Graphical Abstract

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Stereoselective cyanation of 4-formyl and 4-imino-β-lactams: Application to the synthesis of polyfunctionalized γ-lactams

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ABSTRACT

The stereoselective reaction of 4-oxoazetidine-2-carbaldehydes and their corresponding imines with cyanide-based reagents give β-lactam α-aminonitriles, which are chameleonic building blocks for the controlled synthesis of a variety of new compounds including functionalized γ-lactams, succinimide derivatives and diamino-lactams derivatives in optically pure form .

1. Introduction

Functionalized γ-lactams are emerging as a substructure present in natural and synthetic products possessing important bioactivities.[1] In particular, succinimide[2] and pyroglutamic acid[3] cores have considerable chemical and medicinal importance as they are involved in a wide range of relevant processes. On the other hand, the inherent strain and their convenient accessibility make β-lactams an attractive substrate class. In addition of the key role that β-lactams have played in medicinal chemistry, namely, the fight against pathogenic bacteria, enzyme inhibition, in vitro antitumor cytotoxicity, or gene activation,[4] the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established.[5] Besides, α-amino nitriles are versatile synthetic intermediates for the synthesis of a variety of interesting compounds.[6] Both the amino and nitrile groups can be further transformed into a variety of useful functional units. In light of the synthetic utility of both types of compounds, the stereoselective preparation of optically pure β-lactam α-amino nitriles arise as an important endeavour. These polyfunctional hybrid molecules may undergo highly selective reduction and rearrangement reactions making them as potential versatile precursors to functionalized azacycles. In our continued commitment to prepare β-lactams and heterocycles of biological interest,[7] herein we report details of the controlled reactions between 2-azetidinone-derived imines and cyanide-based reagents as a versatile synthetic tool for the preparation of functionalized γ-lactams and succinimide derivatives.

2. Results and discussion

Taking into account our recent report on the cyanosilylation of 4-oxoazetidine-2-carbaldehydes,[8] we decided to explore the cyanation of imino-β-lactams. Imines **1** were prepared by treatment of the appropriate enantiopure β-lactam aldehyde with amines in the presence of molecular sieves (4 Å) in refluxing benzene.[9] Imino-β-lactams **1** were obtained in nearly quantitative yields and were used without further purification. First, the reaction of imines **1a-d** derived from alkyl amines with *tert*-butyldimethylsilyl cyanide (TBDMSiCN) was selected (Table 1). The optimized conditions for the cyanosilylation of β-lactam aldehydes[8] (1.2 equiv. of TBDMSiCN, 25 mol% Na_2CO_3, acetonitrile, RT) were initially adopted. However, prolonged reaction times were needed for a good conversion. Replacement of 25 mol% Na_2CO_3 by 10 mol% tetrabutylammonium cyanide (TBACN), both accelerated the reaction and allowed better isolated yields. α-Aminonitriles **2a–d** were obtained as a mixture of two chromatographically separable diastereomers (*syn*/*anti*, epimers at C4') in reasonable yields (50–85%). The reaction of TBDMSiCN with imines **1e** and **1f** derived from an aryl amine

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afforded the corresponding α-aminonitriles **2e** and **2f**,[10] but as unseparable *syn*/*anti*-mixture (Table 1).

It should be noted that the ^{1}H NMR vicinal coupling constants of the H4 and H4'protons for the *syn*-**2** and *anti*-**2** α-aminonitrile-β-lactams is a useful check of the relative stereochemistry (see supplementary data). For any pair of *syn*-**2** and *anti*-**2** α diastereomers, the vicinal coupling constant between H4 and H4' is higher for *syn*-isomers ($^3J_{H4,H4'}$ = 9.7–4.6 Hz) than for *anti*-isomers ($^3J_{H4,H4'}$ = 8.5–3.4 Hz). The observed *syn*-diastereoselectivity for compounds **2** might be tentatively explained by invoking the Felkin-Anh model, analogously to related addition processes described in our laboratories.[8]

A likely catalytic cycle for the TBACN-catalyzed generation of functionalized β-lactams **2** is outlined in Scheme 1. Initial activation of TBDMSiCN by TBACN gave a pentacoordinate silicon species **3**. Salt **3**, after coordination to the imine **1** affords complex **4**, which suffers an intramolecular cyanide transfer giving rise to α-aminonitriles **2** with concurrent regeneration of the catalyst.

Table 1. Reaction of imino-β-lactams **1** with TBSCN.[a]

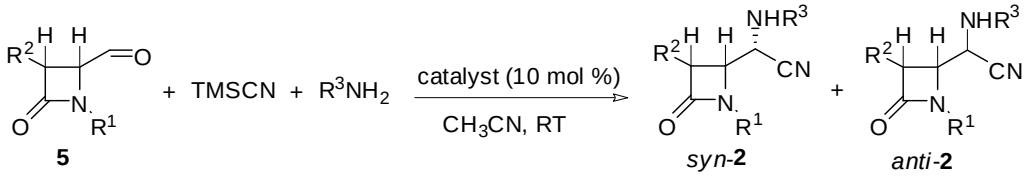
Imine	R^1	R^2	R^3	Catalyst	t (h)	Prod.	*syn*/*anti*[b]	Yield (%)[c]
(+)-**1a**	PMP	MeO	allyl	Na_2CO_3	65	**2a**	78:22[d]	60
(+)-**1a**	PMP	MeO	allyl	TBACN	4.5	**2a**	80:20[d]	68
(+)-**1b**	PMP	MeO	Bn	Na_2CO_3	68	**2b**	74:26	73
(+)-**1b**	PMP	MeO	Bn	TBACN	4.5	**2b**	74:26	85
(+)-**1c**	PMP	MeO	propargyl	Na_2CO_3	97	**2c**	68:32	40[e]
(+)-**1c**	PMP	MeO	propargyl	TBACN	24	**2c**	78:22	50
(+)-**1d**	PMP	MeO	*t*-Bu	TBACN	3.7	**2d**	55:45	85
(+)-**1e**	PMP	MeO	PMP	TBACN	5	**2e**[f]	-----[g]	68
(+)-**1f**	Bn	MeO	PMP	Na_2CO_3	52	**2f**[f]	-----[g]	64
(+)-**1f**	Bn	MeO	PMP	TBACN	3.8	**2f**[f]	-----[g]	65

[a] All reactions were catalyzed by 25 mol% Na_2CO_3 or 10 mol% TBACN and were carried out using an imine/TBDMSiCN ratio of 1/1.2 mmol. [b] The *syn*/*anti* ratio could not be determined by integration in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification, due to the absence of well-resolved signals. The ratio was given in pure product after separation by gravity flow chromatography on deactivated silica gel. [c] Yield of isolated products with correct analytical and spectral data. [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] 30% of the 4-oxoazetidine-2-carbaldehyde precursor was also recovered, arising from the hydrolysis of the starting imine. [f] α-Aminonitriles **2e** and **2f** were obtained as unseparable *syn*/*anti*-mixtures. [g] The *syn*/*anti* ratio could not be determined. PMP = 4-$MeOC_6H_4$.

Scheme 1. Plausible explanation for the reaction of imino-β-lactams **1** with TBDMSiCN/Bu_4NCN.

The conversion of multi-step reactions into more environmentally friendly one-pot processes is convenient in synthetic chemistry. Thus, the direct aminocyanation of β-lactam aldehydes **5** was attempted. The effect of different promoters (I_2, $BiCl_3$, H_3NSO_3, and $InCl_3$) on the aminocyanation of a model substrate, 4-oxoazetidine-2-carbaldehyde **5a**, in the presence of allylamine with trimethylsilyl cyanide (TMSCN) was investigated. Every single Lewis acid was able to catalyze the one-pot formation of α-aminonitrile **2a** (Table 2). These results show that under standard reaction conditions, I_2 provided the best yield and diastereoselectivity. On the basis of the above results, we chose to use I_2 in our study. With the optimal conditions in hand, the scope and limitation of the one-pot reaction was tested with various combinations of aldehydes and amines (Table 2). α-Aminonitriles **2** were obtained as separable diasteromeric mixtures, being the *syn*/*anti* ratio slightly superior to the observed one using TBDMSiCN/TBACN in the sequential process. When aromatic amines were used, both sulphamic acid and molecular iodine catalyzed reactions gave the corresponding imines **1** in quantitative yields instead of the expected α-aminonitrile **2e-f**, which were not observed in any case. On the contrary, $BiCl_3$ was the catalyst of choice for the one-pot reaction with aromatic amines achieving fair yields with a reasonable rate of reaction (Table 2).

Table 2. Direct aminocyanation of β-lactam aldehydes.[a]



Aldehyde	R^1	R^2	R^3	Catalyst	t (h)	Prod.	*syn*/*anti*[b]	Yield (%)[c]
(+)-**5a**	PMP	MeO	allyl	I_2	1.0	**2a**	85:15	79
(+)-**5a**	PMP	MeO	allyl	$BiCl_3$	4.0	**2a**	85:15	72
(+)-**5a**	PMP	MeO	allyl	H_3NSO_3	2.0	**2a**	85:15	73
(+)-**5a**	PMP	MeO	allyl	$InCl_3$	2.5	**2a**	74:26	70
(+)-**5a**	PMP	MeO	Bn	I_2	1.7	**2b**	87:13[d]	87
(+)-**5a**	PMP	MeO	propargyl	I_2	22	**2c**	79:21[d]	66
(+)-**5a**	PMP	MeO	*t*-Bu	I_2	4.5	**2d**	79:21	49
(+)-**5b**	PMP	PhO	allyl	I_2	2.7	**2g**	90:10[d]	71
(+)-**5c**	PMP	BnO	allyl	I_2	1.0	**2h**	84:16	75
(±)-**5d**	*o*-BrC_6H_4	MeO	Bn	I_2	0.7	**2i**	58:42[d]	75

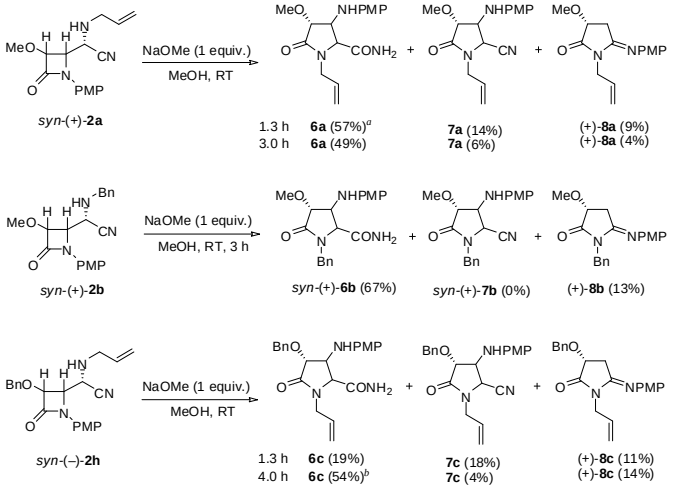
(+)-**5e**	allyl	MeO	propargyl	I_2	4.5	**2j**[e]	66:34	70
(+)-**5f**	3-butynyl	MeO	allyl	I_2	0.8	**2k**	70:30	58
(+)-**5g**	CH_2=$CBrCH_2$	MeO	Bn	I_2	1.2	**2l**[e]	66:34	50
(+)-**5a**	PMP	MeO	PMP	I_2	1	[f]		
(+)-**5a**	PMP	MeO	PMP	H_3NSO_3	4	[f]		
(+)-**5a**	PMP	MeO	PMP	$BiCl_3$	24	**2e**[e]	76:24	67
(+)-**5h**	Bn	MeO	PMP	I_2	1	[g]	-----	
(+)-**5h**	Bn	MeO	PMP	$BiCl_3$	23	**2f**[e]	63:37	66
(+)-**5a**	PMP	MeO	CH_2=$CBrCH_2$	I_2	5[f]	**2m**[h]	71:29	53

[a] All reactions were carried out using an aldehyde/TMSCN ratio of 1/1.5 mmol and an aldehyde/amine ratio of 1/1 mmol. [b] 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. [c] Yield of isolated products with correct analytical and spectral data. [d] The *syn*/*anti* ratio could not be determined by integration in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification, due to the absence of well-resolved signals. The ratio was given in pure product after separation by gravity flow chromatography on deactivated silica gel. [e] α-Aminonitriles **2e**, **2f**, **2j** and **2l** were obtained as unseparable *syn*/*anti*-mixtures. [f] Imine **1e** was obtained in quantitative yield. α-Aminonitrile was not formed at longer reaction times. [g] Imine **1f** was obtained in quantitative yield. α-Aminonitrile was not formed at longer reaction times. [h] Imine **1g** must be isolated first, and then treated with TMSCN and I_2. PMP = 4-$MeOC_6H_4$.

Demands for the efficient generation of functionalized and diverse druglike small molecules continue to stimulate the development of versatile synthetic strategies. By inspecting the possible reactivity of α-aminonitriles **2**, we realized that their rearrangement reactions should provide a stereoselective pathway to polyfunctionalized masked pyroglutamic acids (Scheme 2).[11]

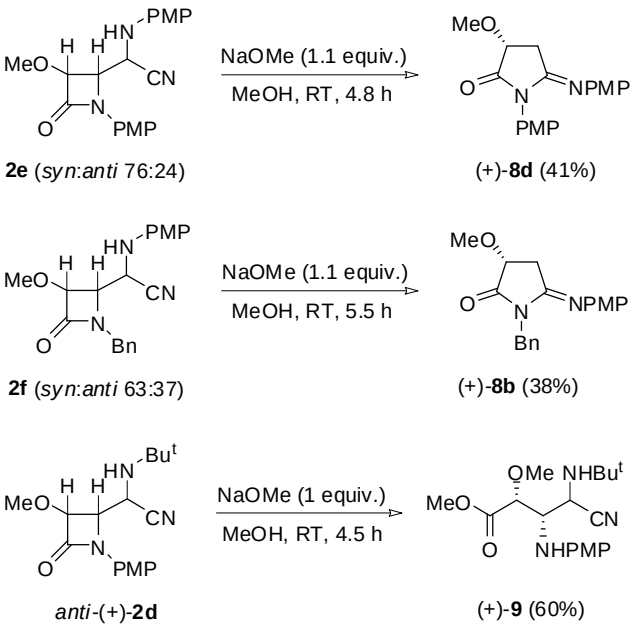
Scheme 2. Possible selective N1–C2 β-lactam ring cleavage/cyclization of 2-azetidinone aminonitrile hybrids.

To successfully achieve our aim, we needed to find an expedient transformation of the β-lactam aminonitrile hybrids into γ-lactam systems. First, sodium methoxide was tested as reagent for the conversion of adducts **2** into the framework of pyroglutamic acids. In the event, the γ-lactam skeleton was obtained from adducts **2a**, **2b**, and **2h**, affording 3,4-disubstituted pyroglutamides **6a–c** as major products (Scheme 3). Amides **6** are formed as consequence of the solvolysis of cyano group in the expected cyanides **7**, probably due to the water present in methanol. 3-Amino-4-alkoxy-5-oxopyrrolidine-2-carbonitriles **7** could be also isolated from aminonitriles **2a** and **2h**. While pyroglutamide **6b** was obtained in enantiopure form, partial epimerization at C5 was observed for related **6a** and **6c**. Surprisingly, in addition of the rearranged adducts **6** and **7**, 5-(arylimino)pyrrolidin-2-ones **8** were obtained as side-products.

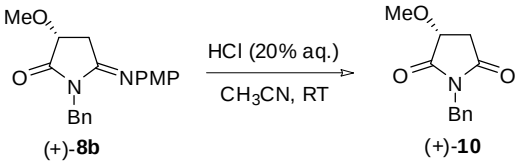


Scheme 3. Sodium methoxide promoted transformation of β-lactam aminonitriles into functionalized pyroglutamides. [a] The *syn*/*anti* ratio for compound **6a** could not be determined by ^{1}H NMR. [b] A 74:26 *syn*/*anti* ratio for compound **6c** was determined by ^{1}H NMR.

When α-(arylamino)nitriles **2e** and **2f** were used as starting materials, 5-(arylimino)pyrrolidin-2-ones **8** were formed as sole products in moderate yields (Scheme 4).[12] By contrast, α-(*t*-butylamino)nitrile **2d** exclusively afforded the acyclic γ-cyano-β-amino ester **9**, which arises from the N1–C2 bond breakage of the β-lactam nucleus. Probably, the steric hindrance of the *tert*-butyl group may explain this different behaviour. Chemical correlation between imino derivative **8b** and its corresponding succinimide **10** was achieved by hydrolysis of the former with 20% aqueous HCl in acetonitrile (Scheme 5).[9]



Scheme 4. Sodium methoxide promoted transformation of β-lactam aminonitriles into imino-γ-lactam and β-amino ester adducts.



Scheme 5. Hydrolysis of 5-(arylimino)pyrrolidin-2-one **8b** into succinimide **10**.

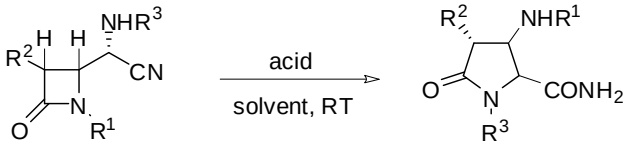
Two competitive processes must be operating for the sodium methoxide promoted transformation of β-lactam aminonitriles **2**, depending on the nature of the R^3 substituent (Scheme 6). When R^3 is aliphatic the rearrangement is the preferred pathway (path A) *via* N1–C2 β-lactam cleavage, being favored the formation of

pyroglutamic acid derivatives **6** and **7**. By contrast, when R^3 is aromatic the above rearrangement is supressed giving rise instead to the 5-(arylimino)pyrrolidin-2-ones **8**, which must be explained invoking a N1–C4 β-lactam cleavage followed by cyclization (path B). In this case, sodium methoxide should act as a base by deprotonating the aminonitrile **2** to give carbanion **11**, which must evolve to enamine species **12** through N1–C4 bond breakage of the β-lactam nucleus. Species **12** isomerizes to the more stable imidoyl cyanide through a desmotropic equilibrium[13] and suffers a final cyclization to the 1-(*p*-anisyl)substituted 5-(imino)pyrrolidin-2-one **8**, which experiments a further isomerization to 1-(alkyl)substituted 5-(imino)pyrrolidin-2-one **8** when R^1 is aromatic. This isomerization should occur due to the attack of the lactam carbonyl group by a nucleophile (methoxide or cyanide), followed by ring-opening and ring-closing of the amidine species **14** through the more basic nitrogen atom.

Scheme 6. Mechanistic explanation for the sodium methoxide promoted transformation of β-lactam aminonitriles **2**.

In order to improve the formation of pyroglutamic acid derivatives **6** and **7** from β-lactam aminonitriles **2**, acidic conditions were explored (Table 3). We performed an initial experiment in which aminonitrile **2h** was treated with 35 mol% aqueous HCl, and we observed the formation of a complex mixture. Happily, when the reactions of aminonitriles **2a**, **2b**, and **2h**, were conducted in a saturated solution of HCl(g) in methanol at room temperature, it gave rise to optically pure pyroglutamides **6a–c** in moderate yields.

Table 3. Acid promoted transformation of β-lactam aminonitriles **2** into functionalized pyroglutamides **6**.

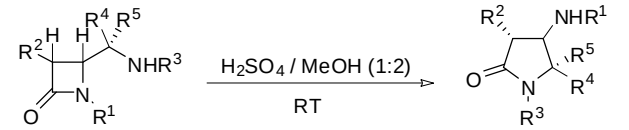


syn-**2** *syn*-**6**

Aminonitrile	R^1	R^2	R^3	Acid/Solvent	t (h)	Product	Yield (%)[a]
syn-(–)-**2h**	PMP	BnO	allyl	HCl conc./MeOH (1:40)	8[b]	----[c]	---
syn-(+)-**2a**	PMP	MeO	allyl	HCl (g)/MeOH	6	*syn*-(+)-**6a**	36
syn-(+)-**2b**	PMP	MeO	Bn	HCl (g)/MeOH	6.3	*syn*-(+)-**6b**	40
syn-(–)-**2h**	PMP	BnO	allyl	HCl (g)/MeOH	6	*syn*-(+)-**6c**	32
syn-(+)-**2b**	PMP	MeO	Bn	H_2SO_4 conc./DCM (1:100)	4.3	*syn*-(+)-**6b**	0
syn-(+)-**2b**	PMP	MeO	Bn	H_2SO_4 conc./DCM (1:50)	44	*syn*-(+)-**6b**	50
syn-(+)-**2b**	PMP	MeO	Bn	H_2SO_4 conc./DCM (1:30)	20	*syn*-(+)-**6b**	19
syn-(+)-**2b**	PMP	MeO	Bn	H_2SO_4 conc./DCM (1:10)	4.5	*syn*-(+)-**6b**	10

[a] Yield of isolated products with correct analytical and spectral data. [b] The experiment was carried out at reflux temperature. [c] A complex reaction mixture was obtained. PMP = 4-$MeOC_6H_4$.

Table 4. Acid promoted transformation of β-lactam aminonitriles **2** into functionalized 5-oxopyrrolidine-2-carbonitriles **7**.



syn-**2** R^4 = CN, R^5 = H
anti-**2** R^4 = H, R^5 = CN

syn-**7** R^4 = CN, R^5 = H
anti-**7** R^4 = H, R^5 = CN

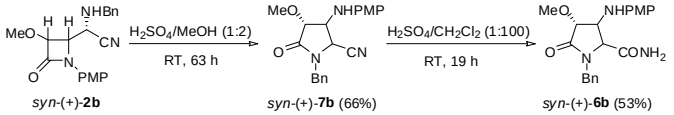
Aminonitrile	R^1	R^2	R^3	t (h)	Product	Yield (%)[a]
syn-(+)-**2a**	PMP	MeO	allyl	64	*syn*-(+)-**7a**	77

anti-(+)-**2a**	PMP	MeO	allyl	63	*anti*-(+)-**7a**	56
syn-(+)-**2b**	PMP	MeO	Bn	63	*syn*-(+)-**7b**	66
syn-(–)-**2h**	PMP	BnO	allyl	54	*syn*-(+)-**7c**	60
syn-(+)-**2c**	PMP	MeO	propargyl	63	*syn*-(+)-**7d**	80
syn-(+)-**2g**	PMP	PhO	allyl	143	*syn*-(+)-**7e**	35
2f [b]	Bn	MeO	PMP	48	*syn*-(+)-**7f**/*anti*-(+)-**7f**	43/25

[a] Yield of isolated products with correct analytical and spectral data. [b] A *syn*/*anti* mixture (63:37) of aminonitrile **2f** was used. PMP = 4-$MeOC_6H_4$.

Attempts were made to improve the above method by using different acidic conditions such as H_2SO_4/DCM in different conditions (Table 3). Interestingly, treatment of aminonitrile **2a** with a H_2SO_4/MeOH (1:2) mixture at room temperature, gave enantiopure 5-cyano-γ-lactam **7a** in a 77% yield without byproducts. To our delight, absence of hydrolysis of the cyanide group was observed. The results with aminonitriles **2** bearing different substituents were similar to the case of **2a** (Table 4). It should be mentioned that starting from the mixture (*syn*/*anti*) of the two chromatographically unseparable diastereomers **2f**, the corresponding 3-amino-4-alkoxy-5-oxopyrrolidine-2-carbonitriles *syn*-**7f** and *anti*-**7f** could be isolated as pure compounds. Besides, a similar behavior was observed for α-(alkylamino)nitriles and α-(arylamino) nitriles under these reaction conditions. The cyclic structures and the stereochemistry of 5-oxopyrrolidine-2-carbonitriles **7** were established by one- and two- dimensional NMR techniques and NOESY-1D experiments (see Fig. S1 and table S2 on supplementary data). The values for vicinal coupling constants show unequivocally a *trans-cis* orientation for protons H3–H4/H4–H5 in compounds syn-**7** and *trans-trans* in compounds anti-**7**, in agreement with that we previously reported for related products.[7d]

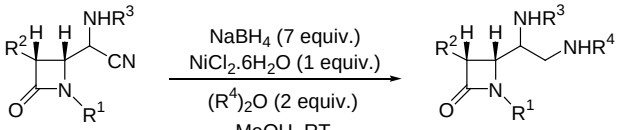
Chemical correlation between cyano derivative **7b** and its corresponding pyroglutamide **6b** was achieved through hydrolysis of the former by treatment at room temperature with a H_2SO_4/CH_2Cl_2 (1:100) mixture (Scheme 7).



Scheme 7. Hydrolysis of 5-oxopyrrolidine-2-carbonitrile **7b** into pyroglutamide **6b**.

Next, we decided to attempt the selective reduction of α-aminonitrile-β-lactams **2**. Among different reducing agents we selected the use of $NiCl_2{\cdot}6H_2O$ with excess of $NaBH_4$ in methanol, namely, our optimized conditions for the reduction of β-lactam cyanohydrins.[8] In the event, the reduction of the cyano group was achieved in a total chemoselective fashion using the $NaBH_4/NiCl_2$/methanol system in the presence of di-*tert*-butyl dicarbonate as trapping agent, to afford diamino-β-lactams **15** in reasonable yields (Table 5). Importantly, the β-lactam ring stereochemistry was unaffected by this process. Interestingly, starting from the *syn*/*anti* mixture of diastereomers **2e** and **2f**, the corresponding diamines *syn*-**15b,c** and *anti*-**15b,c** could be isolated as pure compounds after chromatographic separation. The vicinal coupling constants ($^3J_{4,4'}$) of the two protons (H4 in the β-lactam ring, hydrogen α to the nitrogen) located at the single bond connecting the ring and the diamino moiety were diagnostic of the relative stereochemistry of these stereocenters. The vicinal coupling constants values for major isomers *syn*-**15** (6.0-8.4 Hz) are larger than that for the minor isomers *anti*-**15** (2.2-3.0 Hz).

Table 5. Chemoselective reduction of β-lactam aminonitriles **2** into diamino-β-lactams **15**.



2

15 (R^4 = Boc)
16 (R^4 = Ac)

Aminonitrile	R^1	R^2	R^3	R^4	t (min)	Product	*syn*:*anti ratio*	Yield (%)[a]
syn-(+)-**2b**	PMP	MeO	Bn	Boc	20	*syn*-(+)-**15a**	100:0	36
2e[b]	PMP	MeO	PMP	Boc	25	**15b**	76:24	71
2f[c]	Bn	MeO	PMP	Boc	30	**15c**	63:37	81
2f[c]	Bn	MeO	PMP	Ac	25	**16**[d]	63:37	55

[a] Yield of isolated products with correct analytical and spectral data. [b] A *syn*/*anti* mixture (76:24) of aminonitrile **2e** was used. [c] A *syn*/*anti* mixture (63:37) of aminonitrile **2f** was used. [d] Diamines **16** were obtained as unseparable *syn*/*anti*-mixtures. PMP = 4-$MeOC_6H_4$.

We examined the ability of diamines **15** to react with different reagents. Ring expansion of diamino-β-lactams **15** in presence of sodium methoxide in methanol reliably give 4-amino-5-(aminomethyl)-3-alkoxypyrrolidin-2-ones **17** (Scheme 8). Pyrrolidinone formation through N1–C2 bond cleavage of the β-lactam nucleus must be driven by relief of the strain associated with the four-membered ring on forming a more stable five-membered ring. Next, the exocyclic *p*-anisylamino group in compounds **15** was converted into a *tert*-butyl carbamate by oxidation with (diacetoxyiodo)benzene (DIB) in MeOH/AcOH followed by reaction with di-*tert*-butyl dicarbonate of the resulting primary amino group. In this manner, compounds **18a**,**b** and **19** were prepared in fair yields (Scheme 8). Unfortunately, starting from the unseparable mixture of acetamides **16**, the mixture of isomers (*syn*/*anti*) of compounds **19** could not be separated by bench chromatography. Finally, diamines **16** were transformed into imidazolidinone-β-lactam hybrids **20** by sequential exposure to trifluoroacetic acid and triphosgene in presence of Hünig's base (Scheme 8).

Scheme 8. Transformation of β-lactam diamines **15** into functionalized γ-lactams **17**, dicarbamates **18**, amide carbamate **19**, and imidazolidinones **20**.

3. Conclusions

In conclusion, the stereoselective reaction between 2-azetidinone-derived imines and cyanide-based reagents give the corresponding α-aminonitriles **2**. These enantiopure β-lactam-aminonitrile hybrids are versatile building blocks for the controlled synthesis of a variety of new compounds including functionalized γ-lactams **6** and **7**, succinimide derivatives **8** and diamino-β-lactams derivatives **15**-**20** in optically pure form.

4. Experimental section

4.1. General information

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, 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 taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

4.2. General procedures for the synthesis of β-lactam α-aminonitriles 2

*4.2.1. Reaction of imino-β-lactams **1** with TBDMSiCN. Method A.* A solution of TBDMSiCN (0.80 mmol) in anhydrous acetonitrile (1.1 mL) and TBACN (0.07 mmol) in anhydrous acetonitrile (1.1 mL) were sequentially added dropwise via syringe to a stirred solution of the appropriate imine **1** (0.67 mmol) in the same solvent (2.2 mL) at RT and under argon atmosphere. The mixture was stirred at RT until disappearance of starting material (TLC). Then, a saturated aqueous NaCl solution (7 mL) was added and the resulting mixture was extracted with DCM (4 x 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After flash chromatography of the residue on deactivated silica gel, eluting with hexanes/ethyl acetate mixtures, the two separated *syn*/*anti* isomers of 2-azetidinone aminonitriles **2** were obtained.[13]

*4.2.2. Direct aminocyanation of β-lactam aldehydes **5**. Method B.* The appropriate amine (1 mmol) and TMSCN (1.5 mmol) were sequentially added dropwise via syringe to a stirred solution of the corresponding 4-oxoazetidine-2-carbaldehyde **5** (1 mmol) and catalyst (0.1 mmol of iodine, $BiCl_3$, $InCl_3$ or H_3NSO_3) in anhydrous acetonitrile (5 mL) at RT and under argon atmosphere. The mixture was stirred at RT until disappearance of starting material (TLC). Then, ethyl acetate (30 mL) was added and the resulting mixture was successively washed with water (15 mL) and saturated aqueous NaCl solution (15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After flash chromatography of the residue on deactivated silica gel, eluting with hexanes/ethyl acetate mixtures, the two separated *syn*/*anti* isomers of 2-azetidinone aminonitriles **2** were obtained. [14]

*4.2.3. α-Aminonitrile **2a**.*

4.2.3.1. Method A. By starting from imine (+)-**1a** (62 mg, 0.44 mmol), followed by chromatography of the product residue (hexanes/EtOAc 4:1), the more polar compound *syn*-(+)-**2a** (60 mg, 54%) and the less polar compound *anti*-(+)-**2a** (15 mg, 14%) were obtained.

4.2.3.2. Method B. By starting from imine (+)-**1a** (150 mg, 0.64 mmol) and molecular iodine as catalyst, followed by chromatography of the product residue (hexanes/EtOAc 4:1), the more polar compound *syn*-(+)-**2a** (129 mg, 67%) and the less polar compound *anti*-(+)-**2a** (23 mg, 12%) were obtained.

4.2.3.3. α-Aminonitrile syn-(+)-**2a**. Colourless solid; Mp 85–86 °C; $[\alpha]_D$ = +112.5 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 3.27 (1H, m, NC***H**$_a$*H$_b$), 3.56 (1H, m, NCH$_a$***H**$_b$*), 3.73 (3H, s, C***H**$_3$*O-C3), 3.80 (3H, s, C***H**$_3$*O-C$_6$H$_4$), 4.15 (1H, dd, $J_{4',NH}$ = 11.2 Hz, $J_{4',4}$ = 5.1 Hz, ***H4'***), 4.43 (1H, t, $J_{4,3}$ = $J_{4,4'}$ = 5.1 Hz, ***H4***), 4.75 (1H, d, $J_{3,4}$ = 5.1 Hz, ***H3***), 5.19 (1H, dd, J_{cis} = 10.2 Hz, J_{gem} = 1.4 Hz, CH=C***H**$_{cis}$*H$_{trans}$), 5.27 (1H, dd, J_{trans} = 17.2 Hz, J_{gem} = 1.5 Hz, CH=CH$_{cis}$***H**$_{trans}$*), 5.79 (1H, dddd, J_{trans} = 16.9 Hz, J_{cis} = 10.2 Hz, $J_{CH=,Ha}$ = 6.4 Hz, $J_{CH=,Hb}$ = 5.2 Hz, C***H**=CH$_{cis}$H$_{trans}$), 6.89 (2H, ***AA'**XX'*, 2 C***H**$_{Ar}$ **o***-OCH$_3$), 7.34 (2H, AA'***XX'***, 2 C***H**$_{Ar}$ **m***-OCH$_3$); δ_C (75 MHz, $CDCl_3$) 49.3 (***C4'***), 50.6 (N***C**H$_2$), 55.5 (***C**H$_3$O-C$_6$H$_4$), 56.7 (***C4***), 59.3 (***C**H$_3$O-C3), 82.5 (***C3***), 114.6 (2 ***C**H$_{Ar}$ **m***-N-C=O), 117.0 (***C**N), 118.1 (CH=***C**H$_2$), 119.2 (2 ***C**H$_{Ar}$ **o***-N-C=O), 129.5 (***C**$_{Ar}$ **ipso***-N-C=O), 134.5 (***C**H=CH$_2$), 157.0 (***C**$_{Ar}$ **ipso***-OCH$_3$), 163.4 (N-***C**=O); *m/z* (EI) 301 (M$^{+\cdot}$, 49), 274 (8), 243 (84), 215 (22), 178 (65), 149 (100), 134 (71). Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.92; H, 6.28; N, 13.83.

4.2.3.4. α-Aminonitrile anti-(+)-**2a**. Colourless oil; $[\alpha]_D$ = +355.1 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 3338, 1752 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 3.19 (1H, dd, $J_{a\ b}$= 14.0 Hz, $J_{Ha,CH=}$ = 7.0 Hz, NC***H**$_a$*H$_b$), 3.48 (1H, dd, J_{ab} = 14.0 Hz, $J_{Hb,CH=}$ = 5.0 Hz, NCH$_a$***H**$_b$*), 3.73 (3H, s, C***H**$_3$*O-C3), 3.80 (3H, s, C***H**$_3$*O-C$_6$H$_4$), 4.14 (1H, d, $J_{4',4}$ = 3.4 Hz, ***H4'***), 4.48 (1H, dd, $J_{4,3}$ = 4.9 Hz, $J_{4,4'}$ = 3.9 Hz, ***H4***), 4.77 (1H, d, $J_{3,4}$ = 4.9 Hz, ***H3***), 5.03 (1H, dd, J_{cis} = 10.0 Hz, J_{gem} = 1.2 Hz, CH=C***H**$_{cis}$*H$_{trans}$), 5.12 (1H, dd, J_{trans} = 17.2 Hz, J_{gem} = 1.3 Hz, CH=CH$_{cis}$***H**$_{trans}$*), 5.51 (1H, dddd, J_{trans} = 17.0 Hz, J_{cis} = 10.0 Hz, $J_{CH=,Ha}$ = 6.8 Hz, $J_{CH=,Hb}$ = 5.0 Hz, C***H**=CH$_{cis}$H$_{trans}$), 6.89 (2H, ***AA'**XX'*, 2 C***H**$_{Ar}$ **o***-OCH$_3$), 7.31 (2H, AA'***XX'***, 2 C***H**$_{Ar}$ **m***-OCH$_3$); δ_C (75 MHz, $CDCl_3$) 47.2 (***C4'***), 50.1 (N***C**H$_2$), 55.5 (***C**H$_3$O-C$_6$H$_4$), 57.9 (***C4***), 60.5 (***C**H$_3$O-C3), 83.4 (***C3***), 114.6 (2 ***C**H$_{Ar}$ **m***-N-C=O), 117.9 (***C**N), 118.1 (CH=***C**H$_2$), 119.4 (2 ***C**H$_{Ar}$ **o***-N-C=O), 129.5 (***C**$_{Ar}$ **ipso***-N-C=O), 134.4 (***C**H=CH$_2$), 157.0 (***C**$_{Ar}$ **ipso***-OCH$_3$), 163.8 (N-***C**=O); *m/z* (EI) 301 (M$^{+\cdot}$, 70), 274 (8), 243 (66), 215 (18), 178 (100), 149 (69), 134 (55).

4.3. General procedure for the acid promoted transformation of β-lactam aminonitriles 2 into functionalized pyroglutamides 6.

HCl(g) was bubbled during 1 h through a solution of the appropriate α-aminonitrile **2** (0.17 mmol) in methanol (4.2 mL), and then stirred at RT until disappearance of starting material (TLC). The reaction mixture was concentrated under reduced pressure, diluted with dichloromethane (20 mL), washed with saturated aqueous sodium hydrogen carbonate (2 x 10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After flash chromatography of the residue on silica gel, eluting with hexanes/ethyl acetate (1:1), compounds **6** were obtained.

*4.3.1. Pyroglutamide-syn-(+)-**6a**.* From 50 mg (0.17 mmol) of α-aminonitrile *syn*-(+)-**2a**, compound *syn*-(+)-**6a** (19 mg, 36%) was obtained as a pale brown oil; $[\alpha]_D$ = +60.2 (*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3344, 1683 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 3.51 (1H, dd, J_{ab} = 14.9 Hz, $J_{Ha,=CH}$ = 7.6 Hz, NC***H*****$_a$**H$_b$), 3.65 (3H, s, C***H*****$_3$**O-C3), 3.76 (3H, s, C***H*****$_3$**O-C_6H_4), 4.13-4.38 (4H, m, ***H*****5**, ***H*****4**, ***H*****3** and NCH$_a$***H*****$_b$**), 5.23 (1H, d, J_{trans} = 16.1 Hz, CH=CH$_{cis}$***H*****$_{trans}$**), 5.25 (1H, d, J_{cis} = 9.8 Hz, CH=C***H*****$_{cis}$**H$_{trans}$), 5.74 (3H, m, C***H***=CH$_{cis}$H$_{trans}$ and CON***H*****$_2$**), 6.81 (4H, m, ***Ar***); δ_C (75 MHz, $CDCl_3$) 44.9 (N***C***H$_2$), 55.7 (***C***H$_3$O-C_6H_4), 57.7 (***C*****4**), 59.08 (***C***H$_3$O-C3), 60.10 (***C*****5**), 80.87 (***C*****3**), 114.9, 115.0 (2 ***C***H$_{Ar}$ ***m***-OCH_3 and 2 ***C***H$_{Ar}$ ***o***-OCH_3), 119.4 (CH=***C***H$_2$), 131.3 (***C***H=CH$_2$), 140.0 (***C***$_{Ar}$ ***ipso***-NH), 152.9 (***C***$_{Ar}$ ***ipso***-OCH_3), 171.0, 171.7 (N-***C***=O y ***C***ONH_2).

4.4. General procedure for the acid promoted transformation of β-lactam aminonitriles 2 into functionalized 5-oxopyrrolidine-2-carbonitriles 7.

Concentrated sulphuric acid (3.5 mL) were slowly added to a solution of the appropriate α-aminonitrile **2** (0.30 mmol) in methanol (7 mL), and then stirred at RT, under argon, until disappearance of starting material (TLC). The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate (15 mL) and solid hydrogen carbonate. The reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate (5 x 30 mL. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After flash chromatography of the residue on silica gel, eluting with hexanes/ethyl acetate mixtures, compounds **7** were obtained.

*4.4.1. 5-Oxopyrrolidine-2-carbonitrile sin-(+)-**7a**.* From 96 mg (0.32 mmol) of α-aminonitrile *syn*-(+)-**2a**, compound *syn*-(+)-**7a** (74 mg, 77%) was obtained as a pale brown oil; $[\alpha]_D$ = +140.8 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3362, 1717 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 3.69 (1H, dd, J_{ab} = 15.4 Hz, $J_{Ha,=CH}$ = 7.6 Hz, NC***H*****$_a$**H$_b$), 3.74 (3H, s, C***H*****$_3$**O-C3), 3.77 (3H, s, C***H*****$_3$**O-C_6H_4), 4.02 (1H, d, $J_{5,4}$ = 9.0 Hz, ***H*****5**), 4.19 (1H, dd, $J_{4,5}$ = 9.4 Hz, $J_{4,3}$ = 7.2 Hz, ***H*****4**), 4.38 (1H, dd, J_{ab} = 15.0 Hz, $J_{Hb,=CH}$ = 5.2 Hz, NCH$_a$***H*****$_b$**), 4.57 (1H, d, $J_{3,4}$ = 7.1 Hz, ***H*****3**), 5.35 (1H, d, J_{trans} = 16.8 Hz, CH=CH$_{cis}$***H*****$_{trans}$**), 5.36 (1H, d, J_{cis} = 9.8 Hz, CH=C***H*****$_{cis}$**H$_{trans}$), 5.74 (1H, dddd, J_{trans} = 16.1 Hz, J_{cis} = 10.7 Hz, $J_{=CH,Ha}$ = 7.7 Hz, $J_{=CH,Hb}$ = 5.3 Hz, C***H***=CH$_{cis}$H$_{trans}$), 6.72 (2H, ***AA'***BB', 2 C***H*****$_{Ar}$ ***o***-OCH_3), 6.83 (2H, AA'***BB'***, 2 C***H*****$_{Ar}$ ***m***-OCH_3); δ_C (75 MHz, $CDCl_3$) 44.9 (N***C***H$_2$), 49.9 (***C*****5**), 55.6 (***C***H$_3$O-C_6H_4), 57.8 (***C*****4**), 59.6 (***C***H$_3$O-C3), 80.5 (***C*****3**), 114.8 (***C***N), 115.1, 116.2 (2 ***C***H$_{Ar}$ ***m***-OCH_3 and 2 ***C***H$_{Ar}$ ***o***-OCH_3), 121.2 (CH=***C***H$_2$), 130.0 (***C***H=CH$_2$), 138.6 (***C***$_{Ar}$ ***ipso***-NH), 153.9 (***C***$_{Ar}$ ***ipso***-OCH_3), 169.8 (N-***C***=O); *m/z* (EI) 301 ($M^{+\cdot}$, 100), 286 (3), 256 (21), 179 (37), 164 (57), 149 (33), 134 (35).

4.5. General procedure for the chemoselective reduction of β-lactam aminonitriles 2 into diamino-β-lactams 15.

Sodium borohydride (3.85 mmol) was slowly added over a solution of the appropriate α-aminonitrile **2** (0.55 mmol), nickel(II) chloride hexahydrate (0.55 mmol) and di-*tert*-butyl dicarbonate (1.1 mmol) in methanol (4.6 mL), at 0°C under argon. The reaction mixture was allowed to warm to room temperature and was stirred until disappearance of starting material (TLC). Methanol was evaporated under vacuum and, the resulting crude was diluted with ethyl acetate (110 mL). Then, a saturated aqueous solution of $NaHCO_3$ was added (55 mL). The resulting mixture was filtered through a pad of celite and the filtrate was extracted with ethyl acetate (4 x 55 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel of the residue, eluting with hexanes/ethyl acetate mixtures gave β-lactam carbamates **15**.

*4.5.1. Diamino-β-lactam sin-(+)-**15a**.* From 150 mg (0.43 mmol) of α-aminonitrile *syn*-(+)-**2b**, compound *syn*-(+)-**15a** (70 mg, 36%) was obtained as a colourless oil; $[\alpha]_D$ = +45.9 (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3362, 1717 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 1.42 (9H, s, (C***H*****$_3$**)$_3$C-O), 3.29-3.38 (3H, m, C***H*****$_2$**NCO and ***H4'***), 3.66 (3H, s, C***H*****$_3$**O-C3), 3.74 (1H, d, J_{ab} = 12.9 Hz, NC***H*****$_a$**H$_b$Ph), 3.79 (3H, s, C***H*****$_3$**O-C_6H_4), 3.86 (1H, d, J_{ab} = 13.2 Hz, NCH$_a$***H*****$_b$**Ph), 4.32 (1H, t, $J_{4,3}$ = $J_{4,4'}$ = 5.8 Hz, ***H*****4**), 4.62 (1H, d, $J_{3,4}$ = 5.3 Hz, ***H*****3**), 4.93 (1H, bs, N***H***C=O), 6.86 (2H, ***AA'***XX', 2 C***H*****$_{Ar}$ ***o***-OCH_3), 7.17-7.32 (5H, m, ***Ar***), 7.35 (2H, AA'***XX'***, 2 C***H*****$_{Ar}$ ***m***-OCH_3); δ_C (75 MHz, $CDCl_3$) 28.3 [(***C***H$_3$)$_3$C-O], 40.4 (***C***H$_2$NHCO), 52.0 (N***C***H$_2$Ph), 55.4 (***C***H$_3$O-C_6H_4), 56.8, 58.8 (***C4'*** and ***C*****4**), 59.5 (***C***H$_3$O-C3), 79.2 ((CH$_3$)$_3$***C***-O), 83.1 (***C*****3**), 114.4 (2 ***C***H$_{Ar}$ ***m***-N-C=O), 119.5 (2 ***C***H$_{Ar}$ ***o***-N-C=O), 127.0 (***C***H$_{Ar}$ ***p***-CH$_2$), 127.9, 128.3 (2 ***C***H$_{Ar}$ ***m***-CH$_2$ and 2 ***C***H$_{Ar}$ ***o***-CH$_2$), 130.7 (***C***$_{Ar}$ ***ipso***-N-C=O), 140.1 (***C***$_{Ar}$ ***ipso***-CH$_2$), 156.2 (O***C***=ONH), 156.7 (***C***$_{Ar}$ ***ipso***-OCH_3), 165.2 (N-***C***=O); *m/z* (EI) 455 ($M^{+\cdot}$, 19), 399 (27), 382 (8), 325 (34), 249 (19), 193 (88), 176 (34), 149 (23), 91 (100).

4.6. General procedure for the transformation of β-lactam diamines 15 into functionalized γ-lactams 17.

A solution of the appropriate diamino-β-lactam **15** (0.11 mmol) in methanol (2.6 mL) was added at RT under argon to sodium methoxide (0.13 mmol). The reaction was stirred at room temperature until complete disappearance of the starting material (TLC) and then brine (5 mL) was added. The methanol was removed under reduced pressure, and the aqueous residue was extracted with ethyl acetate (5 x 10 mL). The organic extract was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes (1:3) gave analytically pure compounds **17**.

*4.6.1. Functionalized γ-lactam (+)-**17a**.* From 50 mg (0.11 mmol) of diamino-β-lactam *syn*-(+)-**15a**, compound *syn*-(+)-**17a** (31 mg, 62%) was obtained as a pale brown oil; $[\alpha]_D$ = +31.1 (*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3327, 1701 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 1.45 (9H, s, (C***H*****$_3$**)$_3$C-O), 3.03 (1H, m, C***H*****$_a$**H$_b$NH), 3.40 (1H, dd, J_{ab} = 14.5 Hz, $J_{Hb,5}$ = 8.9 Hz, CH$_a$***H*****$_b$**NH), 3.64 (1H, m, ***H*****5**), 3.69 (3H, s, C***H*****$_3$**O-C3), 3.73 (3H, s, C***H*****$_3$**O-C_6H_4), 3.91 (1H, d, $J_{3,4}$ = 9.3 Hz, ***H*****3**), 4.04 (1H, m, ***H*****4**), 4.29 (1H, d, J_{ab} = 15.0 Hz, NC***H*****$_a$**H$_b$Ph), 4.40 (1H, bs, N***H***C=O), 4.81 (1H, d, J_{ab} = 14.4 Hz, NCH$_a$***H*****$_b$**Ph), 6.67 (2H, ***AA'***BB', 2 C***H*****$_{Ar}$ ***o***-OCH_3), 6.76 (2H, AA'***BB'***, 2 C***H*****$_{Ar}$ ***m***-OCH_3), 7.33-7.35 (5H, m, ***Ar***); δ_C (75 MHz, $CDCl_3$) 28.3 [(***C***H$_3$)$_3$C-O], 37.0 (***C***H$_2$NH), 45.2 (N***C***H$_2$Ph), 55.7 (***C***H$_3$O-C_6H_4), 57.2, 58.1 (***C4'*** and ***C*****4**), 59.2 (***C***H$_3$O-C3), 80.5 [(CH$_3$)$_3$***C***-O], 81.4 (***C*****3**), 115.0 (2 ***C***H$_{Ar}$ ***m***-NH and 2 ***C***H$_{Ar}$ ***o***-NH), 128.1 (***C***H$_{Ar}$ ***p***-CH$_2$), 128.3, 129.0 (2 ***C***H$_{Ar}$ ***m***-CH$_2$ and 2 ***C***H$_{Ar}$ ***o***-CH$_2$), 136.0 (***C***$_{Ar}$ ***ipso***-CH$_2$), 140.8 (***C***$_{Ar}$ ***ipso***-NH), 152.8 (***C***$_{Ar}$ ***ipso***-OCH_3), 156.1 (O***C***=ONH), 171.3 (N-***C***=O); *m/z* (EI) 455 ($M^{+\cdot}$, 68), 399 (100), 382 (17), 354 (15), 293 (49), 123 (46), 91 (80), 57 (20).

4.7. General procedures for transformations of β-lactam diamines 15.

*4.7.1. Preparation of dicarbamates 18 or amide carbamate 19***.** To a solution of diacetoxy iodobenzene (DIB) (0.88 mmol) in a mixture of methanol (2.6 mL) and acetic acid (0.05 mL), a solution of the corresponding diamino-β-lactam **15** (0.22 mmol) in methanol (0.6 mL) was slowly added (over 30 min). Upon complete addition, the reaction was stirred at RT for 30 min. Then, a 10% aq. HCl solution (2.6 mL, wt %) was added. The mixture was stirred for 30 min, at which time a 10% aq. $Na_2S_2O_3$ solution (2.6 mL, wt %) was added, and stirring was allowed to continue for an additional 30 min. After that, sodium carbonate was added until solution was made basic and, a solution of di-*tert*-butyl dicarbonate or acetic anhydride (0.88 mmol) in DCM (1 mL) was added as required. The mixture was stirred overnight at RT. Afterward, methanol was removed under reduced pressure and the resulting mixture was extracted with DCM (4 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel of the residue eluting with hexanes/ethyl acetate mixtures afforded analytically pure carbamates **18** or amide **19**.

*4.7.1.1. Functionalized dicarbamate sin-(+)-**18a***. From 103 mg (0.22 mmol) of diamino-β-lactam *syn*-(+)-**15a**, compound *syn*-(+)-**18a** (31 mg, 31%) was obtained as a colorless solid; Mp 170–173 °C; $[\alpha]_D$ = +36.7 (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3356, 1737, 1681 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 1.40 (9H, s, $(CH_3)_3$C-O), 3.16 (1H, m, CH_aH_b), 3.63 (1H, m, CH_aH_b), 3.70 (3H, s, CH_3O-C3), 3.79 (3H, s, CH_3O-C_6H_4), 4.40 (2H, m, ***H4'*** and ***H4***), 4.66 (1H, d, $J_{3,4}$ = 5.1 Hz, ***H3***), 4.66 (1H, m, CH_2NHC=O), 5.16 (1H, d, $J_{NH,4'}$ = 7.3 Hz, C4′-NHC=O), 6.88 (2H, ***AA'***XX', 2 CH_{Ar} ***m***-NC=O), 7.38 (2H, AA'***XX'***, 2 CH_{Ar} ***o***-N-C=O); δ_C (75 MHz, $CDCl_3$) 28.2, 28.3 (2 x $(CH_3)_3$C-O), 40.5 (CH_2), 55.5 (2 x CH_3O-C_6H_4), 56.4, 56.9 (***C4'*** and ***C4***), 59.4 (CH_3O-C3), 79.4, 79.8 (2 x $(CH_3)_3$C-O), 83.0 (***C3***), 114.6 (2 CH_{Ar} ***m***-N-C=O), 118.9 (2 CH_{Ar} ***o***-N-C=O), 130.2 (C_{Ar} ***ipso***-N-C=O), 152.2, 155.9 (2 x OC=ONH), 156.7 (C_{Ar} ***ipso***-OCH_3), 164.3 (N-C=O); *m/z* (EI) 465 ($M^{+\cdot}$, 19), 365 (26), 309 (48), 149 (52), 130 (80), 57 (100). Anal. Calcd for $C_{23}H_{35}N_3O_7$: C, 59.34; H, 7.58; N, 9.03. Found: C, 59.41; H, 7.62; N, 8.98.

*4.7.2. Preparation of imidazolidinone syn-(+)-**20***. To a solution of the carbamate *syn*-(+)-**15c** (78 mg, 0.17 mmol) in anhydrous dichloromethane (1.2 mL), trifluoroacetic acid (0.38 mL, 5.12 mmol) was slowly added under argon atmosphere at RT. Upon complete addition, the reaction was stirred at RT for 1 h, and a 30% aq. NH_3 solution was added until mixture was made basic. Then, solid NaCl was added, and the aqueous residue was extracted with ethyl acetate (5 x 15 mL). The organic extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. To a solution of the crude diamine in anhydrous dichloromethane (1.3 mL), *N*,*N*-diisopropylethylamine (0.88 mL, 0.51 mmol) was slowly added under argon atmosphere at 0 °C. Upon complete addition, the reaction was stirred at 0 °C for 15 min, and a solution of triphosgene (61 mg, 0.21 mmol) in anhydrous dichloromethane (0.6 mL) was added dropwise. The reaction was stirred at RT for an additional 1 h. The reaction mixture was diluted with dichloromethane (15 mL), washed with water (4 mL) and brine (4 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After flash chromatography of the residue on silica gel, eluting with hexanes/ethyl acetate (2:1), compound *syn*-(+)-**20** (20 mg, 30%) was obtained as a pale brown oil. $[\alpha]_D$ = +4.6 (*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$) 1778, 1748 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 3.48 (1H, d, J_{ab} = 15.0 Hz, NCH_aH_bPh), 3.61 (3H, s, CH_3O-C3), 3.70 (1H, dd, $J_{4,4'}$ = 6.3 Hz, $J_{4,3}$ = 5.2 Hz, ***H4***), 3.72 (1H, t, J_{ab} = $J_{Ha,4'}$ = 10.8 Hz, CH_aH_bNHCO), 3.83 (3H, s, CH_3O-C_6H_4), 3.86 (1H, dd, J_{ab} = 11.5 Hz, $J_{Hb,4'}$ = 3.8 Hz, CH_aH_bNHCO), 4.26 (1H, d, J_{ab} = 15.0 Hz, NCH_aH_bPh), 4.36 (1H, ddd, $J_{4',Ha}$ = 9.9 Hz, $J_{4',4}$ = 6.3 Hz, $J_{4',Hb}$ = 3.8 Hz, ***H4'***), 4.48 (1H, d, $J_{3,4}$ = 5.2 Hz, ***H3***), 6.96 (2H, ***AA'***XX', 2 CH_{Ar} ***o***-OCH_3), 7.08-7.11 (2H, m, ***Ar***) 7.30 (2H, AA'***XX'***, 2 CH_{Ar} ***m***-OCH_3), 7.35-7.37 (3H, m, ***Ar***); δ_C (75 MHz, $CDCl_3$) 45.0, 45.2 (CH_2NHCO and NCH_2Ph), 52.7 (***C4'***), 55.5 (CH_3O-C_6H_4), 57.9 (***C4***), 59.8 (CH_3O-C3), 83.9 (***C3***), 114.8 (2 CH_{Ar} ***m***-N-C=O), 124.8 (2 CH_{Ar} ***o***-N-C=O), 128.3, 129.2 (2 CH_{Ar} ***m***-CH_2 and 2 CH_{Ar} ***o***-CH_2), 128.5 (CH_{Ar} ***p***-CH_2), 128.9 (C_{Ar} ***ipso***-N-C=O), 134.8 (C_{Ar} ***ipso***-CH_2), 158.2 (C_{Ar} ***ipso***-OCH_3 and NC=ONH), 167.6 (N-C=O); *m/z* (EI) 236 (100), 191 (15), 91 (32).

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14. Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supplementary data.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.

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