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Solid-phase Petasis multicomponent reaction for the generation of β-lactams 3-substituted with non-proteinogenic α-amino acids

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ABSTRACT

An efficient protocol for the rapid generation of libraries of biologically promising β-lactams is described. Key step is a solid-phase based multicomponent Petasis reaction.

Introduction

A β-lactam unit is a privileged structure present in numerous bioactive compounds.[1,2] Aside from the well known significance in the field of antibacterial chemotherapy, β-lactam derivatives have recently received more attention mainly because of the development of potent cholesterol absorption inhibitors.[3] In addition, they have been considered for the inhibition of prostate specific antigen,[4] thrombin,[4] human cytomegalovirus protein,[5] human leukocyte elastase,[6] cysteine protease,[7] and human fatty acid amide hydrolase;[8] as well as for chemo and neurotherapeutic research.[9] It is then clear that the exploration of new methodologies and strategies for the generation of β-lactam-based chemical libraries is an interesting option in the search of novel active compounds.

On the other hand, non-proteinogenic amino acids have increasing importance in drug discovery as a result of their potential pharmacological properties and their utility as building blocks in the synthesis of peptidic and non-peptidic compounds.[10] In fact, a survey involving the small-molecule libraries synthesized in 2005, showed that as much as 28% of them include an α-amino acid substructure (natural or unnatural).[11] Among the non-proteinogenic α-amino acids, arylglycines are particularly important: amoxicilin **1**, cefalexin **2**, and nocardicins **3**, as well as many well known commercial β-lactam antibiotics, contain an arylglycine moiety (Fig. 1).[12] This residue is also found in the structure of the glycopeptide antibiotic vancomycin **4**.[13]

Although *N*-aryl-α-amino acids were traditionally obtained by the Strecker reaction and related methodologies,[14] it has been more recently replaced by a more straightforward method such

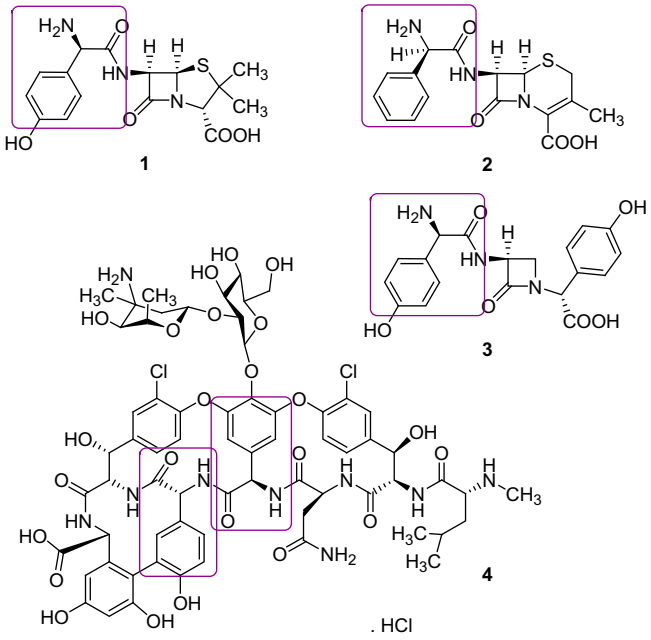

Figure 1.

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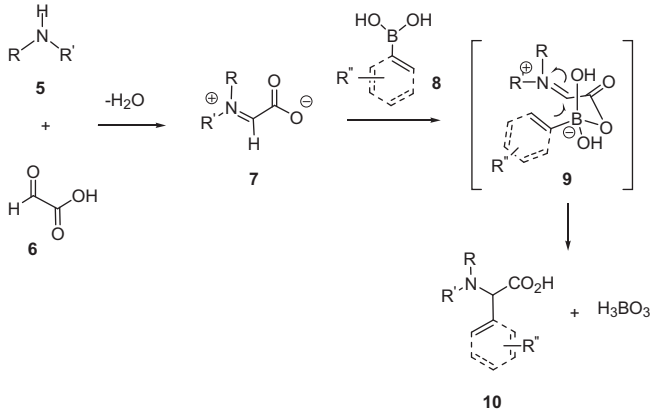
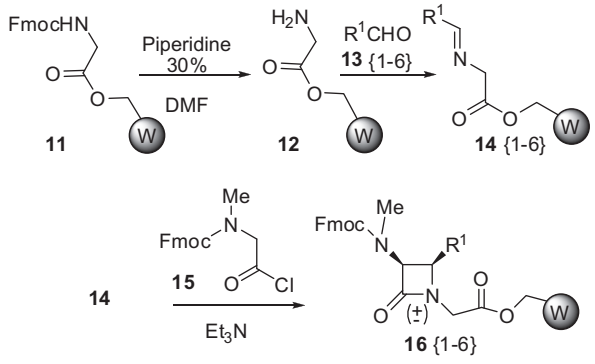
as the boronic Mannich reaction (Petasis reaction).[15] Petasis reaction is a three-component coupling involving an amine, an aldehyde, and a boronic acid derivative. In the case of non-proteinogenic amino acid synthesis, glyoxylic acid is used as the aldehyde component. Condensation between the amine **5** and the glyoxylic acid (**6**) gives the corresponding iminium ion **7** (Scheme 1). According to the generally accepted mechanism, the presence of the adjacent hydroxyl group in the glyoxylic acid, activates the organoboron component **8** by forming the activated 'ate complex' (**9**).[16] This boronate salt **9** favors the intramolecular transfer of the organoboron substituent to give the expected α-amino acid **10**.

This reaction is especially suited for compound library construction since it is a multicomponent condensation, which facilitates diversity generation,[17] and requires mild conditions and non-toxic boronic acids and amines that are readily available.

We envisaged that the combination of solid-phase synthesis and multicomponent reactions (MCRs) could be very useful for the rapid construction of small-molecule libraries, adding to the high convergence of MCRs the advantages of solid-supported strategies: easy automatization, parallelization, and purification.[18] For that reason, we have initiated a research program dealing with the application of Petasis multicomponent reaction for the generation of non-proteinogenic α-amino acids to β-lactam derivatives.[19]



Scheme 1.



Scheme 2.

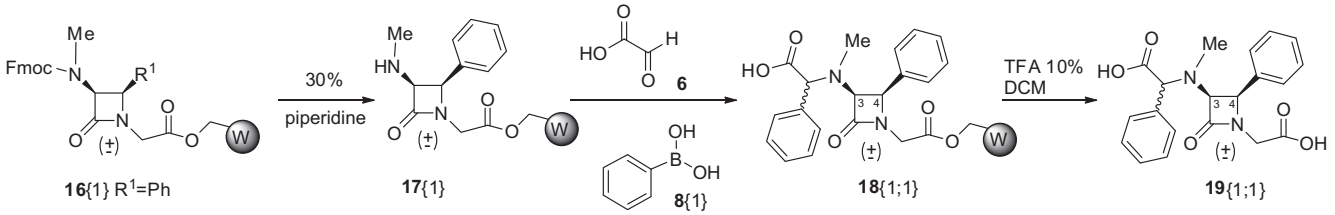
First, we have developed a synthetic sequence for the preparation of the β-lactam precursors (**16**) (Scheme 2). After the removal of the Fmoc protecting group in **11**, the imine formation was carried out using a variety of aromatic aldehydes. Then, the Staudinger reaction, that involves the cycloaddition between an in situ generated ketene and the imines (**14**), was performed. The ketene precursors, the acid chloride derived from Fmoc-protected sarcosine (**15**), and triethylamine were added in excess to a suspension of **14** in dichloromethane (Scheme 2). Formation of the β-lactams **16** was corroborated by the IR spectrum, which showed the β-lactam carbonyl absorption peak at 1770 cm^{-1}.

In an exploratory study for the preparation of non-proteinogenic α-amino acids to β-lactam derivatives, we planned the synthesis of the β-lactam **19**{1;1} (Scheme 3). Thus, after the removal of the Fmoc protecting group in **16**{1} (R^1 = Ph), the immobilized β-lactam **16**{1} was treated with an excess of glyoxylic acid (**6**) and phenylboronic acid (**8**{1}). A variety of conditions were examined, such as different glyoxylic and boronic acid concentrations, solvents, temperatures, and reaction times. Chloranil test was used to verify the reaction ending point.[20] Product **18**{1;1} was cleaved from the support with 10% trifluoroacetic acid (TFA)/dichloromethane for 30 min to give the β-lactam **19**{1;1}. The hydrogens in the 3- and 4-positions of the azetidinone ring show coupling constants of ~4.5 Hz in ^{1}H NMR, which is in full agreement with literature precedents for a 3,4-*cis* stereochemistry.[21]

In a study published in 2005, Nanda and Wesley Trotter performed an analysis of the solvent effect in Petasis MCR.[22] They found that fluorinated alcohols, like trifluoroethanol and hexafluoroisopropanol (HFIP), promote this reaction, although there were some undesirable side-effects for large reaction times. This problem was circumvented by using a mixture of DCM and HFIP, since a 9:1 ratio shortened significantly the reaction time. It was suggested that the presence of the acidic HFIP accelerates iminium formation during the first stage of the Petasis MCR (see Scheme 1).[23]

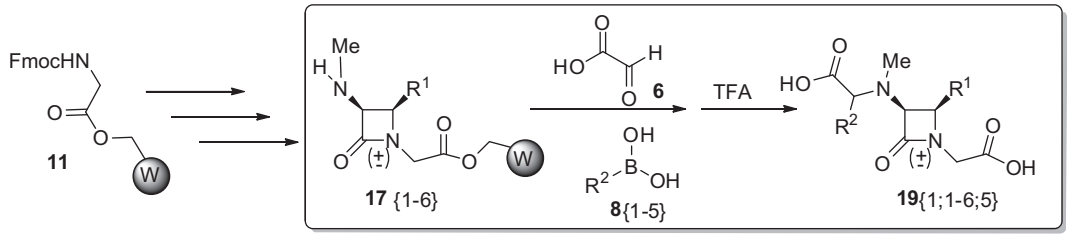
In order to find the optimized conditions we tested the Petasis reaction using a 9:1 mixture of DCM/HFIP for 72 h at room temperature, at the end of the synthetic sequence we obtained the crude β-lactam **19**{1;1} in a mass appreciably lower than that expected. We assumed that the decrease in mass was due to the acidic character of HFIP which led to the premature cleavage of the compound from the resin, especially after prolonged reaction times. Thus, the best reaction conditions for the Petasis MCR were found to be the treatment of **17**{1} with excess (9 equiv) of glyoxylic acid (**6**) and phenylboronic acid (**8**{1}) with dichoromethane as a solvent, at room temperature for 72 h.

After this exploratory stage, we applied the strategy to the generation of a library of new diacid β-lactams (**19**{1;1–6;5}) with two diversity points including the incorporation of non-proteinogenic α-amino acid moieties. Different β-lactams (**17**{1–6}) and diverse



Scheme 3.

Table 1



Entry	Product	R^1	R^2	Purity[a] (%)	Yield[b] (%)	Diastereo-isomeric ratio[a]
1	**19**{1;1}	Ph–	Ph–	95	>95	3.4:1
2	**19**{2;1}	4-MePh–	Ph–	100	>95	2.6:1
3	**19**{3;1}	4-MeOPh–	Ph–	100	53	5.5:1
4	**19**{4;1}	(*E*)-PhCHCH–	Ph–	85	>95	—[c]
5	**19**{5;1}	3,4-$(MeO)_2$Ph–	Ph–	100	70	6:1
6	**19**{6;1}	4-BrPh–	Ph–	61	74	2:1
7	**19**{1;2}	Ph–	(*E*)-PhCHCH–	74	86	10:1
8	**19**{2;2}	4-MePh–	(*E*)-PhCHCH–	100	>95	7.5:1
9	**19**{3;2}	4-MeOPh–	(*E*)-PhCHCH–	75	45	8:1
10	**19**{4;2}	(*E*)-PhCHCH–	(*E*)-PhCHCH–	100	>95	6.2:1
11	**19**{5;2}	3,4-$(MeO)_2$Ph–	(*E*)-PhCHCH–	100	65	3:1
12	**19**{6;2}	4-BrPh–	(*E*)-PhCHCH–	84	67	14:1
13	**19**{2;3}	4-MePh–	(*E*)-Me$(CH_2)_5$CHCH–	100	>95	5.3:1
14	**19**{3;3}	4-MeOPh–	(*E*)-Me$(CH_2)_5$CHCH–	100	55	6:1
15	**19**{4;3}	(*E*)-PhCHCH–	(*E*)-Me$(CH_2)_5$CHCH–	100	>95	3.6:1
16	**19**{5;3}	3,4-$(MeO)_2$Ph–	(*E*)-Me$(CH_2)_5$CHCH–	99	57	4:1
17	**19**{6;3}	4-BrPh–	(*E*)-Me$(CH_2)_5$CHCH–	84	92	2:1
18	**19**{3;4}	4-MeOPh–	4-MeOPh–	49	47	9:1
19	**19**{5;4}	3,4-$(MeO)_2$Ph–	4-MeOPh–	60	30	2.6:1
20	**19**{6;4}	4-BrPh–	4-MeOPh–	32	54	5:1
21	**19**{1;5}	Ph–	6-Methoxynaphthalen-2-yl–	52	46	3.3:1
22	**19**{3;5}	4-MeOPh–	6-Methoxynaphthalen-2-yl–	47	34	4.5:1
23	**19**{5;5}	3,4-$(MeO)_2$Ph–	6-Methoxynaphthalen-2-yl–	25	61	3:1
24	**19**{6;5}	4-BrPh–	6-Methoxynaphthalen-2-yl–	67	45	3.4:1

[a] Determined by HPLC.
[b] Yields are based on the weight of the crude product and are relative to the initial loading level of the resin.
[c] Only one diastereoisomer was obtained, absolute configuration not determined.

boronic acids (**8**{1–5}) were tested in order to obtain the corresponding carboxylic acids (Table 1).[24,25] In all cases the 3,4-*cis* ring fusion for the β-lactams was corroborated. MS-HPLC demonstrated the formation of the two isomers at the newly formed α carbon of the amino acid portion, in a ratio ranged from 2:1 to 10:1, except in the case of the β-lactam **19**{4;1} (entry 4) which gave only one of the diastereoisomers.[26]

In general, the use of phenylboronic acid (**8**{1}) (entries 1–6), *trans*-2-phenyl-vinylboronic acid (**8**{2}) (entries 7–12) and *trans*-1-octen-1-yl boronic acid (**8**{3}) (entries 13–17), gave high yields of the corresponding β-lactams. In the case of 6-methoxy-2-naphtalene- and 4-methoxyphenyl boronic acids, with electron-rich substituents, yields and purities were lower (entries 18–24). The increase in electron density could destabilize the active intermediate **9** (see Scheme 1), leading to a decrease in yields.[27]

In conclusion, we have developed an efficient strategy for the rapid generation of libraries of biologically promising β-lactams. Interestingly, a large number of compounds can be synthesized using this methodology, because this synthesis includes at least two diversity points. Biological evaluation of these compounds against different targets is currently in progress, and will be published in due course.

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24. General procedure for the library of β-lactams bearing nonproteinogenic α-amino acid moieties: Commercially available Fmoc-glycine tethered to the solid support **11** (0.5 g, 0.3 mmol) was used as starting material and then deprotected by treatment with 30% piperidine in DMF (3 ml). After stirring for 50 min at room temperature, the mixture was filtered and washed successively with DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), MeOH (3 × 5 mL), CH_2Cl_2 (1 × 5 mL), and dried under high vacuum to afford resin **12** which was taken immediately onto the next step. The solid-supported amine **12** was suspended in anhydrous DMF containing 1% acetic acid (3 mL) and the corresponding aldehyde (**13**) (5 equiv) was added. The reaction was stirred for 45 min at room temperature under nitrogen atmosphere, after which the resin was filtered, washed with DMF (3 × 3 mL), and resubjected to the same reaction conditions for 45 min. After filtration, the resin **14** was sequentially washed with CH_2Cl_2 (3 × 5 mL), AcOEt (3 × 5 mL), MeOH (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL), and finally dried under high vacuum.
To a suspension of support-bound aldimine **14** (0.3 mmol) in CH_2Cl_2 (3 mL) at 0 °C, triethylamine (0.83 mL, 6 mmol, 20 equiv) and acyl chloride **15** (4.5 mmol, 15 equiv) were successively added dropwise. After 5 min at the same temperature, the mixture was stirred overnight at room temperature filtered, washed successively with CH_2Cl_2 (3 × 5 mL), AcOEt (3 × 5 ml), MeOH (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL), and dried under high vacuum affording the support-bound β-lactam **16**. Then, after Fmoc removal, resin **17** was swelled in CH_2Cl_2 (4 mL) and the corresponding organoboronic acid (9 equiv, 2.7 mmol) and glyoxylic acid monohydrate **6** (9 equiv, 248.5 mg, 2.7 mmol) were added. The reaction was stirred at room temperature. The obtained resin was filtered, washed with CH_2Cl_2 (3 × 5 mL), AcOEt (3 × 5 ml) and MeOH (3 × 5 mL) in an alternating fashion and drying in vacuo to afford the immobilized β-lactam **18**. Finally, a suspension of **18** in 10% TFA solution in CH_2Cl_2 (3 mL) was stirred at room temperature for 50 min. The mixture was filtered and the filtrate was evaporated under reduced pressure and subsequently crude **19** were analized by HPLC–MS.
25. *Data of representative β-lactam products **19** (as their methyl esters)*: Methyl ester of compound **19**{1;1} as an inseparable mixture of diastereoisomers: IR (film) 1760 (β-lactam) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) discernible data for the major isomer δ 2.28 (s, 3H), 3.54 (d, J = 18 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 4.47 (d, J = 18 Hz, 1H), 4.49 (m, 1H), 4.58 (d, J = 4.8 Hz, 1H), 5.01 (d, J = 4.8 Hz, 1H), 6.95 (m, 2H), 7.10–7.49 (8 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 41.0, 51.8, 52.3, 61.8, 67.4, 73.5, 128.3, 128.5, 128.6, 128.7, 128.8, 129.0, 129.7, 133.8, 166.8, 168.3, 171.0; anal. HRMS calcd for $C_{22}H_{25}N_2O_5$ ([M+H]$^+$, m/z): 397.1758; found: 397.1750. Methyl ester of compound **19**{1;2} as an inseparable mixture of diastereoisomers: IR (film) 1755 (β-lactam) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.53 (d, J = 18 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 3.85 (m, 1H), 4.45 (d, J = 18 Hz, 1H), 4.65 (d, J = 4.6 Hz, 1H), 4.98 (d, J = 4.6 Hz, 1H), 6.09 (m, 2H), 7.21–7.38 (10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 41.0, 51.7, 52.4, 61.9, 65.8, 73.8, 122.7, 126.5, 127.8, 128.3, 128.5, 128.6, 134.4, 134.6, 136.4, 167.8, 168.4, 171.3; Anal. HRMS calcd for $C_{24}H_{27}N_2O_5$ ([M+H]$^+$, m/z): 423.1914; found: 423.1909. Methyl ester of compound **19**{1;5} as an inseparable mixture of diastereoisomers: IR (film) 1761 (β-lactam); ^1H NMR (300 MHz, $CDCl_3$) discernible data for the major isomer δ 2.24 (s, 3H), 3.54 (d, J = 18 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 3.89 (s, 3H), 4.47 (d, J = 18 Hz, 1H), 4.49 (s, 1H), 4.57 (d, J = 4.8 Hz, 1H), 4.97 (d, J = 4.8 Hz, 1H), 6.89–7.67 (11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 41.0, 51.6, 52.3, 55.3, 62.0, 67.6, 73.9, 105.5, 118.8, 126.6, 127.0, 127.8, 128.2, 128.4, 128.5, 128.6, 129.5, 130.1, 134.5, 134.6, 157.9, 167.7, 168.4, 171.7; anal. HRMS calcd for $C_{27}H_{28}N_2NaO_6$ ([M+H]$^+$, m/z): 499.1845; found: 499.18332. Methyl ester of compound **19**{3;2} as an inseparable mixture of diastereoisomers: IR (film) 1760 (β-lactam); ^1H NMR (300 MHz, $CDCl_3$) discernible data for the major isomer δ 2.29 (s, 3H), 3.48 (d, J = 17.8 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 3.75 (s, 3H), 3.85 (m, 1H), 4.45 (d, J = 17.8 Hz, 1H), 4.56 (d, J = 4.5 Hz, 1H), 4.92 (d, J = 4.5 Hz, 1H), 6.08 (m, 2H), 6.87–7.38 (9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.8, 40.8, 51.7, 52.3, 55.2, 61.2, 65.5, 73.4, 113.7, 122.6, 125.9, 126.5, 127.8, 128.4, 128.5, 130.0, 134.6, 136.4, 159.9, 167.6, 168.4, 171.3; anal. HRMS calcd for $C_{25}H_{28}N_2NaO_6$ ([M+H]$^+$, m/z): 475.18396; found: 475.18336.
26. Absolute configuration of major or exclusive diasteroisomer (racemic mixture) obtained could not be determinated.
27. Schlienger, N.; Bryceb, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023.