room temperature until complete disappearances of the corresponding Passerini adduct (TLC). After that, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and NH_4Cl aq. sat. (3.3 mL) and stirred at room temperature for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography. **Method C**. To a solution of the appropriate azetidine-2,3-dione **1** (1 mmol) in anhydrous acetonitrile (5 mL), 4-pentynoic acid (1.05 mmol) and TosMIC (1.10 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred at reflux temperature until complete disappearances of the azetidine-2,3-dione **1** (TLC). Then, acetonitrile was evaporated under reduced pressure and CH_2Cl_2 (5 mL), CuI (0.10 mmol), 2,6-lutidine (2 mmol), and benzyl azide (2 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the Passerini adduct (TLC). Then, the mixture was worked-up as indicated above (Method B). **Method D**. To a solution of the appropriate azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (5 mL), 2-azido-benzoic acid (1.05 mmol) and benzyl isocyanide (1.10 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature until complete disappearance of the azetidine-2,3-dione **1** (TLC). Then, CuI (0.10 mmol), 2,6-lutidine (2 mmol), and phenyl acetylene (2 mmol) were sequentially added. The reaction mixture was stirred at room temperature until complete disappearances of the Passerini adduct **2** (TLC). Then, the mixture was worked-up as indicated above (Method B). **Method E**. To a solution of the appropriate azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (5 mL), was added 4-pentynoic acid (1.05 mmol) and benzyl isocyanide (1.10 mmol). The reaction mixture was stirred at room temperature under argon atmosphere until complete disappearance of the azetidine-2,3-dione **1** (TLC). Then, CuI (0.10 mmol), 2,6-lutidine (2 mmol) and the corresponding bis-azide (0.50 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the Passerini adduct (TLC). Then, the mixture was worked-up as indicated above (Method B). **Method F**. To a solution of the appropriate azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (5 mL), 2-azido benzoic acid (1.05 mmol) and benzyl isocyanide (1.10 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearance of the azetidine-2,3-dione **1** (TLC). Then, dichloromethane was evaporated under reduced pressure, and anhydrous DMF (10 mL), $CuSO_4\cdot 5H_2O$ (0.10 mmol), sodium ascorbate (0.20 mmol) and the corresponding bis-alkyne (0.50 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the Passerini adduct (TLC). Then, H_2O (7 mL) and ethyl acetate (10 mL) were added and the aqueous layer was extracted with AcOEt (3 x 5mL). The organic layer was washed with H_2O (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and, the solvent was removed under reduced pressure. The corresponding compound was precipitated with cool hexanes and collected by filtration. **Method G**. To a solution of the appropriate azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (5 mL), 4-pentynoic acid (1.05 mmol) and the appropriate isocyanide (1.10 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the azetidine-2,3-dione **1** (TLC). Then, dichloromethane was evaporated under reduced pressure, and anhydrous DMF (10 mL), $CuSO_4{\cdot}5H_2O$ (0.15 mmol), sodium ascorbate (0.30 mmol) and the corresponding tris-azide (0.33 mmol), were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the Passerini adduct (TLC). Then, the mixture was worked-up as indicated above (Method F). **Method H**. To a solution of the appropriate azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (5 mL), 2-azido benzoic acid (1.05 mmol) and benzyl isocyanide (1.10 mmol) were sequentially added, at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the azetidine-2,3-dione (TLC). Then, dichloromethane was evaporated at reduced pressure, and anhydrous DMF (10 mL), $CuSO_4{\cdot}5H_2O$ (0.15 mmol), sodium ascorbate (0.30 mmol) and the corresponding tris-alkyne (0.33 mmol), were added at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the Passerini adduct (TLC). Then, the mixture was worked-up as indicated above (Method F).

β-Lactam-Triazole Hybrid (–)-6a. **Method A**. From 39 mg (0.08 mmol) of Passerini adduct (+)-**2d**, 27 mg (50%) of compound (–)-**6a** was obtained as a white solid after purification by flash chromatography (hexanes/ethyl acetate, 2:1). **Method B**. From 65 mg (0.22 mmol) of azetidine-2,3-dione (+)-**1a**, 125 mg (80%) of pure compound (–)-**6a** was obtained. Mp.: 75–77 °C; $[\alpha]_D = -6.4$ (*c* 0.5, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.97-7.94 (m, 4H), 7.57 (m, 2H), 7.36-7.25 (m, 6H), 6.88

(m, 2H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.52 (dd, *J* = 14.9, 6.1 Hz, 1H), 4.40 (dd, *J* = 14.8, 5.6 Hz, 1H), 4.33 (q, *J* = 6.7 Hz, 1H), 4.08 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.86 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.80 (s, 3H), 3.07 (t, *J* = 6.6 Hz, 2H), 2.88-2.81 (m, 2H), 2.43 (s, 3H), 1.44 and 1.30 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 170.2, 164.3, 159.6, 157.2, 147.3, 145.1, 137.4, 132.9, 130.4, 130.1, 128.7, 128.6, 127.6, 127.4, 121.2, 120.8, 114.1, 110.2, 86.6, 75.1, 66.6, 64.1, 55.4, 43.8, 32.6, 26.4, 25.0, 21.8, 20.4; IR (KBr, cm^{-1}) υ 3327, 1743, 1661; HRMS (ESI) for $C_{35}H_{38}N_5O_9S^+$ $(M+H)^+$ calcd 704.2385, found 704.2393.

β-Lactam-Triazole Hybrid (+)-6b. **Method B**. From 50 mg (0.17 mmol) of azetidine-2,3-dione (+)-**1a**, 97 mg (85%) of compound (+)-**6b** was obtained as a white solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp.: 154–155 °C; $[\alpha]_D$ = + 25.0 (*c* 0.2, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.00 (s, 1H), 7.99 (m, 2H), 7.63 (m, 2H), 7.37 (m, 2H), 6.90 (m, 2H), 6.19 (bs, 1H), 4.53 (d, *J* = 7.8 Hz, 1H), 4.31 (q, *J* = 6.9 Hz, 1H), 4.11 (dd, *J* = 9.0, 6.9 Hz, 1H), 3.95 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.81 (s, 3H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.87 (t, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 1.48 (s, 3H), 1.34 (s, 9H), 1.31 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 170.0, 163.4, 160.1, 157.1, 147.2, 145.2, 133.1, 130.4, 130.2, 128.7, 121.3, 120.4, 114.0, 110.2, 86.3, 75.4, 66.6, 64.4, 55.4, 52.3, 32.6, 28.4, 26.4, 24.9, 21.8, 20.3; IR (KBr, cm^{-1}) υ 3366, 1761, 1683; HRMS (ESI) for $C_{32}H_{40}N_5O_9S^+$ $(M+H)^+$ calcd 670.2541, found: 670.2564.

β-Lactam-Triazole Hybrid (+)-6c. **Method B**. From 39 mg (0.13 mmol) of azetidine-2,3-dione (+)-**1a**, 78 mg (91%) of compound (+)-**6c** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:2). $[\alpha]_D$ = + 11.7 (*c* 1.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 7.92 (t, *J* = 5.7 Hz, 1H), 7.58 (m, 2H), 7.36-7.21 (m, 11H), 6.87 (m, 2H), 5.40 (s, 2H), 4.75 (d, *J* = 7.2 Hz, 1H), 4.57 (dd, *J* = 15.0, 6.1 Hz, 1H), 4.47 (dd, *J* = 15.0, 5.8 Hz, 1H), 4.34 (q, *J* = 6.9 Hz, 1H), 4.06 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.83 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.80 (s, 3H), 3.06-3.04 (m, 2H), 2.86-2.85 (m, 2H), 1.44 and 1.32 (s, each 3H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 110 ºC) δ 171.7, 166.1, 161.3, 159.0, 147.1, 139.4, 136.1, 132.0, 130.6, 130.2, 130.1, 129.5, 129.0, 128.8, 122.8, 122.6, 116.0, 111.7, 88.6, 78.8, 68.2, 66.3, 57.2, 55.7, 45.4, 34.9, 28.0, 26.7, 22.4; IR ($CHCl_3$, cm^{-1}) υ 3234, 1767, 1674; HRMS (ESI) for $C_{35}H_{37}N_5NaO_7^+$ $(M+Na)^+$ calcd 662.2585, found 662.2588.

β-Lactam-Triazole Hybrid (+)-6d. **Method C**. From 49 mg (0.17 mmol) of azetidine-2,3-dione (+)-**1a**, 88 mg (74%) of compound (+)-**6d** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D$ = + 12.4 (*c* 1.6, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 9.16 (bs, 1H), 7.79 (m, 2H), 7.50 (m, 2H), 7.41-7.38 (m, 3H), 7.31-7.28 (m, 3H), 7.20 (m, 2H), 6.88 (m, 2H), 5.50 (s, 2H), 4.77 (AB, 2H), 4.49 (d, *J* = 6.9 Hz, 1H), 4.32-4.26 (m, 1H), 4.01 (dd, *J* = 8.5, 6.7 Hz, 1H), 3.81 (s, 3H), 3.71 (dd, *J* = 8.6, 6.8 Hz, 1H), 3.09 (bs, 2H), 2.84 (bs, 2H), 2.28 (s, 3H), 1.44 and 1.31 (s, each 3H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 110 ºC) δ 171.8, 166.5, 160.0, 158.7, 146.8, 146.7, 135.7, 135.6, 131.6, 131.3, 130.8, 130.7, 130.5, 129.8, 122.9, 122.3, 115.7, 111.8, 88.4, 79.0, 68.0, 65.4, 62.3, 57.2, 55.9, 34.9, 28.0, 26.6, 23.2, 22.2; IR ($CHCl_3$, cm^{-1}) υ 3193, 1770, 1692; HRMS (ESI) for $C_{36}H_{40}N_5O_9S^+$ $(M+H)^+$ calcd 718.2541, found 718.2560.

β-Lactam-Triazole Hybrid (+)-7. **Method D**. From 54 mg (0.19 mmol) of azetidine-2,3-dione (+)-**1a**, 94 mg (75%) of compound (+)-**7** was obtained as a white solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp.: 125–127 °C; $[\alpha]_D$ = + 37.4 (*c* 0.2, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ 8.14 (s, 1H), 8.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87-7.84 (m, 2H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.65-7.60 (m, 2H), 7.46 (m, 2H), 7.43-7.19 (m, 8H), 6.97 (t, *J* = 5.8 Hz, 1H), 6.82 (m, 2H), 6.78 (d, *J* = 6.4 Hz, 1H), 4.60 (dd, *J* = 15.1, 5.8 Hz, 1H), 4.52 (dd, *J* = 15.0, 6.1 Hz, 1H), 4.18 (q, *J* = 6.7 Hz, 1H), 4.01 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.83 (dd, *J* = 8.9, 6.9 Hz, 1H), 3.79 (s, 3H), 1.40 and 1.29 (s, each 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ 163.9, 163.8, 159.0, 157.2, 148.6, 137.3, 135.7, 133.6, 131.4, 129.9, 129.8, 129.7, 128.8, 128.6, 128.5, 127.6, 127.4, 126.0, 125.8, 125.6, 120.92, 120.87, 114.0, 110.2, 87.2, 74.7, 66.6, 63.9, 55.4, 43.9, 26.3, 25.0; IR (KBr, cm^{-1}) υ 3359, 1766, 1680; HRMS (ESI) for $C_{38}H_{35}N_5NaO_7^+$ $(M+Na)^+$ calcd 696.2429, found 696.2432.

***C_2* Symmetric β-Lactam-Triazole Hybrid (+)-8a**. **Method E**. From 54 mg (0.19 mmol) of azetidine-2,3-dione (+)-**1a**, 97 mg (87%) of compound (+)-**8a** was obtained as a white solid after precipitation with cool hexanes. Mp.: 114–116 °C; $[\alpha]_D$ = + 18.9 (*c* 0.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 120 °C) δ 7.57 (m, 4H), 7.45-7.42 (m, 2H), 7.33-7.21 (m, 16H), 6.89 (m, 4H), 5.38 (s, 4H), 4.66 (d, *J* = 7.3 Hz, 2H), 4.52 (dd, *J* = 15.0, 6.0 Hz, 2H), 4.44 (dd, *J* = 15.1, 5.8 Hz, 2H), 4.35 (q, *J* = 6.9 Hz, 2H), 4.05 (dd, *J* = 8.8, 6.7 Hz, 2H), 3.84 (dd, *J* = 8.8, 6.7 Hz, 2H), 3.80 (s, 6H), 3.05 (t, *J* = 6.6 Hz, 4H), 2.86-2.82 (m, 4H), 1.45 and 1.33 (s, each 6H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 120 °C) δ 171.6, 166.0, 161.4, 159.2, 147.3, 139.3, 136.8, 132.1, 130.1, 130.0, 129.0, 128.8, 123.0, 122.7, 116.1, 111.6, 88.6, 76.9, 68.3, 66.5, 57.2, 55.1, 45.4, 34.9, 27.9, 26.7, 22.4; IR (KBr, cm^{-1}) υ 3246, 1765, 1675; HRMS (ESI) for $C_{64}H_{69}N_{10}O_{14}^+$ $(M+H)^+$ calcd 1201.4989, found 1201.4971.

***C_2* Symmetric β-Lactam-Triazole Hybrid (+)-8b**. **Method E**. From 60 mg (0.21 mmol) of azetidine-2,3-dione (+)-**1a**, 91 mg (74%) of compound (+)-**8b** was obtained as a white solid after precipitation in cooled hexanes. Mp.: 127–129 °C; $[\alpha]_D$ = + 4.5 (*c* 0.6, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 120 °C) δ 7.56 (m, 4H), 7.42 (t, *J* = 5.5 Hz, 2H), 7.37-7.24 (m, 16H), 6.88 (m, 4H), 5.47 (s, 4H), 4.66 (d, *J* = 7.1 Hz, 2H), 4.50 (dd, *J* = 15.0, 5.8 Hz, 2H), 4.42 (dd, *J* = 14.9, 5.4 Hz, 2H), 4.36 (q, *J* = 6.5 Hz, 2H), 4.06 (t, *J* = 7.8 Hz, 2H), 3.84 (t, *J* = 7.7 Hz, 2H), 3.80 (s, 6H), 3.05 (t, *J* = 6.4 Hz, 4H), 2.84 (t, *J* = 6.2 Hz, 4H), 1.44 and 1.33 (s, each 6H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 120 °C) δ 171.6, 166.0, 161.3, 159.1, 143.2, 139.3, 134.6, 132.1, 132.0, 131.3, 130.0, 128.9, 128.8, 123.2, 122.6, 116.0, 111.7, 88.6, 76.8, 68.2, 66.4, 57.2, 52.8, 45.4, 34.8, 28.0, 26.7, 22.4; IR (KBr, cm^{-1}) υ 3336, 1765, 1676; HRMS (ESI) for $C_{64}H_{69}N_{10}O_{14}^+$ $(M+H)^+$ calcd 1201.4989, found 1201.4993.

***C_2* Symmetric β-Lactam-Triazole Hybrid (–)-9a**. **Method F**. From 51 mg (0.17 mmol) of azetidine-2,3-dione (+)-**1a**, 84 mg (71%) of compound (**–**)-**9a** was obtained as a white solid after precipitation with cool hexanes. Mp.: 130–132 °C; $[\alpha]_D$ = – 3.5 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 120

°C) δ 7.97 (d, J = 7.6 Hz, 2H), 7.85 (s, 2H), 7.71 (t, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5Hz, 2H), 7.51 (m, 4H), 7.35-7.327 (m, 16H), 6.87 (m, 4H), 6.74 (bs, 2H), 4.77 (d, J = 6.6 Hz, 2H), 4.74, 4.64 (s, each 4H), 4.54-4.52 (m, 4H), 4.26 (q, J = 6.4 Hz, 2H), 3.98 (t, J = 7.6 Hz, 2H), 3.83-3.79 (m, 2H), 3.79 (s, 6H), 1.40 and 1.29 (s, each 6H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 120 °C) δ 165.3, 164.9, 160.7, 159.2, 147.9, 139.2, 139.1, 137.5, 135.0, 132.8, 131.8, 131.3, 130.1, 129.4, 129.0, 128.9, 127.6, 127.5, 125.5, 122.9, 116.0, 111.7, 89.2, 76.3, 74.0, 68.2, 65.8, 65.3, 57.2, 45.5, 27.9, 26.7; IR (KBr, cm^{-1}) υ 3365, 1766, 1680; HRMS (ESI) for $C_{74}H_{73}N_{10}O_{16}$ (M+H)$^+$ calcd 1357.5201, found 1357.5211.

***C*₂ Symmetric β-Lactam-Triazole Hybrid (+)-9b**. **Method F**. From 52 mg (0.18 mmol) of azetidine-2,3-dione (+)-**1a**, 88 mg (72%) of compound (+)-**9b** was obtained as a white solid after precipitation with cool hexanes. Mp.: 147–149 °C; $[\alpha]_D$ = + 10.5 (c 0.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 120 °C) δ 7.95 (dd, J = 7.8, 1.2 Hz, 2H), 7.86 (s, 2H), 7.68 (td, J = 7.7, 1.5 Hz, 2H), 7.57 (t, J = 7.7 Hz, 2H), 7.50 (m, 4H), 7.50-7.41 (m, 2H), 7.30-7.20 (m, 14H), 6.86 (m, 4H), 6.77 (t, J = 5.5 Hz, 2H), 4.77 (d, J = 6.6 Hz, 2H), 4.76, 4.73 (s, each 4H), 4.51 (d, J = 5.8 Hz, 4H), 4.26 (q, J = 6.5 Hz, 2H), 3.98 (dd, J = 8.6, 6.7 Hz, 2H), 3.82-3.77 (m, 2H), 3.79 (s, 6H), 1.39 and 1.28 (s, each 6H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 120 °C) δ 165.3, 164.9, 160.8, 159.2, 147.8, 139.1, 138.0, 137.4, 135.0, 132.7, 131.8, 131.2, 130.6, 130.1, 129.4, 129.0, 128.8, 127.7, 127.4, 125.6, 122.9, 116.0, 111.7, 89.2, 76.3, 71.8, 68.2, 65.8, 65.3, 57.2, 45.5, 27.9, 26.7; IR (KBr, cm^{-1}) υ 3354, 1766, 1681; HRMS (ESI) for $C_{74}H_{73}N_{10}O_{16}^+$ (M+H)$^+$ calcd 1357.5201, found 1357.5210.

***C*₃ Symmetric β-Lactam-Triazole Hybrid (–)-10a**. **Method G**. From 66 mg (0.27 mmol) of azetidine-2,3-dione (+)-**1a**, 99 mg (75%) of compound (–)-**10a** was obtained as a white solid after precipitation with cool hexanes. Mp.: 132–134 °C; $[\alpha]_D$ = – 6.2 (c 0.5, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 130 °C) δ 7.54 (m, 6H), 7.29-7.21 (m, 21H), 7.02 (s, 3H), 6.87 (m, 6H), 5.35 (s, 6H), 4.68 (d, J = 7.4 Hz, 3H), 4.50 (dd, J = 15.0, 6.1 Hz, 3H), 4.42 (dd, J = 14.8, 5.6 Hz, 3H), 4.37 (q, J = 6.9 Hz, 3H), 4.07 (dd, *J* = 8.8, 6.7 Hz, 3H), 3.84 (dd, *J* = 8.9, 6.7 Hz, 3H), 3.79 (s, 9H), 3.04 (t, *J* = 6.6 Hz, 6H), 2.85 (t, *J* = 6.6 Hz, 6H), 1.44 and 1.33 (s, each 9H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 130 °C) *δ* 171.6, 166.0, 161.5, 159.3, 147.3, 139.4, 138.6, 132.1, 130.0, 129.0, 128.8, 128.7, 123.2, 122.7, 116.1, 111.7, 88.6, 76.9, 68.3, 66.6, 57.2, 54.8, 45.4, 34.9, 27.9, 26.7, 22.4; IR (KBr, cm^{-1}) *υ* 3247, 1766, 1674; HRMS (ESI) for $C_{93}H_{101}N_{15}O_{21}{}^{+2}$ (M+2H)$^{+2}$ calcd 881.8643, found 881.8636; Anal. Calcd for $C_{93}H_{99}N_{15}O_{21}$: C, 63.36; H 5.66; N 11.92. Found: C 63.08; H 5.45; N 12.03.

***C*₃**

***C$_3$* Symmetric β-Lactam-Triazole Hybrid (–)-10b**. **Method G**. From 55 mg (0.20 mmol) of azetidine-2,3-dione (–)-**1c**, 84 mg (73%) of compound (–)-**10b** was obtained as a white solid after precipitation with cool hexanes. Mp.: 114–116 °C; $[\alpha]_D$ = – 61.2 (*c* 0.3, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 120 °C) *δ* 7.28-7.21 (m, 36H), 7.02 (bs, 3H), 5.34 (bs, 6H), 4.76 (d, *J* = 15.0 Hz,3H), 4.46-4.40 (m, 6H), 4.32 (d, *J* = 15.2 Hz, 3H), 4.27-4.03 (m, 6H), 3.95 (dd, *J* = 8.6, 6.4 Hz, 3H), 3.68 (dd, *J* = 8.7, 6.4 Hz, 3H), 3.02 (m, 6H), 2.80 (t, *J* = 6.3 Hz, 6H), 1.33 and 1.31 (s, each 9H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 120 °C) *δ* 171.8, 166.1, 163.9, 147.4, 139.4, 138.5, 136.6, 130.1, 130.0, 129.8, 129.2, 128.9, 128.8, 123.2, 111.5, 89.1, 76.8, 68.2, 64.3, 54.7, 47.6, 45.2, 34.7, 28.0, 26.6, 22.4; IR (KBr, cm^{-1}) *υ* 3245, 1774, 1672; HRMS (ESI) for $C_{93}H_{100}N_{15}O_{18}{}^{+}$ (M+H)$^+$ calcd 1714.7365, found 1714.7377.

***C$_3$* Symmetric β-Lactam-Triazole Hybrid (+)-10c**. **Method G**. From 54 mg (0.19 mmol) of azetidine-2,3-dione (+)-**1a**, 51 mg (50%) of compound (+)-**10c** was obtained as a white solid after precipitation with cool hexanes. Mp.: 130–132 °C; $[\alpha]_D$ = + 26.5 (*c* 0.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 120 °C) *δ* 7.57 (m, 6H), 7.34, 7.10 (s, each 3H), 6.88 (m, 6H), 6.21 (bs, 3H), 5.42 (s, 6H), 4.54 (d, *J* = 7.7 Hz, 3H), 4.34 (q, *J* = 7.0 Hz, 3H), 4.07 (dd, *J* = 8.6, 6.7 Hz, 3H), 3.87 (dd, *J* = 8.7, 6.6 Hz, 3H), 3.80 (s, 9H), 3.06 (t, *J* = 6.6 Hz, 6H), 2.87 (t, *J* = 6.8 Hz, 6H), 1.46 (s, 9H), 1.35 (s, 27H), 1.33 (s, 9H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 120 °C) *δ* 171.6, 164.8, 161.9, 159.0, 147.3, 138.6, 132.1, 128.8, 123.2, 122.4, 116.0, 111.7, 88.5, 77.0, 68.3, 66.6, 57.2, 54.8, 53.7, 34.8, 30.1, 28.0, 26.7, 22.5; IR (KBr, cm^{-1}) υ 3347, 1762, 1680; HRMS (ESI) for $C_{84}H_{107}N_{15}O_{21}^{+2}$ $(M+2H)^{+2}$ calcd 830.8877, found 830.8890.

***C*₃ Symmetric β-Lactam-Triazole Hybrid (+)-11**. **Method H**. From 83 mg (0.28 mmol) of azetidine-2,3-dione (+)-**1a**, 155 mg (84%) of compound (+)-**11** was obtained as a white solid after precipitation with cool hexanes. Mp.: 166–168 °C; $[\alpha]_D$ = + 43.2 (*c* 0.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$, 120 °C) δ 8.04 (s, 3H), 7.97 (dd, *J* = 7.5, 1.5 Hz, 3H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 3H), 7.58 (td, *J* = 7.7, 1.1 Hz, 3H), 7.49 (m, 6H), 7.50-7.40 (m, 3H), 7.34-7.19 (m, 15H), 6.86 (m, 6H), 6.74 (t, *J* = 5.7 Hz, 3H), 5.67 (s, 6H), 4.78 (d, *J* = 6.3 Hz, 3H), 4.52 (d, *J* = 5.6 Hz, 6H), 4.26 (q, *J* = 6.5 Hz, 3H), 3.98 (dd, *J* = 8.7, 6.6 Hz, 3H), 3.83-3.79 (m, 3H), 3.77 (s, 9H), 1.38 and 1.27 (s, each 9H); ^{13}C-NMR (75 MHz, $C_2D_2Cl_4$, 120 °C) δ 174.6, 165.2, 164.8, 160.8, 159.2, 144.9, 139.1, 137.3, 135.1, 132.8, 131.7, 131.4, 130.1, 129.0, 128.9, 127.9, 127.4, 126.7, 122.9, 116.1, 111.7, 89.2, 76.3, 68.2, 65.7, 62.9, 57.2, 45.5, 27.8, 26.7; IR (KBr, cm^{-1}) υ 3351, 1766, 1681; HRMS (ESI) for $C_{102}H_{98}N_{18}O_{24}^{+2}$ $(M+2H)^{+2}$ calcd 979.3495, found 979.3500.

ACKNOWLEDGMENTS

We would like to thank MICINN (Project CTQ2009-09318), Comunidad Autónoma de Madrid (CAM) (Project S2009/PPQ-1752) and UCM-Santander (Grant GR35/10-A) for financial support. R. C. thanks the MEC for a predoctoral grant.

Supporting Information

X-ray crystallographic data for (+)-**6b** (CIF). Crystal structure of (+)-**6b** and copies of NMR spectra (^{1}H, ^{13}C) for compounds **2–11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) X-ray data of (+)-**6b**: crystallized from hexanes/CH_2Cl_2 at 20 ºC; $C_{32}H_{39}N_5O_9S$ (Mr = 669.74); orthorhombic; space group = P2(1)2(1)281); a =9.3080 (7), b = 12.2700(9), c = 31.682 (2) Å; α = 90, β

= 90, γ = 90; V = 3618.3 (5) $Å^3$; Z = 4; ρ_{calcd} = 1.229 mg m^{-3}; μ = 0.145 mm^{-1}; F(000) = 1416. A transparent crystal of dimensions 0.40 x 0.10 x 0.08 mm^3 was used; 7105 [R(int) = 0.0781] independent reflections were collected. Data were collected [Mo Kα radiation (λ = 0.71073 Å)] over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s and 30 s covered 0.3 in γ. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). The nonhydrogen atoms were refined anisotropically. The hydrogen atoms were refined only in terms of their coordinates. CCDC-873490 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.cam.ac.uk/data_request/cif.