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Solid phase β-lactams synthesis using the Staudinger reaction, monitored by ^{19}F NMR spectroscopy

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Abstract—We report the use of ^{19}F NMR as a simple means to monitor reactions on a solid phase. Multi-step sequences including protection, coupling, deprotection, condensation, cycloaddition and cleavage steps are described in the case of multicomponent reactions involving fluorinated α-aminoesters, aldehydes and acid chlorides.

1. Introduction

The fast development of Solid-Supported Combinatorial Chemistry has increased in a spectacular way the complexity and the diversity of reactions using solid support.[1–9] This has resulted in a crucial need for non-destructive, simple and effective analytical methods to control and optimize such reactions.[10,11] Indeed, the classical chromatographic techniques, useful for the study of reactions in solution, cannot be used as long as the starting materials, substrates and reagents remain attached to the solid support. In order to solve the lack of quantitative informations on the advancement of reactions, and to control the possible synthetic problems such as unexpected isomerization reactions or formation of secondary products, it is necessary to have useful methods, beside classical IR spectroscopy,[12–16] to analyze the products still anchored to the resins.

We previously showed that the imines of alkyl glyoxylates act as good partners for Diels–Alder[17–19] and Staudinger cycloadditions.[20] The imine of methyl glyoxylate obtained from L-threonine, was used successfully in the stereoselective synthesis of optically pure β-lactamic-α-amino esters.[21] As part of our program directed towards the development of the Staudinger reaction on solid-phase, we considered the use of imines coming from commercially available fluorinated α-amino-acids. Thus, the three chemical functions already present in these substrates can be used for the realization of the following synthetic pathway: the acid function is used to anchor the substrate on a Merrifield or Wang resin; the amine function is transformed into the corresponding imine moiety by the condensation of an aldehyde and finally, the fluorine atom is used as an analytical probe for the recording of NMR spectra. Thus, each of the chemical products linked to the resin is characterized by a single ^{19}F NMR-signal while the respective chemical shift value is related to each chemical step according to the close group modifications. The ^{19}F NMR spectroscopy shows the following advantages: great sensitivity due to the natural abundance of ^{19}F and broad spreading out of the chemical shift values related to the strong polarizability of the fluorine atom. Consequently, the simplicity of the analytical follow-up—both qualitative and quantitative—allows the rapid development of any new synthetic step. In addition, such a simple technique is able to produce a good quality spectrum in a usual NMR tube with an ordinary NMR instrument. Indeed, the method is entirely based on the fact that the resolution allows distinguishing between the different species bond to the resin.

Manatt and colleagues (1980) were the first to use ^{19}F NMR to control the advancement of peptide synthesis on Merrifield resin.[22] Starting from this observation, this technique was used successfully in several studies,[23–30] showing undeniable advantages such as save of time, money and specific instrumentations compared to more sophisticated techniques, such as magic angle spinning,[31–36] as well as presaturation of the signals of the support,[37] generally applied to the common nuclei such as ^{1}H and ^{13}C NMR and others.[38–40] However, the limitation of the simple method is reached when the chemical shifts difference between the substrate and the subsequent product (or by-product) become lower than the resolution. Such limitations, due to the solid state NMR interaction that broaden lines, could be overcome if High Resolution Magic Angle Spinning techniques were used.

Keywords: solid-phase synthesis; ^{19}F NMR spectroscopy; α-amino-esters; β-lactams; Staudinger cycloaddition.

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In this paper we thus report the effectiveness, the simplicity but the limitations of ^{19}F NMR for the follow-up of a complete chemical sequence using Merrifield and Wang resins including the anchoring, deprotection, condensation, cycloaddition and finally cleavage reactions.

2. Results and discussion

2.1. Solid-phase synthesis

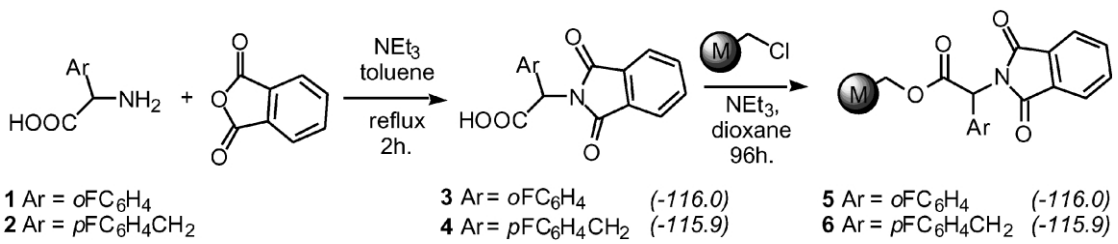
2.1.1. Protected amino-acid attachment to the solid support followed by deprotection of the amine function. *ortho*-Fluorophenylglycine **1** and *para*-fluorophenylalanine **2**, protected as their respective phthalimide derivatives **3** and **4**, were easily linked to Merrifield resin (Scheme 1) *via* a classical synthetic method using triethylamine as a base to give the corresponding supported-compounds **5** and **6**.[41] In the following Schemes, we indicate in italic and between brackets, the observed chemical shift value of the ^{19}F signal of the considered compound.

The chemical reaction follow-up using ^{19}F NMR spectroscopy shows that the release of the amine function leading to resin **7** is not as simple as previously predicted.[41] Indeed, the hydrazine which has been used to cleave the phthalimide group of **5**, also leads to formation of the hydrazide derivative **9** thus cleaving, partially or totally, the linkage ester of **5** (Scheme 2).

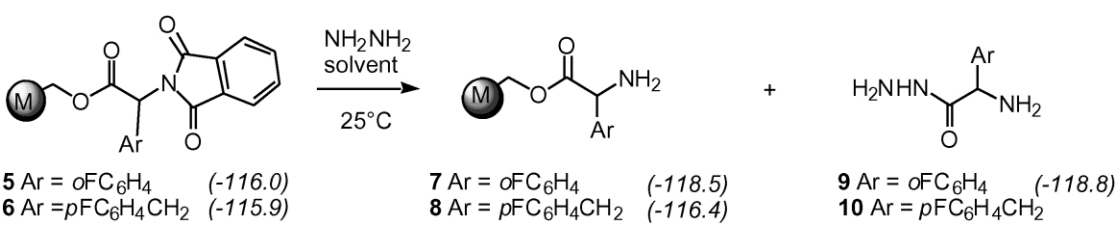
The ^{19}F NMR analysis of both **7** and the washed residues containing **9**, made possible the optimization of the amine deprotection by completely avoiding the hydrazide formation, using 3 equiv. of hydrazine in ethanol, at room temperature during 48 h. The use of a large excess of hydrazine led to the formation of **9** whereas a shorter reaction time, or the use of DMF as solvent, gave only a partial release of the amine group and consequently led to the formation of a mixture of resins **5** and **7**. The chemical shift value observed for the hydrazide **9** (−118.8 ppm) is very close to that of methyl DL-2-fluorophenylglycine ester **21** (−118.9 ppm), showing that the formation of **9** involved the elimination of the phthaloyl group. On the other hand, in identical experimental conditions, resin **6** was transformed into **8** without the release of corresponding hydrazide **10**. Consequently, thereafter, we preferred to start from the respective *N*-Boc-protected fluorinated amino acids **11** and **12** (Scheme 3). The anchoring to the Merrifield resin was carried out in a dioxane/triethylamine mixture, while the action of trifluoroacetic acid (2×10 min at room temperature) on resins **13** and **14**, totally induced the release of the amine group.

The ^{19}F chemical shift values observed for resins **7** and **8**, are very close—or even identical—to those observed in solution, for their corresponding methyl esters analogues (methyl *ortho* fluorophenylglycine ester (**21**): −118.9 ppm, methyl *para* fluorophenylalanine ester (**22**): −116.4 ppm) respectively.

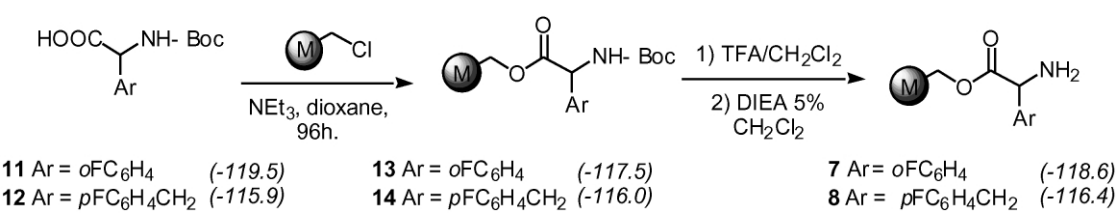
In the case of the Wang resin, the fluorinated α-amino acids were linked after protection using the Fmoc group. The



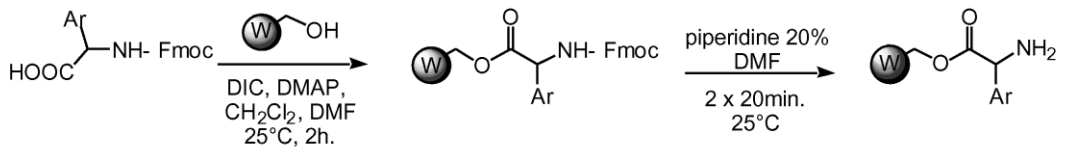
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

release of the respective free amine of **17** and **18** resulted from the action of a solution of 20% piperidine in DMF. This procedure had to be repeated twice in order to be quantitative (Scheme 4). Reproducibility of these results has been confirmed by the systematic analysis of the different resins.

2.1.2. Imine formation. Merrifield resin-bound amines **7** and **8** reacted with 20 equiv. of benzaldehyde in a 1:1 mixture of methyl orthoformiate and dichloromethane as solvent (Scheme 5).[42] These chemical transformations have been easily followed up using ^{19}F fast NMR analysis due to a significative chemical shift variation (+0.3 ppm (from **7** to **23**) and −0.2 ppm (from **8** to **24**)).

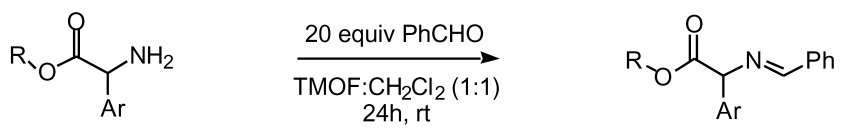
Using the same experimental conditions, the Wang resin-bound amines **19** and **20** were transformed into imines **25** and **26**, respectively. Despite the small difference in chemical shifts observed between the resin-amine signals in **19** and **20**, and the resin-imine signals in **25** and **26** (between 0.1 and 0.3 ppm), the reproducibility of these values was significant enough to follow this transformation until its term. At room temperature, the optimal experimental reaction time was 24 h.

The similar formation of methyl glyoxylate imines was unsuccessful. It has to be reported, however that using standard liquid phase experimental reaction conditions (3 Å-molecular sieves, CH_2Cl_2, rt), the protected threonine efficiently condenses with methyl glyoxylate.[21] The experimental studies were carried out at room temperature using both Merrifield and Wang resin, by modifying the quantity of methyl glyoxylate (4–20 equiv.), the reaction time (3–24 h), and the nature of the solvent used (TMOF, TMOF–CH_2Cl_2 mixture). IR analysis of the resins provided poor informations compared to ^{19}F NMR analysis (showing several signals). Thus, condensation of methyl glyoxylate on the Wang resin-bound amine **19** gave a mixture of compounds highlighted by ^{19}F NMR technique (peaks centered at −113.4 ppm) whereas in the case of the Wang resin-bound amine **20**, peaks centered at −115.7 ppm were observed. Thereafter, we demonstrated that these mixtures did not allow the Staudinger reaction.

2.1.3. Staudinger reaction and cleavage step. Using the Merrifield resin-bound imine **24** in dichloromethane, the cycloaddition was carried out between −78°C and room temperature by addition of benzyloxyacetyl chloride (15 equiv.) in the presence of triethylamine (20 equiv.) (Scheme 6). ^{19}F NMR spectra of resin-bound cycloadduct **31** showed two peaks (−115.9 and −116.1 ppm) corresponding to the two *cis* diastereoisomers **30** already obtained in liquid phase (respectively −115.9 and −116 ppm) as described later on. Cleavage of resin **31** using sodium methylate resulted in the two *cis* β-lactam derivatives **34** with a 67:33 ratio as shown by ^{1}H NMR and GC analyses. After purification of the reaction mixture by chromatography on silica gel, the two diastereoisomers **34a** and **34b** were obtained in 68% yield (based on an initial loading of the Merrifield resin of 1.2 mmol of Cl/g).

In a similar way, the Merrifield resin-bound imine **23** was treated with phenoxyacetyl or benzyloxyacetyl chlorides. The advancement of the reaction was followed by ^{19}F NMR and comparison of the chemical shifts with those observed in solution. GC analysis of the mixtures obtained from the cleavage steps showed the presence of the respective cycloadducts **32** and **33** in the same diastereoisomeric ratio as the one measured using ^{19}F NMR on resins **29** and **30**, respectively. Thus, resins **29** and **30** were transformed into the two corresponding *cis* diastereoisomeric mixtures **32a** and **32b**, and **33a** and **33b**, respectively, in 81 and 87% yield with respective diastereoisomeric ratios of 73:27 and 77:23.

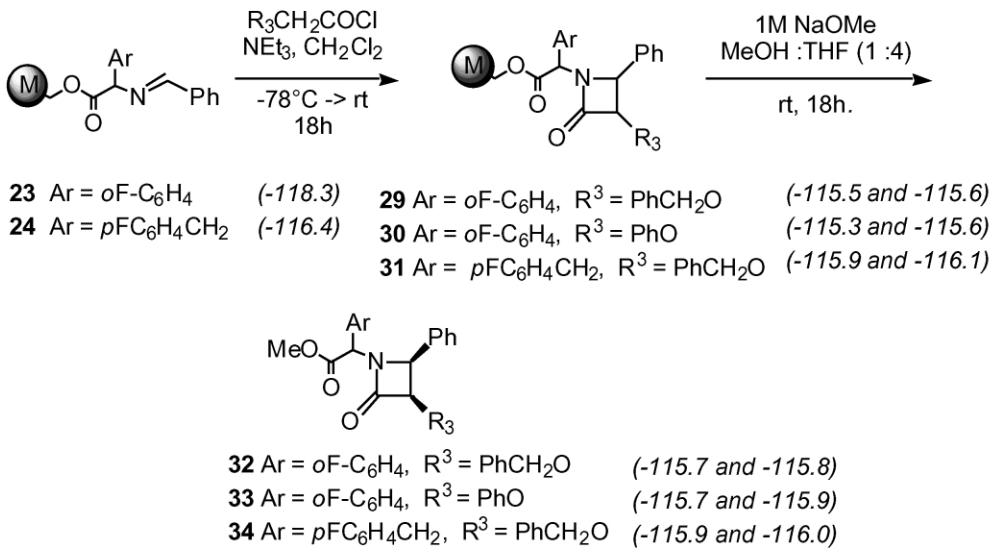
Using the Wang resin, we developed a β-lactam ring formation from imine **26** prepared from DL-*para*-fluorophenylalanine (Scheme 7).



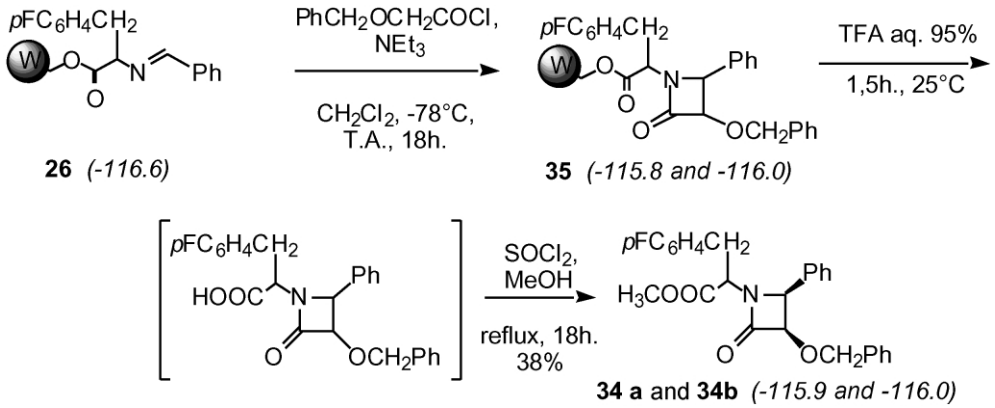
7 R = M Ar = oFC_6H_4 *(-118.6)*
8 R = M Ar = $pFC_6H_4CH_2$ *(-116.4)*
19 R = W Ar = oFC_6H_4 *(-118.6)*
20 R = W Ar = $pFC_6H_4CH_2$ *(-116.3)*
21 R = Me Ar = oFC_6H_4 *(-118.9)*
22 R = Me Ar = $pFC_6H_4CH_2$ *(-116.4)*

23 R = M Ar = oFC_6H_4 *(-118.3)*
24 R = M R = M Ar = $pFC_6H_4CH_2$ *(-116.6)*
25 R = W R = W Ar = oFC_6H_4 *(-118.5)*
26 R = W R = W Ar = $pFC_6H_4CH_2$ *(-116.6)*
27 R = Me R = Me Ar = oFC_6H_4 *(-118.5)*
28 R = Me R = Me Ar = $pFC_6H_4CH_2$ *(-116.6)*

Scheme 5.



Scheme 6.



Scheme 7.

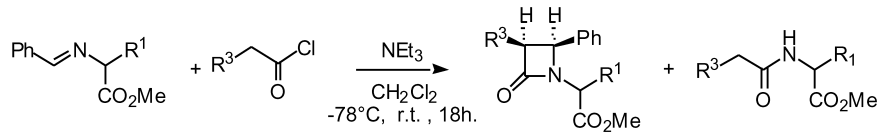
The cycloaddition step has been performed under the same experimental reaction conditions as those already used for the Merrifield resin. The ^{19}F NMR spectra of **35** showed two peaks at −115.8 and −116.0 ppm, corresponding to the cycloadducts obtained in solution (−115.9 and −116.0) or on the Merrifield resin (−115.9 and −116.1). The treatment of **35** with a 95% trifluoroacetic acid aqueous solution, followed by a standard esterification reaction of the reaction mixture using thionyl chloride in methanol, gave β-lactams **34a** and **34b** in 38% yield with a 65:35 ratio (with an initial loading of the Wang resin of 1.0 mmol/g). In addition, the use of sodium methylate in methanol was also applied to **35** and led to a *cis* cycloadduct mixture of **34a** and **34b**, with a diastereoisomeric ratio of 69:31 in 87% yield.

^{19}F NMR was finally used to monitor all the synthetic sequences leading to compounds **1** to **34**. Good quality spectra, equal or better than 10 Hz resolution were obtained using a classical liquid NMR probe at low field (Bruker AC100 operating at 94.2 MHz for ^{19}F observation). Approximately 80 mg of resin were swelled in 0.4–0.5 mL of $CDCl_3$ for 15 min and then sonicated for 1 min to enhance the homogeneity of the considered mixture. We assume that sonication improve the swelling of the resin-bound compound without breaking any chemical bond. The ^{19}F NMR linewidth for the compounds linked to the resin was generally about 40 Hz.

2.2. Solution-phase synthesis

We have carried out the same series of reactions in solution, in order to compare the results with those previously obtained on solid phase. We focused our attention on the imines of DL-*ortho*-fluorophenylglycine **1**, DL-*para*-fluorophenylalanine **2** and their corresponding non-fluorinated analogs. We applied the Staudinger's experimental reaction conditions described by Ojima to imines of the benzaldehyde **27**, **28**, **35** and **36**: Addition to the imine of 2.1 equiv. of triethylamine in a dichloromethane solution at −78°C, followed by the dropwise addition of 2 equiv. of benzyloxyacetyl and phenoxyacetyl chlorides. After the usual workup, the GC analysis of the crude product showed beside the desired *cis* β-lactams, the presence of unreacted imines or amides corresponding to the hydrolysis of the iminium salt itself resulting from the condensation of acid chloride with the corresponding imine. Then a preparative chromatography on silica gel gave the expected cycloadducts as a diastereoisomeric mixture, as reported in Table 1.

Table 1. Staudinger reactions in solution



27-28 and 35-36 **32-34 and 37-39** **40-45**

Entry	R^1	Imine	R^3	Acyl chloride	Product ratio (%)[a]			β-Lactams **5**	
					Imine	β-lactam	Amide	Yield[b]	d.r.[c]
1	C_6H_5	**3a**	$PhCH_2O$	**4a**	**3a** (0)	**5a** (92)	**6a** (8)	43	67/33
2	$C_6H_4CH_2$	**3b**	$PhCH_2O$	**4a**	**3b** (37)	**5b** (63)	**6b** (0)	34	58/42
3	$C_6H_4CH_2$	**3b**	PhO	**4b**	**3b** (7)	**5c** (93)	**6c** (0)	51	55/45
4	*o*F-C_6H_4	**3c**	$PhCH_2O$	**4a**	**3c** (33)	**5d** (57)	**6d** (10)	35	74/26
5	*o*F-C_6H_4	**3c**	PhO	**4b**	**3c** (2)	**5e**(95)	**6e** (3)	57	74/26
6	*p*F-$C_6H_4CH_2$	**3d**	$PhCH_2O$	**4a**	**3d** (68)	**5f** (31)	**6f** (1)	20	63/37

[a] Determined by GC analysis of the crude product.
[b] (%) Determined after chromatographic purification.
[c] The diastereoisomeric ratio was determined by GC analysis and by ^1H and ^{19}F NMR spectroscopy.

The value of the coupling constants of the C3 and C4 vicinal protons (~4.7 Hz) is in agreement with the *cis* β-lactam cycles. The diastereoisomeric ratios were determined by ^1H, ^{19}F NMR and GC analyses. Interestingly, the diastereoisomeric excesses obtained with the fluorinated amino acids were slightly higher than those obtained with the corresponding unfluorinated analogues. This result was even more pronounced with the use of DL-*ortho* fluorophenylglycine, for which the fluorine atom is located closer to the reaction center. The diastereoisomeric ratios obtained for the cycloadducts using solid phase synthesis (Merrifield and Wang resins) were close to those obtained in liquid phase while yields were higher in the solid phase case. The syntheses described herein complete the results already obtained by Gallop et al. using Sasrin resin.[43]

3. Conclusion

We have developed some very versatile multi-steps solid phase syntheses for the preparation of β-lactams from imines of benzaldehyde derived from fluorinated α-amino acids. The easy control of the reactions was performed using ^{19}F NMR on the intermediates, using classical liquid NMR parameters. This alternative to more sophisticated techniques such as HR MAS—not always available—works well provided the chemical shifts difference between the substrate and the subsequent product is higher than 0.1 ppm.

4. Experimental

4.1. General methods and materials

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. CH_2Cl_2 was dried over potassium carbonate distilled and stored over 4 Å molecular sieves. Et_3N was dried over KOH (pellets). Reactions were carried out under an atmosphere of argon. TLC was carried out on Merck silica gel 60 F_{254} analytical Plate (0.2 mm thickness) visualised by using UV light, iodine vapor, or by means of a 5% ethanolic solution of molybdophosphoric acid. Column chromatography was performed using Macherey–Nagel silica gel 60 (63–200 μm). GC was carried out on a Shimadzu GC-14A chromatograph with a J&W capillary column SE 30 (5%), 30 m length, 0.32 mm i.d., with 1 bar N_2 carrier gas pressure. The chromatograph was interfaced with a Shimadzu C-R6A chromatopac integrator. Retention times (t_R) are given for the following oven programmed heating (injector at 250°C): from 110°C (5 min) to 280°C (5 min) at 3°C/min rate. Distillations with Kugelrohr apparatus were performed on a Büchi GRK-51 instrument. ^1H and ^{13}C NMR spectra were obtained on a Brucker AC 200 spectrometer, for solutions in $CDCl_3$. Chemical shifts are reported as δ values in parts per million (ppm) relative to residual $CHCl_3$ (δ_H 7.27 ppm) and $CDCl_3$ (δ_C 77.23 ppm) as internal standards respectively. H-decoupled ^{19}F NMR spectra were recorded with a Bruker AC 100 spectrometer operating at 94.2 MHz for resin suspensions in $CDCl_3$. ($CFCl_3$ δ 0.00 ppm as internal standard). A standard pulse sequence was used (pulse 8 μs; relax. delay 2 s; 64 scans). The samples were prepared in a 5-mm i.d. standard NMR tube, with the appropriate resin (ca. 80 mg), swelled in $CDCl_3$ (0.5 mL) and sonicated for 1 min. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Coupling constants *J* are given in Hertz. All structures were assigned after extensive 2D NMR studies (COSY and HSQC). Infrared (IR) spectra were obtained using an IR-FT Nicolet 20 SXB spectrophotometer (KBr pellets) and are reported in cm^{-1}. Solid-phase syntheses were performed on a Merrifield resin (France Biochem or Sigma; 200–400 mesh, approx. 1.2 mmol/g) or a Wang resin (Advanced ChemTech PS/1%DVB, 100–200 mesh, 1.0 mmol/g).

4.2. *N*-Phthaloyl-protected fluoro-amino acids 3 and 4

Finely powdered phthalic anhydride (876 mg, 5.9 mmol) and Et_3N (80 μL) were added to a suspension of the fluoroamino acid (DL-2-fluorophenylglycine **1** or DL-4-fluorophenylalanine 2, 5.9 mmol) in toluene (20 mL). The mixture were refluxed for 3 h. After solvent evaporation, the crude solid residue was diluted with cold water (12 mL) and 0.12 mL HCl were added. After stirring for 3 h at room temperature, the filtration then washing with cold H_2O

(10 mL) and drying (IR lamp) afforded a white solid: *N*-phthaloyl-DL-2-fluorophenylglycine **3**, yield 84%, ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: −116.0, GC t_R 20 min, or *N*-Phthaloyl-DL-4-fluorophenylalanine **4**, yield 97%, ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: −115.9; GC t_R 28 min.

4.3. Merrifield resin-bound *N*-phthaloyl-protected fluoro-amino acids 5 and 6

To the Merrifield resin (1 g, 1.2 mmol), swelled in dioxane (15 mL), was added the appropriate *N*-phthaloyl-protected fluoro-amino acid (3 or 4, 6 mmol) and the reaction was mixed at 101°C for 96 h. The resin was filtered, washed with a 1:1:1 solution of dioxane–H_2O–HCl (v:v:v, 60 mL), 1:1 solution of dioxane–H_2O (v:v, 60 mL), ethanol (60 mL) and CH_2Cl_2, dried in vacuo overnight and analyzed by ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: **5** −116.0; **6** −115.9.

4.4. General procedure for the deprotection of Merrifield resin-bound *N*-phthaloyl fluoro-amino acids 5 and 6

To the appropriate phthaloyl Merrifield resin (**5** or **6**, 200 mg, 0.2 mmol), swelled in ethanol (3 mL) was added hydrazine monohydrate (3 equiv. 0.6 mmol) and the suspension was mixed at room temperature for 48 h. The resin was filtered, washed with EtOH (2×20 mL), CH_2Cl_2 (2×20 mL), and dried in vacuo overnight. Resin-bound amino acid **7** and **8** were then analyzed ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: **7** −118.5; **8** −116.4. The combined organic washes were evaporated and the residues were also analyzed by NMR ^{19}F ($CDCl_3$, 94.2 MHz) hydrazide **9** δ: −118.8.

4.5. General procedure for the deprotection of Merrifield resin-bound *N*-*t*Boc-fluoro-amino acids 13 and 14

The appropriate *t*Boc-protected Merrifield resin (**13** or **14**, 600 mg) was treated at room temperature with a 1:1 solution of TFA/CH_2Cl_2 (v:v, 10 mL) for 10 min, washed with CH_2Cl_2 (20 mL), and treated again with a 1:1 solution of TFA/CH_2Cl_2 (v:v, 10 mL) for 10 min. The resin was shaken twice in 15 mL of a 5% solution of iPr$_2$NEt in CH_2Cl_2 (v:v). The collected resin (**7** or **8**) was washed with CH_2Cl_2 (2×40 mL), dried in vacuo, and analyzed by NMR ^{19}F as previously.

4.6. General procedure for the preparation of *N*-*t*Boc-protected fluoro-amino acids 11 and 12

To the amino-acid **1** or **2** (3 mmol) in a 2:1:1 mixture of dioxane/H_2O/NaOH 1N (v:v:v, 12 mL) cooled to 0°C, di-*tert*-butyl-pyrocarbonate (720 mg, 3.3 mmol) was added, under stirring. The resulting mixture was shaken at room temperature for 30 min then cooled to 0°C. EtOAc was added (9 mL) and the resulting solution was acidified to pH 2–3 by addition of a 10% solution of citric acid in H_2O. The aqueous layer was further extracted with EtOAc (3×20 mL) and the combined organic layers were washed with H_2O (2×10 mL), dried (Na_2SO_4) and concentrated to afford the *N*-*t*-Boc-amino-acid **11** or **12** quantitatively. *N*-*t*Boc-DL-2-fluorophenylglycine **11** NMR ^{19}F ($CDCl_3$, 94.2 MHz) δ: −119.5; GC t_R 19 min; *N*-*t*Boc-DL-4-fluorophenylalanine **12** ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: −115.9; GC t_R 21 min.

4.7. Merrifield resin-bound *N*-*t*-Boc-protected fluoro-amino acids 13 and 14

To the Merrifield resin (482 mg, 0.58 mmol), swelled in dioxane (30 mL) were added the appropriate *N*-*t*-Boc-fluoro-amino-acid (**11** or **12**, 2.9 mmol) followed by Et_3N (1.22 mL) and the reaction mixture was refluxed for 96 h. The reaction was filtered and the resin whashed with a 1:1:1 solution of dioxane–H_2O–HCl (v:v:v; 60 mL), 1:1 solution of dioxane–H_2O (v:v; 60 mL), dioxane (60 mL), EtOH (60 mL), CH_2Cl_2 (60 mL). The resins were dried in vacuo and analyzed by ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: **13** −117.5; **14** −116.0.

4.8. Fmoc-fluoro-amino acids 15 and 16

The fluoro-amino acid (**1** or **2**, 5 mmol) was dissolved in a 10% Na_2CO_3 solution (10 mL) at 0°C, and then the 9-fluorenylmethyl-*N*-hydroxysuccinimide (Fmoc-Osu, 4.2 mmol) in dioxane (10 mL) was added. The resulting solution was mixed at room temperature until no Fmoc-Osu remains by TLC analysis (typically 5 h). The mixture is diluted in H_2O (120 mL) and the aqueous layer is extracted with Et_2O (30 mL) and EtOAc (2×10 mL). The aqueous layer was then cooled to 0°C, acidified to pH 2 by addition of HCl 6N, and the resulting suspension was extracted by EtOAc (6×10 mL). The combined organic extracts were washed with a saturated NaCl solution, dried over Na_2SO_4, and concentrated by evaporation. The product was obtained by precipitation upon addition of petroleum ether. Fmoc-DL-2-fluorophenylglycine **15**: yield 83%; ^{19}F NMR (CD_3OD, 94.2 MHz) δ: −115.4; Fmoc-DL-4-fluorophenylalanine **16**: yield 75%; ^{19}F NMR (CD_3OD, 94.2 MHz): δ: −114.95.

4.9. Wang resin-bound Fmoc-protected fluoro-amino acids 17 and 18

Wang resin (1 g, 1 mmol/g), DMAP (0.049 g, 0.4 mmol), and Fmoc-protected fluoro amino acid **15** or **16** (4 mmol) were suspended in a 4:3 solution of CH_2Cl_2/DMF (v:v, 17.5 mL). To this suspension DIC (4 mmol, 0.625 mL) was added and the resulting mixture was shaken for 2 h at room temperature. The resin was collected by filtration, washed with DMF (4×10 mL) and CH_2Cl_2 (4×10 mL), dried in vacuo, and analyzed by ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: **17** −117.5; **18** −115.7.

4.10. Deprotection of the Wang resin-bound Fmoc-fluoro-amino acids 17 and 18

To the Fmoc-Wang resins (**17** or **18**, 0.5 g) was added 20% piperidine/DMF solution (5 mL), and the suspension was mixed at room temperature for 20 min. The resin was filtered, and the same treatment repeated again. The resin was filtered, washed with DMF (2×10 mL), CH_2Cl_2 (2×10 mL), dried in vacuo overnight, and analyzed by ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: **19** −118.6; **20** −116.3.

4.11. General procedure for the preparation of methyl esters of fluoro-amino acids 21 and 22

To the fluoro-amino acid (**1** or **2**, 2.95 mmol) suspended in MeOH (10 mL), $SOCl_2$ (280 μL 3.84 mmol) was slowly added, and the mixture was refluxed for 18 h. After evaporation of MeOH and excess of $SOCl_2$, the amino ester hydrochloride, was suspended in CH_2Cl_2 (10 mL) and Et_3N was added (826 μL 5.8 mmol). The mixture was stirred at room temperature for 10 min and concentrated in vacuo. The crude residue is suspended in Et_2O, and after filtration of Et_3N, HCl and evaporation of the solvent, amino-ester was obtained quantitatively. Methyl 2-fluorophenyl glycinate **21**: GC t_R 6.5 min; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.37–7.00 (m, 4H, C_6H_4F); 4.83 (s, 1H, CH); 3.69 (s, 3H, $COOCH_3$); 2.03 (s, 2H, NH_2); ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: −118.9.; methyl 4-fluorophenyl alaninate **22**: GC t_R 8.4 min; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.27–6.94 (m, 5H, C_6H_5); 3.74 (t, 1H, CH); 3.70 (s, 3H, $COOCH_3$); 2.94 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: −116.4.

4.12. Solution phase procedure for the preparation of imines 27 and 28

To a stirred solution of benzaldehyde (165 μL, 1.63 mmol) in CH_2Cl_2 (20 mL) at room temperature, under argon, were added the α-amino-ester (**21** or **22**, 1.63 mmol) and 300 mg of 4 Å molecular sieves. The mixture was stirred until no aminoester remains by GC analysis (typically 24 h), and then filtered. The solvent was evaporated in vacuo to give the corresponding crude imine. Methyl (benzylidene-amino)-(2-fluorophenyl)-acetate 27 ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.35 (s, 1H, CH═N); 7.81–6.99 (m, 9H, C_6H_5 and C_6H_4F); 5.5 (s, 1H, CH); 3.69 (s, 3H, $COOCH_3$); NMR ^{19}F ($CDCl_3$, 94.2 MHz) δ: −118.5; GC t_R 21.9 min. Methyl 2-(benzylidene-amino)-3-(4-fluorophenyl)-propionate 28 ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.68 (s, 1H, CH═N); 7.66–7.37 (m, 5H, C_6H_5); 7.25–6.86 (m, 4H, C_6H_4F); 4.12 (m, 1H, CH); 3.73 (s, 3H, $COOCH_3$); 3.22 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ −116.6; GC t_R 22.7 min.

4.13. Solid phase procedure for the preparation of imines 23 and 24

To the appropriate Merrifield resin-amine **7** or **8**, or Wang resin-amine **19** or **20** (0.2 mmol, 1 equiv.), swelled in a 1:1 solution of TMOF/CH_2Cl_2 (v:v, 8 mL), was added benzaldehyde (4 mmol, 20 equiv.) and the reaction mixed at room temperature for 24 h. The resin was washed with CH_2Cl_2 (2×20 mL), MeOH (2×20 mL), CH_2Cl_2 (20 mL), dried in vacuo and analyzed by ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: Merrifield resin-bound imine **23** −118.3; Merrifield resin-bound imine **24** −116.6; Wang resin-bound imine **25** −118.5; Wang resin-bound imine **26** −116.6.

4.14. Solution phase procedure for the synthesis of β-lactams

To a stirred solution of crude imine (**158**, **159**, **139** or **160**, 1 mmol) and Et_3N (2.3 mmol), in dry CH_2Cl_2 (5 mL), under argon, the substituted acid chloride (benzyloxy-acetyl chloride or phenoxy-acetyl chloride, 2.1 mmol)., was added dropwise, via syringe, at −78°C. The resulting mixture was stirred at room temperature for 18 h. Then, the mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), HCl 0.1 M (10 mL), saturated solution of $NaHCO_3$ (10 mL), then with a saturated solution of NaCl. The organic phase was dried over $MgSO_4$, then filtered. The solvent was evaporated under reduced pressure to give the crude β-lactam. A sample of the crude product was used to measure the isomers ratio either by GC and ^{1}H NMR. The product was further purified by silica gel column chromatography, then conveniently characterized.

4.14.1. *cis*-Methyl(3-benzyloxy-2-oxo-4-phenyl-azetidin-1-yl)-(2-fluoro-phenyl)acetate 32a-b. Major isomer: (74%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.96 (m, 14H, 2 C_6H_5 and C_6H_4F); 5.75 (s, 1H, C**H**C_6H_4F); 5.13 (d, 1H, J=4.64 Hz, CH_{cycle}); 5.00 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.16 (m, 2H, C**H**$_2$Ph); 3.75 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169 (C═O); 167 (C═O); 136.3 (C_{ipso} arom); 133.6 (C_{ipso} arom); 130, 129, 128 (CH arom); 124 (C–F); 115 (CHarom); 83.7(**C**HPh); 72.4 (**C**H_2Ph); 62.9 (CH_{cycle}); 53.0 (CH_{cycle}); 52.3 (CH_3); GC t_R 38.6 min.; minor isomer (26%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.96 (m, 14H, 2 C_6H_5 and C_6H_4F); 5.51 (s, 1H, C**H**C_6H_4F); 4.88 (d, 1H, J=4.62 Hz, CH_{cycle}); 4.70 (d, 1H, J=4.62 Hz, CH_{cycle}); 4.16 (m, 2H, C**H**$_2$Ph); 3.62 (s, 3H, $COOCH_3$). ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: −115.7; −115.8; GC t_R 39.1 min; calcd for $C_{25}H_{22}NFO_4$ C, 71.59; H, 5.29; N, 3.34; found C, 71.49; H, 5.30; N, 3.27.

4.14.2. *cis*-Methyl(3-phenoxy-2-oxo-4-phenyl-azetidin-1-yl)-(2-fluoro-phenyl)acetate 33a-b. Major isomer: (74%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.95 (m, 14H, 2C_6H_5 and C_6H_4F); 5.81 (s, 1H, C**H**C_6H_4F); 5.56 (d, 1H, J=4.64 Hz, CH_{cycle}); 5.32 (d, 1H, J=4.64 Hz, CH_{cycle}); 3.78 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.1 (C═O); 166.2 (C═O); 156.8 (C_{arom}–O); 132.7 (C_{ipso} arom); 131, 130, 129, 128, 127 (CH arom); 124 (C–F); 122 (CH arom); 115 (CH arom); 82.0 (**C**HC_6H_4F); 63.1 (CH_{cycle}); 53.1 (CH_{cycle}); 52.5 (CH_3); GC t_R 37.3 min; minor isomer (26%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.95 (m, 14H, 2 C_6H_5 and C_6H_4F); 5.57 (s, 1H, C**H**C_6H_4F); 5.46 (d, 1H, J=4.62 Hz, CH_{cycle}); 4.93 (d, 1H, J=4.62 Hz, CH_{cycle}); 3.64 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ: 168.4 (C═O); 166.0 (C═O); 157.9 (C_{arom}–O); 132.8 (C_{ipso} arom); 131, 130, 129, 128, 127 (CH arom); 124 (C–F); 122 (CH arom); 115 (CH arom); 81.6 (**C**HC_6H_4F); 63.5 (CH_{cycle}); 53.4 (CH_{cycle}); 52.9 (CH_3). ^{19}F NMR ($CDCl_3$, 94.2 MHz) δ: −115.7; −115.9; GC t_R 37.6 min. Calcd for $C_{24}H_{20}NFO_4$ C, 71.10; H, 4.97; N, 3.45; found C, 71.06; H, 5.06; N, 3.41.

4.14.3. *cis*-Methyl(3-benzyloxy-2-oxo-4-phenyl-azetidin-1-yl)-3-(4-fluoro-phenyl) propionate 34a-b. Major isomer: (63%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.31–6.85 (m, 14H, 2C_6H_5 and C_6H_4F); 4.81 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.67 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.15 (m, 2H, C**H**$_2$Ph); 3.95 (m, 1H, C**H**CH_2); 3.64 (s, 3H, $COOCH_3$); 3.27 (d, 2H, CHC**H**$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 133 (C_{ipso} arom); 132 (C_{ipso} arom); 131–128 (CH arom); 116–115 (CH in C_6H_4F); 83.3 (**C**HCH_2); 72.4 (**C**H_2Ph); 62.9 (CH_{cycle}); 58 (CH_{cycle}); 52.7 (CH_3); 34.7 (CH_2); GC t_R 39.8 min; minor isomer (37%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.31–6.85 (m, 14H, 2 C_6H_5

and C_6H_4F); 4.80 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.61 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.16 (m, 2H, C**H**$_2$Ph); 3.95 (m, 1H, C**H**CH_2); 3.68 (s, 3H, $COOCH_3$); 3.20 (d, 2H, CHC**H**$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 133 (C_{ipso} arom); 132 (C_{ipso} arom); 131, 130, 129, 128 (CH arom); 116, 115 (CH in C_6H_4F); 83.3 (**C**HCH_2); 72.4 (**C**H$_2$Ph); 63.4 (CH_{cycle}); 58 (CH_{cycle}); 52.6 (CH_3); 35.3 (CH_2). NMR ^{19}F($CDCl_3$, 94.2 MHz) δ: −115.9; −116.0; GC t_R 40.6 min; MS: 91 (100), 109 (13), 210 (19), 286 (11), 433 (0.8); calcd for $C_{26}H_{24}NFO_4$ C, 72.04; H, 5.58; N, 3.23; found C, 71.99; H, 5.60; N, 3.15.

4.14.4. *cis*-Methyl (3-benzyloxy-2-oxo-4-phenyl-azetidin-1-yl)-phenyl acetate 37a-b. Major isomer: (67%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.35–6.89 (m, 10H, 2 C_6H_5); 5.5 (s, 1H, C**H**Ph); 5.09 (d, 1H, J=4.57 Hz, CH_{cycle}); 4.95 (d, 1H, J=4.55 Hz, CH_{cycle}); 4.15 (m, 2H, C**H**$_2$Ph); 3.71 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169 (C═O); 167 (C═O); 136 (C_{ipso} arom); 132 (C_{ipso} arom); 129, 128, 127 (CH arom); 83.2 (**C**HPh); 72 (**C**H$_2$Ph); 62.8 (CH_{cycle}); 58.2 (CH_{cycle}); 52.7 (CH_3); GC t_R 38.3 min; minor isomer: (33%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ: 7.35–6.89 (m, 10H, 2 C_6H_5); 5.32 (s, 1H, C**H**Ph); 4.82 (d, 1H, J=4.66 Hz, CH_{cycle}); 4.63 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.08 (m, 2H, C**H**$_2$Ph); 3.54 (s, 3H, $COOCH_3$); NMR ^{13}C ($CDCl_3$, 50 MHz) δ: 168.8 (C═O); 166.9 (C═O); 136 (C_{ipso} arom); 134 (C_{ipso} arom); 129, 128, 127 (CH arom); 83.0 (**C**HPh); 72.3 (**C**H$_2$Ph); 63.1 (CH_{cycle}); 59.6 (CH_{cycle}); 52.5 (CH_3); GC t_R 38.6 min.

4.14.5. *cis*-Methyl 2-(3-benzyloxy-2-oxo-4-phenyl-azetidin-1-yl)-3-phenyl propionate 38a-b. Major isomer: (58%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.30–6.85 (m, 15H, 3 C_6H_5); 4.79 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.69 (d, 1H, J=4.64 Hz, CH_{cycle}); 4.09 (m, 3H, C**H**CH_2 and C**H**$_2$Ph); 3.62 (s, 3H, $COOCH_3$); 3.30 (d, 2H, J=5.12 Hz, CHC**H**$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.9 (C═O); 167.6 (C═O); 137, 136, 133 (C_{ipso} arom); 129, 128, 127 (CH arom); 83 (**C**HCH_2); 72.1 (**C**H$_2$Ph); 62.7 (CH_{cycle}); 58.3 (CH_{cycle}); 52 (CH_3); 35 (CH_2); GC t_R 39.7 min; minor isomer: (42%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.30–6.85 (m, 15H, 3 C_6H_5); 4.78 (d, 1H, J=4.62 Hz, CH_{cycle}); 4.50 (d, 1H, J=4.62 Hz, CH_{cycle}); 4.09 (m, 3H, C**H**CH_2 and C**H**$_2$Ph); 3.67 (s, 3H, $COOCH_3$); 3.23 (d, 2H, J=5.12 Hz, CHC**H**$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.8 (C═O); 167.1 (C═O); 137, 136, 134 (C_{ipso} arom); 129, 128, 127 (CH arom); 83 (**C**HCH_2); 72.3 (**C**H$_2$Ph); 63.4 (CH_{cycle}); 56.5 (CH_{cycle}); 52 (CH_3); 36 (CH_2); GC t_R 40.0 min; calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37; found C, 74.92; H, 6.26; N, 3.17.

4.14.6. *cis*-Methyl 2-(3-phenoxy-2-oxo-4-phenyl-azetidin-1-yl)-3-phenyl propionate 39a-b. Major isomer: (55%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.95 (m, 15H, 3 C_6H_5); 5.34 (d, 1H, CH_{cycle}); 4.88 (d, 1H, J=4.88 Hz, CH_{cycle}); 4.07 (m, 1H, C**H**CH_2Ph); 3.62 (s, 3H, $COOCH_3$); 3.34 (d, 1H, J=5.14 Hz, H_a in CH_2); 3.02 (d, 1H, H_b in CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.6 (C═O); 166.4 (C═O); 136.8 (C_{ipso} arom); 133.2 (C_{ipso} arom); 129, 128, 127 (CH arom); 121 (CH arom); 115 (CH arom); 81.6 (**C**HCH_2); 62.7 (CH_{cycle}); 58.5 (CH_{cycle}); 52.6 (CH_3); 35.3 (CH_2); GC t_R 38.8 min; minor isomer: (45%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.95 (m, 15H, 3 C_6H_5); 5.31 (d, 1H, CH_{cycle}); 4.68 (d, 1H, J=4.62 Hz, CH_{cycle}); 4.07 (m, 1H, C**H**CH_2Ph); 3.67 (s, 3H, $COOCH_3$); 3.27 (d, 1H, J=4.88 Hz, H_a in CH_2); 3.03 (d, 1H, H_b in CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.7 (C═O); 165.9 (C═O); 136.2 (C_{ipso} arom); 132.4 (C_{ipso} arom); 129, 128, 127 (CH arom); 121 (CH arom); 115 (CH arom); 81.4 (**C**HCH_2); 63.5 (CH_{cycle}); 56.6 (CH_{cycle}); 52.5 (CH_3); 35.9 (CH_2); GC t_R 39.1 min; calcd for $C_{25}H_{23}NO_4$ C, 74.79; H, 5.77; N, 3.48; found C, 74.44; H, 5.88; N, 3.21.

4.15. Solid phase (Merrifield or Wang resins) procedure for the synthesis of β-lactams

To the Merrifield-imine resin (**23** or **24**, 0.2 mmol) or Wang-imine resin (**35**, 0.2 mmol) swelled in CH_2Cl_2 (5 mL) was added slowly, at −78°C, Et_3N (560 μL, 4 mmol), and dropwise, the substituted acid chloride R_3CH_2COCl (benzyloxyacetyl chloride or phenoxyacetyl chloride, 3 mmol). The reaction was mixed at room temperature for 18 or 24 h, then filtered. The resin was washed with DMF (2×15 mL), CH_2Cl_2 (2×15 mL), MeOH (2×15 mL), Et_2O (2×15 mL), CH_2Cl_2 (20 mL), and dried in vacuo, to provide resins Merrifield-β-lactam-resin **29**, **30** and **31**, or Wang-β-lactam-resin **35** analyzed by NMR ^{19}F ($CDCl_3$, 94.2 MHz) δ: **29** −115.58 and −115.6; **30** −115.3 and −115.6; **31** −115.8 and −116.1; **35** −115.8 and −116.0.

4.16. General procedure for recovery and analysis of β-lactams from Merrifield resins

To the Merrifield-β-lactam-resin (**29**, **30** or **31**, 150 mg, 0.180 mmol) swelled in a 1:4 MeOH/THF solution (v:v, 6 mL) was added a 1 M solution of NaOMe in MeOH (40 μL) and the suspension was mixed at room temperature 18 h. The resin was filtered, washed with 1:1 solution of MeOH/THF (v:v, 40 mL), THF (40 mL), MeOH (40 mL), and CH_2Cl_2 (40 mL). The combined organic washes were evaporated, after drying, to provide the crude β-lactams analyzed by GC and NMR. For ^{1}H and ^{19}F NMR, see above. GC **32a-b**: (61 mg, 81%) 73:27 t_R 38.6 and 39.1 min; **33a-b**: (63 mg, 87%) 77:23 t_R 37.3 and 37.6 min; **34a-b**: (53 mg, 68%) 67:33 t_R 39.8 and 40.6 min.

4.17. Cleavage of cycloadducts from Wang resin

4.17.1. By TFA treatment and esterification. The resin **35** (150 mg, 0.15 mmol) was treated with a 5% solution of TFA in H_2O (7.5 mL) and the suspension shaken for 1.5 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (2×20 mL). Filtration and evaporation in vacuo produced an oily residue (50 mg) to which $SOCl_2$ (16 μL) was added in MeOH (5 mL), and the mixture was then refluxed for 18 h. Concentration in vacuo afforded 25 mg (38%) of **34a-b** GC 65:35 t_R 39.8 and 40.6 min.

4.17.2. By MeONa/MeOH treatment. To a suspension of resin **35** (150 mg, 0.15 mmol) in a 1:4 solution of MeOH/THF (5 mL) was added a 1 M solution of NaOMe in MeOH (22 μL) and the mixture was shaken for 18 h at room temperature. The resin was separated by filtration, washed with THF (20 mL), MeOH (20 mL), and CH_2Cl_2 (20 mL). The combined organic washes were dried, evaporated, and

the residues were analyzed by GC, as above. **34a**-**b** 69:31 (56 mg, 87%).

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