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ARTICLE TYPE

Investigation of the Passerini and Ugi Reactions in β-Lactam Aldehydes. Synthetic Applications

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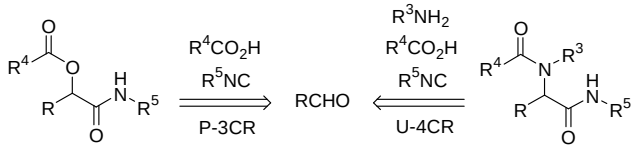
Passerini (P-3CR) and Ugi (U-4CR) reactions were investigated in 4-oxoazetidine-2-carboxaldehydes affording the corresponding Passerini and Ugi adducts with moderate diastereoselectivity in high yields. Fortunately, the obtained mixtures of isomers *syn/anti* were separated in most cases. The scope of both IMCRs has been studied using a variety of isocyanides, carboxylic acids and amines. Ugi adducts were used for the preparation of unusual 2-azetidinones fused to medium-sized rings via RCM. In addition, β-lactam-diketopiperazine hybrids have also been prepared from the corresponding Ugi adducts.

Introduction

Isocyanides are very useful reagents in synthetic chemistry, due to their versatile reactivity.[1] In fact, isocyanides can react with electrophiles, nucleophiles, and radicals under different reaction conditions to afford primary imine adducts. However, the chemistry of isocyanides is most well known by their use in multicomponent reactions; isocyanide multicomponent reactions (IMCR).[2] In particular, Passerini (P-3CR) and Ugi (U-4CR) reactions are the most celebrated IMCRs (Scheme 1). Besides, both methodologies have been successfully applied to the synthesis of potentially active and interesting molecules.[3] In connection with our ongoing project aimed at the asymmetric synthesis of nitrogen containing compounds,[4] and the study of multicomponent reaction processes,[5] we became interested in the study of the P-3CR and U-4CR in 4-oxoazetidine-2-carboxaldehydes, very useful bifunctional substrates for the preparation of a variety of substances of biological interest.[6]



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

Results and Discussion

Passerini Reaction of 4-Oxoazetidine-2-carboxaldehydes

In a previous report we described the Passerini reaction of azetidine-2,3-diones using different carboxylic acids and isocyanides.[5a] It was found that the nucleophilic addition proceed with complete diastereoselectivity and high yields under mild reaction conditions. Thus, we were particularly interested in evaluating the same process in β-lactam aldehydes. 4-Oxoazetidine-2-carboxaldehydes required for our study were easily prepared using standard methodology, as single *cis*-enantiomers from imines of (*R*)-2,3-O-isopropylideneglyceraldehyde, through Staudinger reaction with the corresponding alkoxy(aryloxy)acetyl chloride in the presence of Et_3N, followed by sequential acidic hydrolysis and oxidative cleavage.[6]

To explore the reactivity of compounds **1**, we selected aldehyde **1a** as a model substrate. Passerini reaction of aldehyde **1a**, benzyl isocyanide and benzoic acid was studied using methanol, acetonitrile or dichloromethane as solvents at room temperature. In the event, we observed that when the reaction is performed in methanol, only conversion of 40% was observed (Table 1, entry 1). However, the use of acetonitrile and dichloromethane revealed full conversion and compound **2a** was afforded in good yield (75 and 77% respectively), as a mixture of *syn/anti* isomers (62:38 and 60:40, respectively) (Table 1, entries 2 and 3). Fortunately, both isomers were separated by flash chromatography. Taking into account that the reaction rate in acetonitrile was slower than with dichloromethane, we decided to explore the scope of the reaction with other β-lactam aldehydes **1** in dichloromethane as solvent.

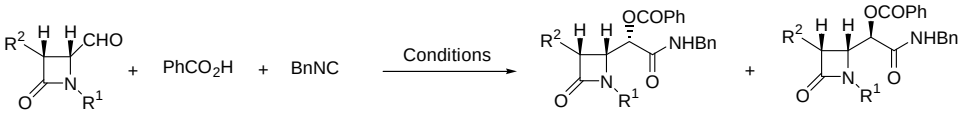
In order to investigate the diastereoselectivity issues involved in the process, we decided to carry on our investigations using different substituted β-lactam aldehydes **1**. In fact, when the reaction was performed using aldehyde (+)-**1b**, with a phenoxy group in C3-position, the diastereoselectivity slightly increased in compound **2b** (65:35 d.r., 88% yield) (Table 1, entry 4). Treatment of aldehyde **1c**, with an aliphatic substituent at the nitrogen, in the above reaction conditions, afforded Passerini-adduct **2c** in moderate yield (65%) with a slightly increased of the diastereoselectivity value (72:28) (Table 1, entry 5).[7] Unfortunately, the mixture of isomers was not separated by flash chromatography. When the reaction of aldehyde **1c** was studied at

lower temperature (–20°C and –78°C) the same diastereoselectivity in compound **2c** was detected and an increased reaction time was also observed (Table 1, entries 6 and 7).

Then, we decided to study the scope of the P-3CR. Reaction of aldehyde (+)-**1a** with acetic acid and BnNC gave the corresponding adducts **2d** in very good yield (84%) and poor diastereoselectivity (60:40) (Table 2, entry 1). Analogous results were obtained when the reaction was studied with aldehyde (+)-**1a**, using acetic acid and *t*-BuNC, affording adduct **2e** in 88% yield and poor diastereoselectivity (60:40), (Table 2, entry 2). When the reaction was tested using aldehyde (–)-**1d**, 2-iodo benzoic acid and *t*-BuNC, P-3CR adduct **2f** was isolated in 61% yield and moderate diastereoselectivity (73:27) (Table 2, entry 3). However, compound **2f** was isolated as an inseparable mixture of isomers. When we studied the P-3CR with aldehyde (–)-**1d**, phthalimidoacetic acid and ethyl isocyanoacetate we obtained better results. Thus, compound **2g** was obtained in 72% yield and moderate diastereoselectivity (77:23). Fortunately, both isomers were isolated by flash chromatography. Besides, P-3CR adduct **2g** is an interesting example due the presence of a depsipeptide structure. On the other hand, TosMIC and *p*-methoxyphenyl isocyanide ranked into the least reactive isocyanides tested. In fact, when the Passerini reaction was studied using TosMIC, longer reaction rate (100 h) was observed and moderate diastereoselectivy (68:32) was obtained in P-3CR adduct **2h** (Table 2, entry 5). We thought that the reaction could proceed with rate enhancement by heating in a sealed tube at 80°C. Indeed, we found that the thermal process proceeded faster than the reaction at room temperature. In addition, poor diastereoselectivity (63:37) was also obtained in 20h (Table 2, entry 6). Finally, the use of *p*-methoxyphenyl isocyanide gave P-3CR adduct **2i** in 37% conversion after 100h at room temperature (Table 2, entry 7).

Thus, to summarize, the diastereoselectivity is independent on the carboxylic acid and isocyanide studied, and it must be controlled by the substituent at N1 and C3 positions of the β-lactam aldehyde **1**. In fact, the best diastereoselectivity values were obtained for aldehyde **1** with an aliphatic substituent (2-propynyl) at N1 position and a bulky substituent (phenoxy group) at C3 position (Table 1, entries 5–7).

Table 1 Optimization of the Passerini reaction of aldehydes **1** with benzoic acid and benzyl isocyanide[a]

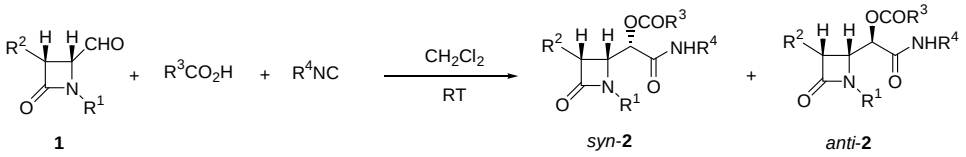


1 *syn*-**2** *anti*-**2**

Entry	Aldehyde	R^1	R^2	Conditions	t(h)[b]	Conv (%)[c]	Product	*syn/anti*[d]	Yield (%)[e]
1	(+)-**1a**	PMP[f]	MeO	MeOH/RT	144	40	**2a**	57:43	–[g]
2	(+)-**1a**	PMP[f]	MeO	MeCN/RT	25	100	**2a**	62:38	46:29
3	(+)-**1a**	PMP[f]	MeO	CH_2Cl_2/RT	3	100	**2a**	60:40	46:31
4	(+)-**1b**	PMP[f]	PhO	CH_2Cl_2/RT	4.5	100	**2b**	65:35	56:32
5	(+)-**1c**	2-propynyl	PhO	CH_2Cl_2/RT	4	100	**2c**	72:28	65[h]
6	(+)-**1c**	2-propynyl	PhO	CH_2Cl_2/–20°C	6.5	100	**2c**	72:28	63[h]
7	(+)-**1c**	2-propynyl	PhO	CH_2Cl_2/–78°C	24	100	**2c**	72:28	51[h]

[a]All reactions were performed by using an aldehyde/isocyanide/carboxylic acid ratio of 1.0:1.1:1.05 mmol. [b]Reaction progress was followed by TLC. [c]The conversion was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz). [d]The *syn/anti* ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [e]Yield of pure, isolated isomers with correct analytical and spectral data. [f]PMP = 4-MeOC_6H_4. [g]The crude reaction mixture was not purified. [h]Yield of pure, isolated mixture of isomers.

Table 2. Scope of the Passerini reaction of aldehydes **1** with a variety of carboxylic acids and isocyanides[a]

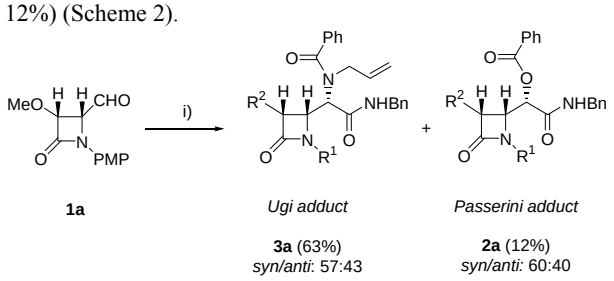


Entry	Aldehyde	R^1	R^2	R^3	R^4	t(h)[b]	Conv (%)[c]	Product	*syn/anti*[d]	Yield (%)[e]
1	(+)-**1a**	PMP[f]	MeO	Me	Bn	1	100	**2d**	60:40	51:33
2	(+)-**1a**	PMP[f]	MeO	Me	*t*-Bu	2	100	**2e**	60:40	53:35
3	(–)-**1d**	2-propenyl	PhO	2-IC_6H_4	*t*-Bu	4	100	**2f**	73:27	61[h]
4	(–)-**1d**	2-propenyl	PhO	CH_2Phth[g]	CH_2CO_2Et	4	100	**2g**	77:23	55:17
5	(+)-**1a**	PMP[f]	MeO	Me	CH_2Ts	100	100	**2h**	68:32	58:28
6[i]	(+)-**1a**	PMP[f]	MeO	Me	CH_2Ts	20	100	**2h**	63:37	56:33
7	(+)-**1a**	PMP[f]	MeO	Me	PMP	100	37	**2i**	57:43	–[j]

[a]All reactions were performed by using an aldehyde/isocyanide/carboxylic acid ratio of 1.0:1.1:1.05 mmol. [b]Reaction progress was followed by TLC. [c]The conversion was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz). [d]The *syn/anti* ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [e]Yield of pure, isolated isomers with correct analytical and spectral data. [f]PMP = 4-$MeOC_6H_4$. [g]Phth = Phtalimido. [h]Yield of pure, isolated mixture of isomers. [i]The reaction was carried out at 80°C in a sealed tube. [j]The crude reaction mixture was not purified.

Ugi Reaction of 4-Oxoazetidine-2-carboxaldehydes

Our next objective was to test the Ugi reaction in β-lactam aldehyde (+)-**1a**, allylamine, benzoic acid and benzyl isocyanide in dichloromethane at room temperature. In the event, we observed the formation of the expected Ugi product **3a** in poor diastereoselectivity and good yield (*syn/anti*: 57:43, 63%) and Passerini adduct **2a** as a by-product (*syn/anti*: 60:40, 12%) (Scheme 2).



Scheme 2 Ugi reaction of aldehyde **1a**. Conditions: (i) allylamine, $PhCO_2H$, BnNC, CH_2Cl_2, rt, 6h.

Although the Ugi reaction consists on the "one-pot" reaction of four components, we were interested in obtaining selectively the corresponding Ugi adduct. Thus, we decided to study the reaction in two steps: 1) formation of the imine; 2) addition of the carboxylic acid and the isocyanide, the three component Ugi reaction (U-3CR). We sought to explore the Ugi reaction on imino-β-lactams derived from allylamine and *p*-anisidine as representative examples of aliphatic and aromatic amines, respectively.[8]

Reaction of allylimine derived from aldehyde (+)-**1a** with benzoic acid and benzyl isocyanide gave adduct **3a** in good yield (78%) and moderate diastereoselectivity (65:35) (Table 3, entry 1A). However, the existence of rotamers for both isomers *syn*-(+)-**3a** and *anti*-(+)-**3a** complicated ^{1}H NMR analysis at room temperature. Thus, we decided to study the reaction of compound (+)-**1a** with a less hindered carboxylic acid, such as formic acid. In the event, we obtained the expected formamides **3b** in moderate yield (69%) and diastereoselectivity (Table 3, entry 2A). Once again, analysis of ^{1}H NMR of compound **3b** showed the presence of rotamers at 25°C. When the U-3CR was studied with imino-β-lactam derived aldehyde (+)-**1a**, acetic acid, and benzyl isocyanide, acetamide **3c** was isolated in moderate yield and low diastereoselectivity (54%, 57:43) (Table 3, entry 3A). Analogous results were obtained when acetic acid was replaced by bromoacetic acid and phthalimidoacetic acid affording Ugi adducts **3d** and **3e** in good yield (74% and 91%, respectively) and comparable diastereoselectivity values (Table 3, entries 4A and 5A). Fortunately, U-3CR adducts **3c–e** were analyzed by ^{1}H NMR without conformational problems. On the other hand, reaction of imino-β-lactam derived of aldehyde (+)-**1a**, acetic acid and *t*-BuNC afforded the corresponding Ugi adduct **3f** with similar diastereoselectivity (60:40) and excellent yield (90%), however longer reaction time (22h) was observed (Table 3, entry 6A). Probably, the steric hindrance of the *tert*-butyl group of the isocyanide component may explain this different behavior. Thus, we can confirm that both carboxylic acid and isocyanide components do not affect the diastereoselectivity of the multicomponent process.

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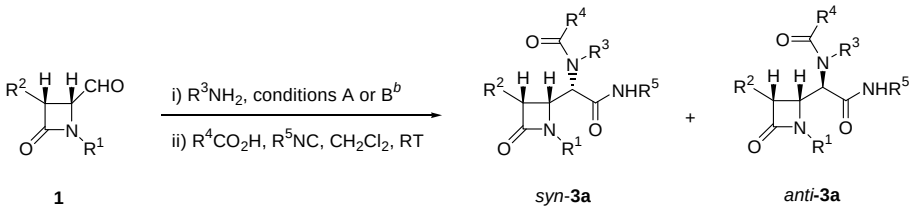
Table 3. Study of the Ugi reaction of aldehydes **1** with a variety of carboxylic acids and isocyanides[a]



Entry[b]	Aldehyde	R[1]	R[2]	R[3]	R[4]	R[5]	t(h)[c]	Product	*syn/anti*	Yield (%)
1A	(+)-**1a**	PMP[d]	MeO	2-propenyl	Ph	Bn	16	**3a**	65:35[e]	50:28[f]
2A	(+)-**1a**	PMP[d]	MeO	2-propenyl	H	Bn	6	**3b**	55:45[g]	38:31[f]
3A	(+)-**1a**	PMP[d]	MeO	2-propenyl	Me	Bn	4	**3c**	57:43[g]	54[h]
4A	(+)-**1a**	PMP[d]	MeO	2-propenyl	CH_2Br	Bn	5	**3d**	60:40[g]	44:30[f]
5A	(+)-**1a**	PMP[d]	MeO	2-propenyl	CH_2Phth	Bn	6	**3e**	57:43[g]	52:39[f]
6A	(+)-**1a**	PMP[d]	MeO	2-propenyl	Me	*t*-Bu	22	**3f**	60:40[g]	54:36[f]
7A	(+)-**1b**	PMP[d]	PhO	2-propenyl	Me	Bn	4	**3g**	65:35[g]	37:20[f]
8A	(+)-**1e**	Bn	MeO	2-propenyl	Me	Bn	4	**3h**	76:24[g]	62[i]
9A	(−)-**1d**	2-propenyl	PhO	2-propenyl	Me	Bn	5	**3i**	77:23[g]	53:16[f]
10A	(−)-**1d**	2-propenyl	PhO	2-propenyl	CH_2Br	Bn	7	**3j**	68:32[e]	58:28[f]
11B	(+)-**1a**	PMP[d]	MeO	PMP[d]	Me	Bn	23	**3k**	60:40[g]	34:23[f]
12B	(−)-**1d**	2-propenyl	PhO	PMP[d]	Me	Bn	21	**3l**	70:30[g]	46:19[f]

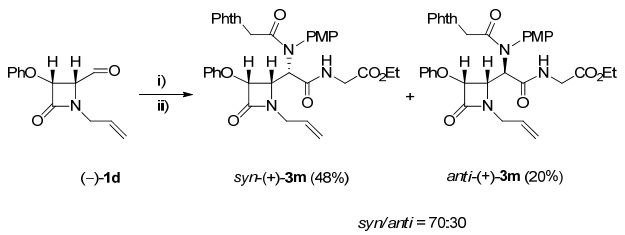
[a]All reactions were performed by using an imine/isocyanide/carboxylic acid ratio of 1.00: 1.1:1.05 mmol. [b]"A" refers to the use of allylamine (Method A described in the Exp. Section for the preparation of adducts **3**) and "B" refers to the use of *p*-anisidine (Method B described in the Exp. Section for the preparation of adducts **3**). [c]Reaction progress was followed by TLC analysis. [d]PMP = 4-$MeOC_6H_4$. [e]The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) after purification. [f]Yield of pure, isolated isomers with correct analytical and spectra data. [g]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. [h]Yield of pure, isolated mixture of isomers. [i]Yield of isomer *syn*-(−)-**3h**. Isomer *anti* was not isolated pure for its characterization.

Our next purpose was to evaluate the influence of the substituents in the β-lactam aldehyde. Reaction of imino-β-lactam derived of aldehyde (+)-**1b**, with a phenoxy group in C3 position, acetic acid and benzyl isocyanide produced the corresponding adduct **3g** in good yield (57%) with a slightly better diastereoselectivity (65:35) (Table 2, entry 7A). To our delight, when we carry out the reaction of imino-β-lactam derived of aldehyde (+)-**1e**, with an aliphatic substituent at the nitrogen position, acetic acid and benzyl isocyanide, compound **3h** was isolated in 62% yield with a better diastereoselectivity (76:24) (Table 3, entry 8A). Similar reasonable diastereoselectivity was obtained for aldehyde (−)-**1d**, using allylamine, benzyl isocyanide and acetic acid, affording U-3CR adducts **3i** in moderate yield (Table 3, entry 9A). Unfortunately, lower diastereoselectivity (68:32) was obtained in adduct **3j** when bromoacetic acid was used as acidic component (Table 3, entry 10A).

When an aromatic amine was used, *p*-anisidine, using aldehydes (+)-**1a** and (−)-**1d**, acetic acid and benzyl isocyanide, U-3CR adducts **3k** and **3l** were obtained in good yields (57% and 65%) and moderate diastereoselectivities (60:40 and 70:30, respectively) (Table 3, entries 11B and 12B). However, in both cases these experiments needed longer reaction times.

Next, we decided to study the reaction of *p*-anisidine imino-β-lactam derived of aldehyde (−)-**1d**, phtalimidoacetic acid and ethyl isocyanoacetate. In the event, we obtained the desired orthogonally protected β-lactam tripeptide **3m** in 70:30

diastereoselectiviy and 68% yield (Scheme 3).



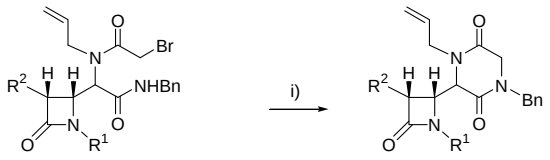
(–)-**1d** *syn*-(+)-**3m** (48%) *anti*-(+)-**3m** (20%)

syn/*anti* = 70:30

Scheme 3. Synthesis of an orthogonally protected β-lactam tripeptide via Ugi reaction. Conditions: (i) $PMPNH_2$, 4Å-molecular sieves, MeCN, reflux, 4h. (ii) $PhthCH_2CO_2H$, $CNCH_2CO_2Et$, CH_2Cl_2, rt, 15h.

Synthetic Applications

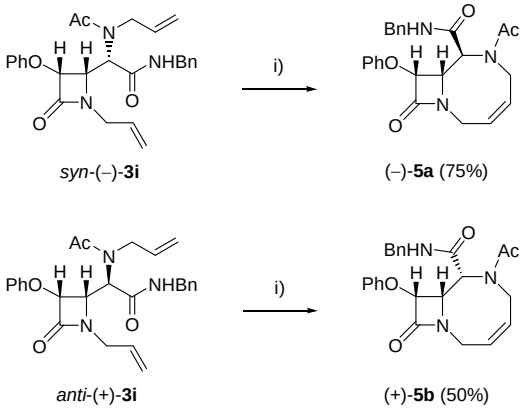
Once we studied both Passerini and Ugi reactions, we decided to perform straightforward synthetic transformations in some of the obtained Ugi adducts. One of the most important applications of Ugi adducts is the aliphatic or acyl nucleophilic substitution reaction.[9] Thus, for our purpose we selected Ugi adducts **3d** and **3j**. Both compounds are ideal substrates to experiment an intramolecular nucleophilic substitution between the nitrogen of the amide group and the carbon at α position to the bromide. In this manner, we could access to β-lactam-diketopiperazine hybrids,[10] in a single and easy operational step. After testing with different bases, we found that the reaction of Ugi adducts *syn*-**3d**, *syn*-**3j** and *anti*-**3j** with sodium hydride in anhydrous THF promoted the nucleophilic substitution at room temperature. Thus, β-lactam-diketopiperazine hybrids *syn*-**4a**, *syn*-**4b** and *anti*-**4b** were isolated in moderate yields (Scheme 4).



syn-(+)-**3d**	R^1 = PMP	R^2 = MeO	*syn*-(+)-**4a** (2h, 42%)
syn-(–)-**3j**	R^1 = 2-propenyl	R^2 = PhO	*syn*-(+)-**4b**(6h, 55%)
anti-(+)-**3j**	R^1 = 2-propenyl	R^2 = PhO	*anti*-(+)-**4b**(6h, 64%)

Scheme 4. Synthesis of β-Lactam-Diketopiperazine Hybrids **4** from Ugi Adducts **3**. Conditions: (i) NaH, THF, rt.

Ring closing metathesis is a very fascinating reaction particularly appropriate for the assembly of medium-sized rings, which is always a demanding task.[11] Then, we selected Ugi adducts **3i** with two propenyl groups to study a ring closing metathesis between both of them. This substrate would be an excellent compound to obtain bicyclic β-lactams fused to an eight-membered ring.[12] Treatment of Ugi adducts *syn*- and *anti*-**3i** with first generation Grubbs' catalyst afforded bicyclic β-lactams **5a** and **5b** in good to moderate yields (75% and 50%, respectively) (Scheme 5).



syn-(–)-**3i** (–)-**5a** (75%)

anti-(+)-**3i** (+)-**5b** (50%)

Scheme 5. Synthesis of bicyclic β-lactams **5** via RCM of Ugi adducts **3**. Conditions: (i) 5 mol% $Cl_2(Cy_3P)_2RuCHPh$, anhydrous toluene, reflux, 8h.

The structure of adducts **2**–**5** has been assigned by NMR studies. In addition, chemical shifts and vicinal coupling constants between H3/H4 and H4/H4' for P-3CR adducts **2** have been gathered in a table (see Table S1 in Supporting Information). From these results, we have observed that the corresponding signal of C4' in isomers *syn*-**2** come at higher chemical shifts in ^{13}C NMR than for isomer *anti*-**2**. In addition, the stereochemistry was confirmed unequivocally by single crystal X-ray analysis of compound *anti*-(+)-**2d**.[13] On the other hand, the NMR data of compounds **3** show that the signal of H4' in isomers *syn*-**3** come at higher chemical shifts in ^1H NMR that isomers *anti*-**3** (see Table S2 in Supporting Information). By contrast, ^{13}C NMR show that the C4' signal come at lower chemical shifts for N-allylamides *syn*-**3c–j**. This behavior is overturned in N-(*p*-methoxyphenyl)amides, probably due to electronic effects. In addition, the coupling constant between H4 and H4' in both *syn/anti* isomers are very similar ($^3J_{H4,\,H4'}$ = 8.6-10.6 Hz) which is in accordance with an antiperiplanar disposition between H4 and H4'. Thus, both isomers are in a monoconformational disposition independently of the configuration of the new stereogenic center. On the other hand, the stereochemistry of adducts **3** has been established by comparation with the NOE results of the bicyclic systems **5** (see NOE experiments in Supporting Information). Besides, the stereochemistry of the four-membered ring is set during the cyclization step to form the bicyclic system.

The observed *syn*-diastereoselectivity for P-3CR and U-4CR adducts might be explained by the Felkin-Anh model.[6]

Conclusions

In conclusion, we have presented a detailed study of the Passerini and Ugi reactions in β-lactam aldehydes. The scope of both reactions have been achieved by using a representative family of 4-oxoazetidine-2-carboxaldehydes and a variety of amines, carboxylic acids and isocyanides, affording P-3CR and U-4CR adducts in reasonable diastereoselectivities and good yields. It has been observed that the diastereoselectivity can be modulated by the adequate functionalization of the β-lactam aldehyde. Interestingly, selected Ugi adducts showed to be

valuable starting materials for the synthesis of β-lactam-diketopiperazine hybrids and bicyclic β-lactams.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer in $CDCl_3$ except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). Low and high resolution mass spectra were performed on a AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) 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 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 phosphomolybdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL EtOH) was used to develop the plates.

General Procedure for the P-3CR of aldehydes 1. Synthesis of Compounds 2.

Method A. The corresponding carboxylic acid (1.05 mmol) and the appropriate isocyanide (1.1 mmol) were sequentially added to a well stirred solution of aldehyde **1** (1 mmol) in anhydrous dichloromethane (5 mL) at room temperature under argon atmosphere. After disappearance of the starting material (TLC), the mixture was diluted with dichloromethane (10 mL) and, then a saturated aqueous solution of sodium hydrogen carbonate (5 mL) was added. The aqueous phase was extracted with dichloromethane (3 x 5 mL). The organic extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate mixtures. **Method B**. Acetic acid (1.05 mmol) and TosMIC (1.1. mmol) were sequentially added to a well stirred solution of aldehyde (+)-**1a** (1 mmol) in anhydrous dichloromethane (5 mL) at room temperature under argon atmosphere. The reaction mixture was heated at 80°C in a sealed tube until complete disappearances of the starting material (TLC). The mixture was allowed to warm to room temperature and was worked up as indicated above (Method A).

Passerini adduct 2a. **Method A.** From 45 mg (0.19 mmol) of aldehyde (+)-**1a**, compound **2a** was obtained as a mixture of isomers in a *syn/anti* ratio (60:40). After flash chromatography using *n*-hexane/ethyl acetate (2:1) as eluent, the less polar compound *syn*-(+)-**2a** (42 mg, 46%) and the more polar compound *anti*-(+)-**2a** (28 mg, 31%) were obtained. ***syn*-(+)-2a**. White solid; mp 89–91°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +108.4 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.93-7.90 (m, 2H), 7.57 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.44 (AA'*XX'*, 2H), 7.44-7.40 (m, 2H), 7.25-7.23 (m, 3H), 7.05-7.02 (m, 2H), 6.80 (*AA'*XX', 2H), 6.42 (t, *J* = 5.6 Hz, 1H), 5.80 (d, *J* = 3.2 Hz, 1H), 5.15 (dd, *J* = 5.2, 3.1 Hz, 1H), 4.72 (d, *J* = 5.3 Hz, 1H), 4.42 (dd, *J* = 14.9, 6.0 Hz, 1H), 4.26 (dd, *J* = 14.9, 5.7 Hz, 1H), 3.75 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 168.2, 165.3, 164.6, 156.8, 136.9, 133.7, 130.2, 130.0, 128.8, 128.6, 128.5, 127.6, 127.5, 119.8, 114.3, 82.7, 70.4, 59.6, 57.7, 55.4, 43.4; IR (KBr, cm^{-1}) ν 3347, 1744, 1669; HRMS (ESI) calcd for $C_{27}H_{27}N_2O_6^+$ $[M+H]^+$: 475.1864; found: 475.1858. ***anti*-(+)-2a**. White solid; mp 152–154°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +139.6 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 8.03-8.00 (m, 2H), 7.60 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 2H), 7.31 (AA'*XX'*, 2H), 7.32-7.21 (m, 5H), 6.81 (*AA'*XX', 2H), 6.66 (t, *J* = 5.6 Hz, 1H), 6.10 (d, *J* = 3.4 Hz, 1H), 4.97 (dd, *J* = 5.2, 3.4 Hz, 1H), 4.74 (d, *J* = 5.3 Hz, 1H), 4.54 (dd, *J* = 14.9, 6.3 Hz, 1H), 4.33 (dd, *J* = 14.8, 5.5 Hz, 1H), 3.75 (s, 3H), 3.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 167.2, 165.0, 164.5, 156.7, 137.4, 133.8, 130.0, 129.8, 128.6, 128.5, 127.7, 127.6, 118.8, 114.4, 83.3, 69.1, 60.1, 58.2, 55.4, 43.4; IR (KBr, cm^{-1}) ν 3336, 1750, 1667; HRMS (ESI) calcd for $C_{27}H_{27}N_2O_6^+$ $[M+H]^+$: 475.1864; found: 475.1857.

General Procedure for the U-4CR of aldehydes 1. Synthesis of Compounds 3. Method A. 1) Preparation of imino-β-lactams. A solution of allylamine (2 mmol) in anhydrous dichloromethane (1 mL) was added to a well stirred suspension of the corresponding aldehyde **1** (1 mmol) and anhydrous $MgSO_4$ (1.7 g) in anhydrous dichloromethane (5 mL) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for 15h. Then, $MgSO_4$ was filtered off over a short path of celite and the solvent was removed under reduced pressure. Imino-β-lactams were obtained in nearly quantitative yields and were used without further purification. **2) Ugi Reaction**. The corresponding carboxylic acid (1.05 mmol) and the appropriate isocyanide (1.1 mmol) were sequentially added to a well stirred solution of the obtained imine in anhydrous dichloromethane (5 mL) at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the reaction mixture was diluted with dichloromethane (10 mL) and a saturated aqueous sodium hydrogen carbonate (5 mL) was added. The aqueous phase was extracted with dichloromethane (3 x 5 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate mixtures. **Method B. 1) Preparation of imino-β-lactams**. A solution of *p*-anisidine (1 mmol) in anhydrous acetonitrile (1.6 mL) was added to a well stirred suspension of the corresponding aldehyde **1** (1 mmol) and 4Å-molecular sieves (1 g) in anhydrous acetonitrile (6 mL) at room temperature under argon atmosphere. The reaction mixture was stirred at reflux temperature for 4h. The mixture was allowed to warm to room temperature. Then, molecular sieves were filtered off and the solvent was removed under reduced pressure. Imino-β-lactams were obtained in nearly quantitative yields and were used without further purification. **2) Ugi Reaction**. Acetic acid (1.05 mmol) and benzyl isocyanide (1.1 mmol) were sequentially added to a well stirred solution of the obtained imine in anhydrous dichloromethane (5 mL) at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the reaction mixture was worked

up as indicated above (Method A).

Ugi adduct 3i. **Method A.** From 68 mg (0.30 mmol) of aldehyde (–)-**1d**, compound **3i** was obtained as a mixture of isomers in a *syn/anti* ratio (77:23). After flash chromatography using *n*-hexane/ethyl acetate (1:1) as eluent, the less polar compound *anti*-(+)-**3i** (21 mg, 16%) and the more polar compound *syn*-(−)-**3i** (71 mg, 53%) were obtained. ***syn*-(−)-3i**. Colorless oil; $[\alpha]_D$ −38.9 (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.28-7.22 (m, 5H), 7.18-7.15 (m, 2H), 7.03-6.95 (m, 3H), 6.50 (t, *J* = 5.6 Hz, 1H), 5.81-5.57 (m, 2H), 5.53 (d, *J* = 10.0 Hz, 1H), 5.38 (d, *J* = 4.9 Hz, 1H), 5.26-5.13 (m, 4H), 4.69 (dd, *J* = 10.0, 5.1 Hz, 1H), 4.29 (dd, *J* = 14.6, 6.1 Hz, 1H), 4.19 (dd, *J* = 14.7, 5.6 Hz, 1H), 4.15-4.06 (m, 2H), 3.94 (dd, *J* = 17.1, 6.8 Hz, 1H), 3.60 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 172.5, 168.1, 166.2, 157.5, 137.4, 132.8, 131.9, 129.3, 128.6, 128.0, 127.4, 122.4, 117.9, 116.2, 81.4, 56.2, 55.1, 48.4, 43.7, 43.3, 22.1; IR ($CHCl_3$, cm^{-1}) ν 3314, 1759, 1644; HRMS (ESI) calcd for $C_{26}H_{30}N_3O_4^+$ $[M+H]^+$: 448.2231; found: 448.2252; ***anti*-(+)-3i**. Colorless oil; $[\alpha]_D$ +50.7 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.35-7.23 (m, 7H), 7.13 (t, *J* = 6.0 Hz, 1H), 7.05-6.95 (m, 3H), 5.83-5.54 (m, 2H), 5.28 (d, *J* = 4.7 Hz, 1H), 5.32-5.13 (m, 4H), 5.09 (d, *J* = 10.4 Hz, 1H), 4.68 (dd, *J* = 10.1, 4.7 Hz, 1H), 4.39 (dd, *J* = 14.8, 6.0 Hz, 1H), 4.34 (dd, *J* = 14.8, 5.9 Hz, 1H), 4.05-3.81 (m, 3H), 3.61 (dd, *J* = 15.6, 6.1 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 172.4, 169.3, 166.0, 157.2, 137.6, 133.1, 131.6, 129.6, 128.7, 127.7, 127.6, 122.2, 118.3, 117.5, 115.2, 80.5, 58.1, 55.6, 49.3, 43.8, 43.5, 21.5; IR ($CHCl_3$, cm^{-1}) ν 3338, 1761, 1654; HRMS (ESI) calcd for $C_{26}H_{30}N_3O_4^+$ $[M+H]^+$: 448.2231; found: 448.2225.

General Procedure for the synthesis of β-lactam-diketopiperazine hybrids 4. Sodium hydride (1.1 mmol) was added in small portions to a well stirred solution of Ugi adduct **3** (1 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature until complete disappearances of the starting material (TLC). Then, water (5 mL) was added and THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (4 x 10 mL). The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate mixtures.

β-Lactam-diketopiperazine hybrid *syn*-(+)-4a. From 53 mg (0.10 mmol) of Ugi adduct *syn*-(+)-**3d**, and after flash chromatography of the residue using *n*-hexane/ethyl acetate (1:1) as eluent, compound *syn*-(+)-**4a** (19 mg, 42%) was obtained as a colorless oil; $[\alpha]_D$ +129.8 (c 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.39 (AA'*XX'*, 2H), 7.36-7.25 (m, 5H), 6.95 (*AA*'XX', 2H), 5.54-5.42 (m, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.92 (dd, *J* = 5.6, 2.8 Hz, 1H), 4.91 (d, *J* = 14.2 Hz, 1H), 4.76 (d, *J* = 2.6 Hz, 1H), 4.64 (d, *J* = 5.6 Hz, 1H), 4.64-4.58 (m, 1H), 4.46 (d, *J* = 17.2 Hz, 1H), 4.24 (d, *J* = 14.3 Hz, 1H), 3.86 (d, *J* = 17.1 Hz, 1H), 3.82 (s, 3H), 3.75 (d, *J* = 17.0 Hz, 1H), 3.34 (s, 3H), 3.21 (dd, *J* = 15.4, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 164.5, 164.1, 163.3, 157.0, 134.8, 131.1, 129.8, 128.8, 128.6, 128.2, 118.8, 118.5, 114.9, 82.8, 59.9, 59.3, 55.8, 55.5, 50.0, 49.7, 47.5; IR ($CHCl_3$, cm^{-1}) ν 1753, 1662; HRMS (ESI) calcd for $C_{25}H_{28}N_3O_5^+$ $[M+H]^+$: 450.2024; found: 450.2044.

β-Lactam-diketopiperazine hybrid *syn*-(+)-4b. From 51 mg (0.10 mmol) of Ugi adduct *syn*-(−)-**3j**, and after flash chromatography of the residue using *n*-hexane/ethyl acetate (1:2) as eluent, compound *syn*-(+)-**4b** (24 mg, 55%) was obtained as a colorless oil; $[\alpha]_D$ +64.6 (c 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.30-7.23 (m, 7H), 7.08-7.00 (m, 3H), 5.85-5.70 (m, 2H), 5.22 (d, *J* = 4.5 Hz, 1H), 5.30-5.21 (m, 4H), 4.80 (d, *J* = 14.3 Hz, 1H), 4.59 (d, *J* = 4.5 Hz, 1H), 4.62-4.55 (m, 1H), 4.44-4.37 (m, 1H), 4.36 (t, *J* = 4.7 Hz, 1H), 4.35 (d, *J* = 14.5 Hz, 1H), 3.93 (d, *J* = 17.6 Hz, 1H), 3.81 (d, *J* = 17.6 Hz, 1H), 3.74-3.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 165.3, 163.9, 163.1, 157.2, 134.5, 131.2, 130.7, 129.7, 128.8, 128.6, 128.1, 123.2, 120.3, 119.5, 116.7, 81.8, 56.7, 56.0, 49.5, 49.4, 47.4, 43.8; IR ($CHCl_3$, cm^{-1}) ν 1762, 1664; HRMS (ESI) calcd for $C_{26}H_{28}N_3O_4^+$ $[M+H]^+$: 446.2074; found: 446.2063.

β-Lactam-diketopiperazine hybrid *anti*-(+)-4b. From 35 mg (0.07 mmol) of Ugi adduct *anti*-(+)-**3j**, and after flash chromatography using *n*-hexane/ethyl acetate (1:1) as eluent, compound *anti*-(+)-**4b** (19 mg, 64%) was obtained as a colorless oil; $[\alpha]_D$ +95.7 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.34-7.23 (m, 7H), 7.09-7.03 (m, 3H), 5.83-5.64 (m, 2H), 5.33 (d, *J* = 5.1 Hz, 1H), 5.27-5.10 (m, 4H), 4.79 (d, *J* = 14.3 Hz, 1H), 4.65 (d, *J* = 5.7 Hz, 1H), 4.67-4.60 (m, 1H), 4.33 (t, *J* = 5.3 Hz, 1H), 4.35-4.27 (m, 1H), 4.17 (d, *J* = 14.5 Hz, 1H), 3.98 (d, *J* = 17.4 Hz, 1H), 3.85 (d, *J* = 17.4 Hz, 1H), 3.73 (dd, *J* = 15.8, 6.6 Hz, 1H), 3.45 (dd, *J* = 15.5, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 165.3, 164.5, 163.8, 156.9, 134.6, 131.7, 130.5, 129.8, 129.0, 128.6, 128.4, 123.0, 120.0, 118.0, 115.9, 81.0, 59.2, 57.7, 49.9, 49.4, 47.6, 43.6; IR ($CHCl_3$, cm^{-1}) ν 1755, 1692; HRMS (ESI) calcd for $C_{26}H_{28}N_3O_4^+$ $[M+H]^+$: 446.2074; found: 446.2095.

General Procedure for the synthesis of bicyclic β-lactams 5 via RCM. $Cl_2(Cy_3P)_2Ru$=CHPh (0.05 mmol) was added in small portions to a well stirred solution (protected from the sunlight) of Ugi adduct **3** (1 mmol) in anhydrous toluene (30 mL) at room temperature under argon atmosphere. The resulting mixture was heated at reflux temperature for 8h. Then, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate mixtures.

Bicyclic β-Lactam 5a. From 46 mg (0.10 mmol) of Ugi adduct *syn*-(−)-**3i**, and after flash chromatography using *n*-hexane/ethyl acetate (1:4) as eluent, compound (−)-**5a** (32 mg, 75%) was obtained as a colorless oil; $[\alpha]_D$ −117.2 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.28-7.23 (m, 5H), 7.12-7.09 (m, 2H), 7.01 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.96-6.93 (m, 2H), 6.66 (bs, 1H), 5.88-5.74 (m, 2H), 5.58 (d, *J* = 10.6 Hz, 1H), 5.27 (d, *J* = 4.7 Hz, 1H), 4.66 (dd, *J* = 10.6, 4.7 Hz, 1H),

4.44-4.36 (m, 1H), 4.35 (dd, J = 14.6, 6.5 Hz, 1H), 4.25-4.09 (m, 2H), 4.18 (dd, J = 14.6, 5.2 Hz, 1H), 3.78 (d, J = 16.5 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 171.9, 167.7, 164.2, 157.3, 137.5, 130.9, 129.4, 128.6, 127.7, 127.5, 122.5, 121.2, 115.9, 79.7, 55.6, 53.9, 46.5, 43.2, 36.1, 21.5; IR ($CHCl_3$, cm^{-1}) ν 3330, 1756, 1652; HRMS (ESI) calcd for $C_{24}H_{24}N_3O_4^-$ $[M-H]^-$: 418.1772; found: 418.1775.

Bicyclic β-Lactam 5b. From 49 mg (0.11 mmol) of Ugi adduct *anti*-(+)-**3i**, and after flash chromatography using *n*-hexane/ethyl acetate (1:4) as eluent, compound (+)-**5b** (23 mg, 50%) was obtained as a colorless oil; $[\alpha]_D$ +110.7 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.27-7.21 (m, 7H), 7.01 (t, J = 7.4 Hz, 1H), 6.92-6.89 (m, 2H), 6.46 (t, J = 5.1 Hz, 1H), 6.20 (td, J = 10.2, 6.5 Hz, 1H), 5.97 (dt, J = 9.8, 8.0 Hz, 1H), 5.50 (s, 1H), 5.16 (d, J = 5.3 Hz, 1H), 4.67 (dd, J = 15.8, 10.4 Hz, 1H), 4.54 (dd, J = 14.7, 6.4 Hz, 1H), 4.26 (dd, J = 14.8, 5.3 Hz, 1H), 4.22 (d, J = 7.6 Hz, 2H), 4.04 (dd, J = 5.1, 1.5 Hz, 1H), 3.53 (dd, J = 15.6, 6.3 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 170.6, 167.1, 163.8, 157.0, 137.7, 131.7, 129.6, 128.6, 127.9, 127.4, 126.9, 122.6, 115.7, 78.6, 58.9, 52.7, 43.4, 41.6, 37.1, 21.4; IR ($CHCl_3$, cm^{-1}) ν 3311, 1756, 1675, 1634; HRMS (ESI) calcd for $C_{24}H_{26}N_3O_4^+$ $[M+H]^+$: 420.1918; found: 420.1931.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Compound characterization data for compounds **2b–h**, **3a–h** and **3j–m**, NOE experiments for compounds **5**, copies of the NMR spectra of all new compounds, representative chemical shifts and vicinal coupling constants of ^{1}H and ^{13}C NMR of compounds **2** and **3** (Tables S1 and S2, respectively), X-Ray data for compound *anti*-(+)-**2d**. See DOI: 10.1039/b000000x/

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