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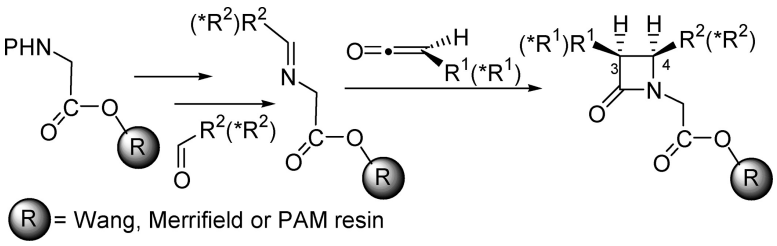

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Exploring the Solid-Phase Synthesis of 3,4-Disubstituted β-Lactams: Scope and Limitations

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This work describes a comprehensive study on the solid-phase synthesis of 3,4-disubstituted β-lactams. In situ generated ketenes react with immobilized aldimines under mild conditions to generate libraries of β-lactams in good to very good overall isolated yields. Different commercially available solid supports were studied, with the cost-effective Wang resin proving to be the most effective. The utility of the protocol was also demonstrated by the highly efficient asymmetric versions when homochiral ketenes or homochiral aldimines were used. A practical technique for the preparation of manual solid-phase parallel libraries of biologically interesting β-lactam compounds, using Mukaiyama's salt as dehydrating agent, is also presented. Reactions were easily monitored by FT-IR and gel-phase ^{13}C NMR using conventional equipment.

Introduction

Combinatorial chemistry and high-throughput screening (HTS) have been established as key technologies in drug discovery.[1] At the beginning of combinatorial chemistry, concepts for the synthesis of large numbers of compounds by a split and mix strategy on solid phase as well as the synthesis of compounds in mixtures attracted much interest in academia and, especially, in pharmaceutical research. A conceptual shift could be observed over recent years away from the synthesis of large numbers of nonpurified compounds in mixtures to the parallel solid-phase synthesis of discrete single compounds with high purity.[2]

Synthesis on a solid support shows several indisputable advantages as compared to solution chemistry.[3] Purification is facilitated by simple filtration, avoiding time-consuming separation techniques; subsequent building blocks and reagents can be added in excess to drive reactions to completion. Also, the "pseudo-dilution effect",[4] which is the result of using the polymeric solid support, makes intramolecular macrocyclization a suitable reaction that could be carried out efficiently on solid phase rather than in solution. High dilution is generally required for efficient macrocyclization in solution.

It has since been more than seven decades since Fleming observed the antibacterial action of penicillin[5] and about 60 years since penicillin and its congeners were introduced in clinical practice. They were acclaimed as "miracle drugs" that eliminate bacteria without affecting cells of the treated individuals. In the 1980s, as a result of the saturation of the market, many large pharmaceutical companies lost interest in antibiotic drugs and research in the area evidently decreased. Unfortunately, in the past several years a rapid emergence of bacterial resistance has been observed not only to single but also to multiple antibiotics, thanks to mutation and gene exchange.[6] Bacterial resistance to antibiotic drugs is also aggravated by the overuse of antibiotics in humans and animals and the noncompliance to the course of treatment by patients. One of the most feared pathogens are strains of methicillin-resistant *Staphylococcus aureus* (MRSA).[7] These bacteria are resistant to all antibiotics except vancomycin. The constant need for new antibiotics to combat the problem of bacterial resistance to traditional drugs has maintained and even increased the interest in the chemistry of β-lactams.

Apart from their antibacterial properties, β-lactams also show biological activities that include inhibition of prostate specific antigen,[8] thrombin,[9] human cytomegalovirus protein,[10] human leukocyte elastase,[11] cholesterol absorption,[12] and cysteine protease.[13]

Additional impetus has been provided by the introduction of the β-lactam synthon methodology,[14] according to which enantiomerically pure β-lactams can be employed as useful intermediates for organic synthesis. The use of monocyclic β-lactams as a synthon for the synthesis of the side chain of taxol has solved a challenging problem in the synthesis of this compound from baccatin.[15] These compounds have also been considered as peptidomimetics,[16] which mimic certain properties of proteins, such as three-dimensional structure, while conferring unique properties, such as enhanced stability to degradation or inhibition of normal peptide processing. Thus, any new synthesis that produces homochiral β-lactams is crucial, stimulating the research efforts toward the enantioselective synthesis of β-lactams.

The application of solid-phase methodologies to the synthesis of the β-lactam ring is a very attractive challenge as a starting point for the development of combinatorial libraries for biological screening. Recently, a series of papers have been published by us[17] and others[18] dealing with the application of solid-phase methodologies to the synthesis of β-lactam compounds.

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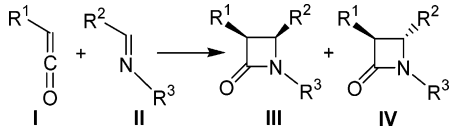
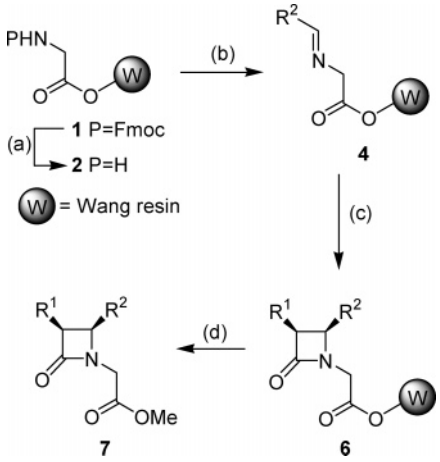
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) 30% piperidine in DMF. (b) R^2CHO (**3**) (5 equiv), 1% v/v AcOH in DMF. (c) Et_3N (20 equiv), R^1CH_2COCl (**5**) (15 equiv), 0 °C then r.t. overnight. (d) (i) 10% TFA in CH_2Cl_2. (ii) CH_2N_2.

Among the different strategies developed for the construction of the β-lactam ring, the Staudinger reaction[19] is the most frequently used and is considered to be the most effective. The Staudinger reaction involves the cycloaddition between an in situ generated ketene (**I**) and an imine (**II**) leading to cis (**III**), trans (**IV**), or a mixture of both β-lactams (Scheme 1). The generation of ketenes can be achieved from suitable precursors in a variety of ways: thermally,[20] photochemically from metal carbenes,[21] or, far more often, from acid chlorides or activated carboxylic acids in the presence of tertiary amines.[22]

Herein, we wish to report in full detail[23] the solid-phase synthesis of 3,4-disubstituted β-lactams using different Staudinger reaction variants, including synthetic scope, stereochemistry, and studies on the effect of the solid support on the reaction efficiency.

Results and Discussion

We started by studying the formation of 2-azetidinone (β-lactam ring) on commercially available solid supports such as Wang, Merrifield, and PAM resins,[24] using the "classical" Staudinger reaction between an imine and an acid chloride, in the presence of a tertiary amine for the in situ generation of the ketene.

First, we decided to attempt the synthesis using a Fmoc−Wang resin strategy (Scheme 2). Then, the starting Fmoc protected glycine attached to Wang resin (**1**) was treated with 30% piperidine in DMF to give the polymer-supported amine **2**. Fmoc removal was detected by the positive Kaiser test[25] that indicates the presence of free amines on the resin. Imine formation is a well-established methodology on solid support, with the use of trimethyl orthoformate as dehydrating agent reported to be one of the most successful methods.[26] However, in our hands this procedure failed to give an efficient condensation. The best results were obtained when resin **2** was suspended in 1% acetic acid in DMF and 3,4-dimethoxybenzaldehyde (**3a**, R^2 = 3,4-dimethoxyphenyl) was added in 5-fold molar excess.[27] Formation of the aldimine **4a** was monitored by gel-phase ^{13}C NMR.[28] Figure 1A shows that reasonable spectra can be obtained from gel-phase samples using a conventional 200 MHz NMR apparatus since most of the expected signals can be detected, without the need for magic-angle spinning.

The [2+2] cycloaddition was performed by adding phenoxylacetyl chloride (**5a**, R^1 = phenoxy) and triethylamine in excess to a suspension of **4a** in dichloromethane (Scheme 2). The resulting product gave negative Kaiser test and the solid-phase IR[29] spectrum showed the β-lactam carbonyl absorption peak at 1772 cm^{-1}. Final characterization of the resin-bound β-lactam **6aa** was achieved by gel-phase ^{13}C NMR (Figure 1B). The spectrum showed the presence of the β-lactam linked to the polymer support, especially from the peaks at 82.46 and 62.46 ppm, corresponding to C-3 and C-4, respectively. Product **6aa** was cleaved from the support at low concentration of trifluoroacetic acid (TFA): a solution of 10% (v/v) TFA/dichloromethane for 30 min was enough for a mild and efficient cleavage. Finally, esterification with diazomethane gave the β-lactam **7aa** in 78% overall yield after isolation by column chromatography (on the basis of the initial loading level of the Wang resin). The hydrogens in the 3- and 4-positions of the azetidinone ring at compound **7aa** show vicinal scalar coupling constants of ∼4.5 Hz in ^1H NMR, which is in full agreement with literature precedents for a 3,4-cis stereochemistry.[30]

A library of β-lactam compounds has been developed using this solid-phase strategy (Table 1). Overall, yields ranged from good to very good for the five-step synthetic sequence and exclusive formation of the cis isomer was detected in all cases. Different β-lactam derivatives with various substituents at positions 3 and 4 were obtained including many potential intermediates for the synthesis of active compounds. For instance, 3,4-dimethoxyphenyl, *p*-methoxyphenyl, and styryl groups undergo facile functional group transformations (entries 1, 3, 4, 10−12, 15), and a phthalimido group allows the introduction of a C-3 amide side chain, present in most of the β-lactam antibiotics (entries 10−13).[31]

A similar reaction sequence was attempted using a Merrifield resin−Boc strategy (Scheme 3). Starting from commercially available Boc−glycine linked to Merrifield resin (**8**), deprotection with 25% TFA in dichloromethane gave the free amine that was checked by the Kaiser test. Condensation with 3,4-dimethoxybenzaldehyde (**3a**) using the above protocol led to the resin-bound imine **9a** (R = Merrifield resin), which underwent [2+2] cycloaddition with excess of phenoxylacetyl chloride (**5a**) and triethylamine. At this stage, the resin **10aa** (R = Merrifield resin) showed a weak absorption for the carbonyl of the β-lactam in the IR spectrum. Likewise, the gel-phase ^{13}C NMR spectrum showed small peaks for C-3 and C-4. After cleaving with aluminum chloride[17a] and esterification with diazomethane, the expected product **7aa** was obtained only in 12% yield. When the sequence was repeated using benzaldehyde (**3b**), β-lactam **7ab** was isolated again in low yield (29%).

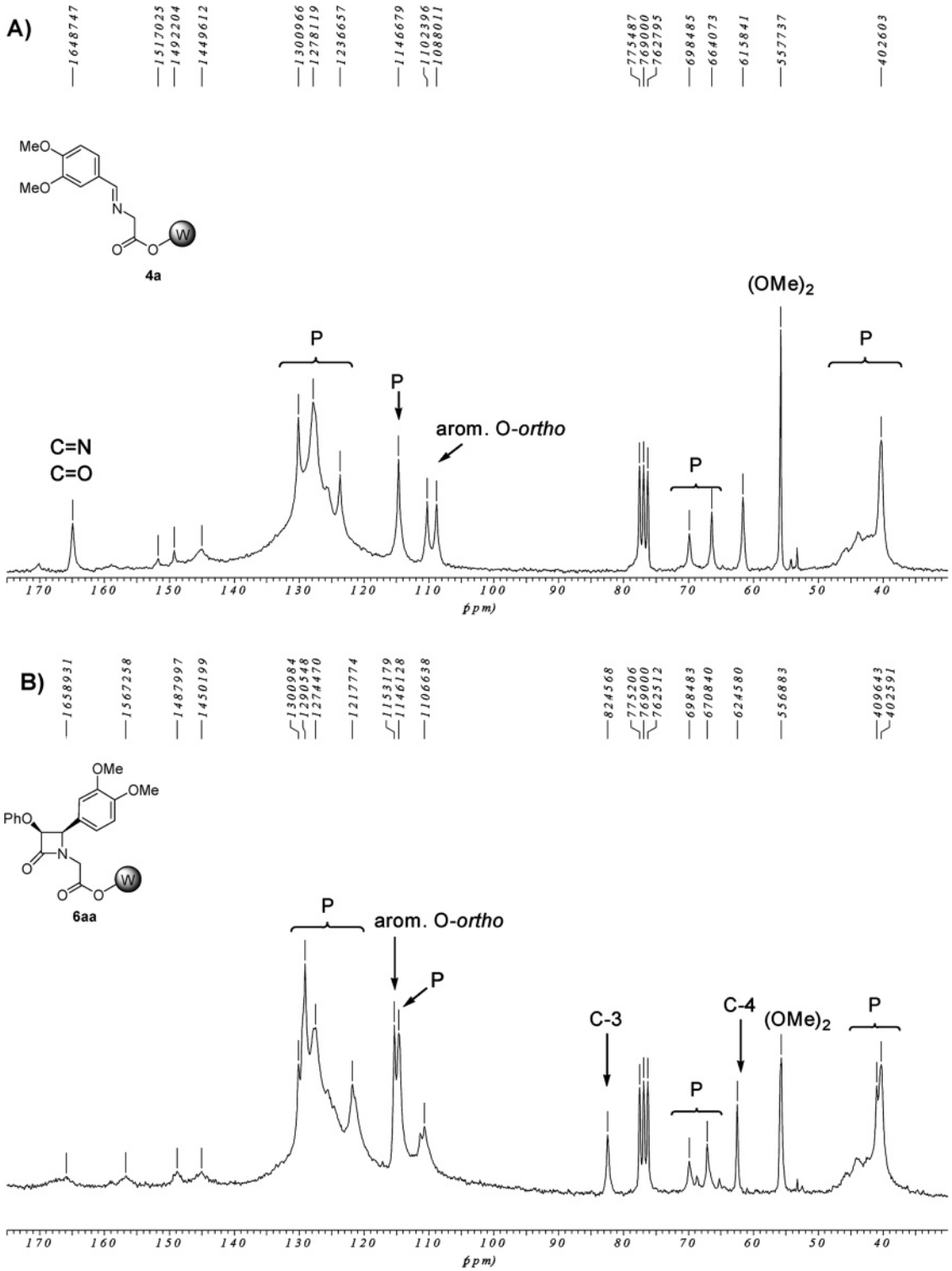


Figure 1. Conventional 50 MHz ^{13}C NMR spectra of resins **4a** (A) and **6aa** (B) in $CDCl_3$ (P = polymer support).

The 4-(hydroxymethyl)-phenylacetamidomethyl-resin (PAM resin) has been used in solid-phase peptide synthesis for the preparation of large peptides by the Boc chain extension methodology.[32] The benzyl ester in PAM resin is 100 times more stable to trifluoroacetic acid than the corresponding ester in Merrifield resin, making PAM resin more difficult to be removed under mild conditions. Interestingly, when the [2+2] cycloaddition of PAM resin-bound imine **9a** (R = PAM resin) with excess of phenoxylacetyl chloride (**5a**) and triethylamine was carried out, the gel-phase ^{13}C NMR spectrum of the product **10aa** (R = PAM resin) showed strong peaks for C-3 and C-4 (Figure 2), suggesting a high-yielding reaction.

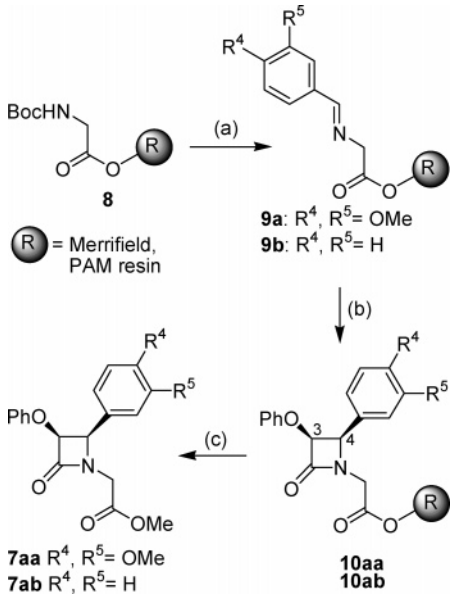
However, treatment of **10aa** (R = PAM resin) with aluminum chloride failed to produce the cleavage. Interestingly, treatment of β-lactam **10aa** (R = PAM resin) with trimethyltin hydroxide (TMTOH) in 1,2-dichloroethane for 24 h at room temperature, followed by esterification with diazomethane, furnished the β-lactam **7aa** in 63% yield. TMTOH has been recently reported as an efficient agent for the selective detachment of amino acids and dipeptides from Merrifield, PAM, and Wang resins.[33]

Table 1. Solid-Phase Synthesis of β-Lactams

entry	comp.	R^1	R^2	yield (%)[a]
1	**7aa**	PhO	3,4-$(MeO)_2$Ph	78
2	**7ab**	PhO	Ph	84
3	**7ac**	PhO	4-MeOPh	68
4	**7ad**	PhO	(*E*)-Ph-CH=CH	51
5	**7ae**	PhO	2-furyl	48
6	**7af**	PhO	4-BrPh	81
7	**7ag**	PhO	4-CH_3Ph	78
8	**7ah**	PhO	4-ClPh	50
9	**7ai**	PhO	2-BrPh	69
10	**7ba**	phthaloyl	3,4-$(MeO)_2$Ph	51
11	**7bc**	phthaloyl	4-MeOPh	38
12	**7bd**	phthaloyl	(*E*)-Ph-CH=CH	44
13	**7be**	phthaloyl	2-furyl	53
14	**7cb**	MeO	Ph	69
15	**7cc**	MeO	4-MeOPh	70
16	**7cf**	MeO	4-BrPh	55
17	**7cg**	MeO	4-CH_3Ph	66

[a] Overall isolated yield after flash chromatography (on the basis of the initial loading level of Fmoc−Gly−Wang resin).

Scheme 3[a]



[a] Reagents and conditions: (a) (i) 25% TFA in CH_2Cl_2, 50 min. (ii) aldehyde (**3a**, **b**) (5 equiv), 1% v/v AcOH in DMF. (b) Et_3N (20 equiv), $PhOCH_2COCl$ (**5a**) (15 equiv), 0 °C then r.t. overnight. (c) See text and Table 2.

Model cleavage studies for β-lactams linked to PAM and Merrifield resin with TMTOH are shown in Table 2. When the PAM resin/TMTOH cleavage strategy was repeated using benzaldehyde (**3b**), β-lactam **7ab** (R = PAM resin) was isolated in 40% yield (entry 2). Detachment of Merrifield resin-bound β-lactams with TMTOH led to the products **7aa** and **7ab** in 25% and 24% yield, respectively (entries 3−4), which were similar to the yields obtained by using aluminum chloride.

Effect of the Polymer Support. As it has been pointed out by Janda and others, polymer supports are not just "little spheres with molecules appended to them".[34] In our case, Wang resin is the most effective support for solid-phase synthesis of β-lactams. Many factors, such as the influence of solvent in pore and the cross-linked polystyrene inhomogeneity and swelling, could influence the reaction rate. We surveyed the swelling properties[35] of Fmoc−Gly−Wang, Boc−Gly−Merrifield, and Boc−Gly−PAM resins in aprotic solvents such as dichloromethane; however, the results were quite similar for all the tested resins.

Although a complete understanding of how the structure of a support affects the reactivity of an attached reactant would need further investigation,[36] in the Merrifield resin, we believe that incomplete couplings could occur because of the steric hindrance of the polystyrene backbone. A clear disadvantage of an integral linker, such as Merrifield resin, is that the reaction takes place directly on the resin, with the whole range of steric and electronic effects having an influence over the synthesis outcome.[37] When using Merrifield resin, the reaction site is very close to the polymer backbone, while in the Wang resin, the linker keeps the polymer backbone away from the reaction site. In principle, PAM resin seems to be a useful support for our sequence; however, an efficient methodology for the final cleavage remains to be found.

Other Approaches for the Solid-Phase Synthesis of β-Lactams. The early days of combinatorial chemistry were dominated by split−pool synthesis, a technique for the generation of large libraries of compounds as mixtures. This tendency has now been replaced by arrays of fewer and well-characterized compounds using parallel synthesis. However, parallel synthesis can be quite expensive for low-budget laboratories. For these laboratories, easy-to-handle reagents are an interesting alternative since they require less sophisticated equipment.

The use of an acid chloride for the in situ formation of the ketene is probably the major problem of the "classical" Staudinger reaction. Acid chlorides are sometimes unstable or difficult to prepare. For this reason, we decided to investigate other options for the activation of the carboxylic acid. Among the several activating agents that have been applied to the Staudinger reaction in solution-phase chemistry, Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) has been one of the most successful.[38]

To test the reaction on solid phase, we carried out the cycloaddition between different Wang resin-bound aldimines **4** with various carboxylic acids **11** (Table 3). The best results were obtained when 2.5 equiv of the acid and 6 equiv of triethylamine were added to a suspension of the polymer-supported imine in chloroform, followed by the addition of 3 equiv of 2-chloro-1-methylpyridinium iodide (**12**) and stirring at reflux temperature for 2 h (entries 1−8). Good to very good isolated yields were obtained, including some improvement compared to the "classical" Staudinger version when *N*-phthaloylglycine (**11b**) was used (entries 5−8). Besides, this methodology allows the synthesis of α-vinyl-β-lactams (entries 9 and 10) which could not be prepared by using crotonyl chloride under the classical Staudinger reaction on solid support. The α-vinyl-β-lactams are key intermediates for the synthesis of 3-alkyl-, 3-hydroxyalkyl-, or 3-acetylcarbapenem antibiotics.[39] Nevertheless, unlike in the use of acid chloride synthesis, mixtures of cis and trans β-lactams were found in some cases (entries 4 and 8−10).

The accepted mechanism for the Staudinger reaction[40] involves an initial attack of the nitrogen of *E*-imine **4** at the

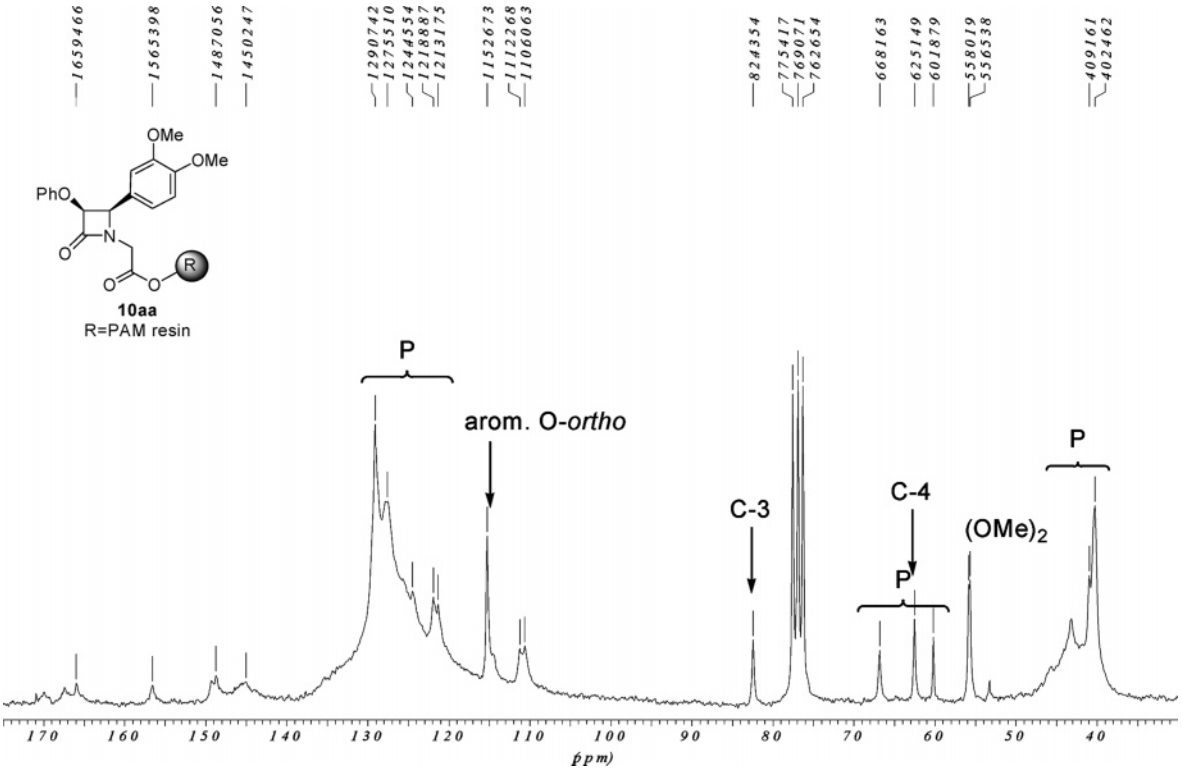
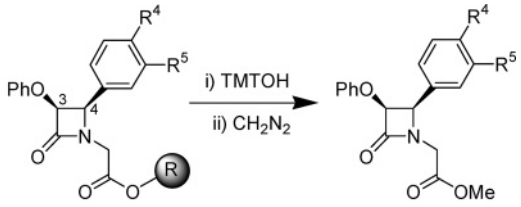


Figure 2. ^{13}C NMR spectra of **10aa** (R = PAM resin) at conventional 200 MHz apparatus in $CDCl_3$ (P = polymer support).

Table 2. Detachment of β-Lactams Linked to PAM and Merrifield Resin with TMTOH[a]

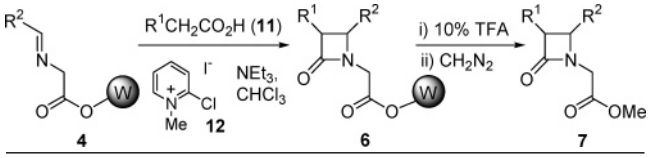


entry	product	resin	R^4	R^5	yield (%)[b]
1	**7aa**	PAM	MeO	MeO	63
2	**7ab**	PAM	H	H	40
3	**7aa**	Merrifield	MeO	MeO	25
4	**7ab**	Merrifield	H	H	24

[a] Conditions: TMTOH (3 equiv), 1,2-dichloroethane, 24 h, rt. [b] Overall isolated yield after flash chromatography (on the basis of the initial loading level of Boc−Gly−PAM or Boc−Gly−Merrifield resin).

central carbon of the ketene **A** to form a zwiterionic intermediate **C** (Scheme 4). Alternatively, the activated acid could acylate *E*-imine **4** to form iminium **B** which, upon deprotonation, would lead to the same intermediate **C**. Since the double bonds in **C** are not coplanar, the C−N bond has to rotate to the eclipsed arrangement **D**, following the least motion principle. Then, conrotatory ring closure generates exclusively the thermodynamically less stable *cis*-β-lactam **6**. The formation of the trans isomer under our reaction conditions might be explained by the isomerization of imine **4** or intermediate **C**, which occur by heating.[41] Keeping this fact in mind and considering the difficulties involved in heating several reactions at the same time, we decided to carry out the reaction at room temperature for 24 h. As expected, the use of lower temperatures led to mixture of

Table 3. Solid-Phase Synthesis of β-Lactams Using Mukaiyama's Reagent



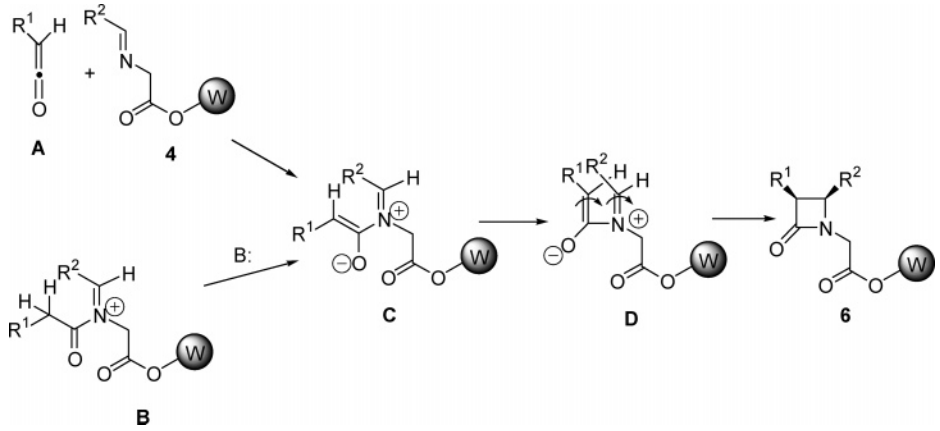
entry	comp.	R^1	R^2	conditions[a]	yield (%)[b]	cis/trans ratio[c]
1	**7aa**	PhO	3,4-$(MeO)_2$Ph	A	68	cis
2	**7ab**	PhO	Ph	A	85	cis
3	**7ac**	PhO	4-MeOPh	A	69	cis
4	**7ae**	PhO	2-furyl	A	47	1:3
5	**7ba**	Phthaloyl	3,4-$(MeO)_2$Ph	A	69	cis
6	**7bb**	Phthaloyl	Ph	A	74	17:1
7	**7bc**	Phthaloyl	4-MeOPh	A	71	25:1
8	**7be**	Phthaloyl	2-furyl	A	55	2.5:1
9	**7db**	CH_2=CH[d]	Ph	A[e]	60	1:2
10	**7dc**	CH_2=CH[d]	4-MeOPh	A[e]	64	1:1.8
11	**7aa**	PhO	3,4-$(MeO)_2$Ph	B	74	cis
12	**7ae**	PhO	2-furyl	B	42	cis
13	**7ba**	Phthaloyl	3,4-$(MeO)_2$Ph	B	65	cis
14	**7bb**	Phthaloyl	Ph	B	72	20:1
15	**7be**	Phthaloyl	2-furyl	B	48	8:1

[a] Conditions for the synthesis of **6**: A: reflux, 2 h. B: r.t., 24 h. [b] Overall isolated yield after flash column chromatography of the methyl ester (**7**) [on the basis of the initial loading level of Fmoc−Gly−Wang resin (**1**), five reaction steps]. [c] Determined by ^1H NMR of the crude reaction mixtures prior to purification. [d] In these cases, the starting acid **11** was crotonic acid. [e] The chemical reaction was repeated to ensure complete formation of the product.

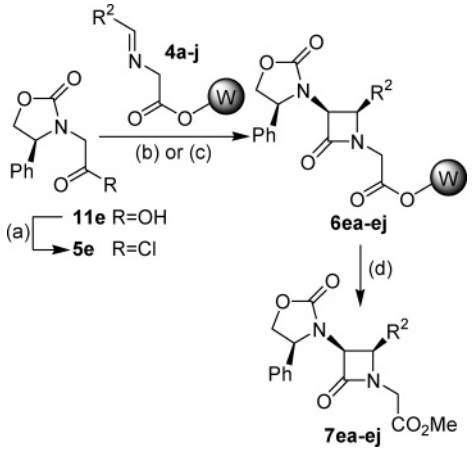
products with better cis selectivity, without decreasing the overall yield (Table 3, entries 11−15).

Asymmetric Solid-Phase Synthesis of β-Lactams. Asymmetric synthesis of β-lactams on solid support is crucial for the generation of combinatorial libraries of novel optically active carbacephems and other multicyclic β-lactam deriva-

Scheme 4



Scheme 5[a]



[a] Reagents and conditions: (a) $(COCl)_2$, toluene, 3 h, 60 °C. (b) **4a**−**j:** CH_2Cl_2, Et_3N (20 equiv), **5e** (15 equiv), 0 °C then r.t. overnight. (c) **4a**−**e:** $CHCl_3$, **11e** (2.5 equiv), Et_3N (6 equiv), then **12**, r.t. 24 h. (d) (i) 10% TFA in CH_2Cl_2. (ii) CH_2N_2.

tives. Therefore, we carried out an asymmetric version of the solid-phase Staudinger reaction using a chiral auxiliary at C-3. Thus, the homochiral (*S*)-4-phenyloxazolidinylacetic acid (**11e**) was prepared according to the Evans procedure (Scheme 5).[42] The asymmetric Staudinger reaction on solid support was then performed by adding (*S*)-(4-phenyloxazolidinyl)ketene, generated in situ by treating the crude acid chloride **5e** with triethylamine at low temperature, to suspensions of different resin-bound aldimines **4a**−**j** yielding the optically active *β*-lactams (**7ea**−**ej**) (Scheme 5, path b). Good to very good overall isolated yields were achieved with very high diastereoselectivity (entries 1−5, Table 4).

From a practical point of view, the acid chloride **5e** has to be prepared in situ by treating the acid **11e** with oxalyl chloride in toluene at 60 °C for, at least, 3−4 h. In the case of using Mukaiyama's reagent (**12**), this pretreatment is not necessary since the stable acid **11e** is the starting material. Consequently, we decided to test the solid-phase asymmetric Staudinger reaction of the homochiral acid **11e** with several aldimines **4a**−**e**, using 2-chloro-1-methylpyridinium iodide (**12**) as activating agent (Scheme 5, path c). Optically active *β*-lactams **7ea**−**ee** were obtained in very good overall isolated yields for the five reaction steps (entries 6−10, Table 4). For all these compounds, we have found a ratio of >25/1 of the two possible diastereomeric cis products with no trans-

Table 4. Asymmetric Solid-Phase Synthesis of *β*-Lactams from Homochiral Ketenes

entry	comp.	R^2	conditions[a]	yield (%)[b]	dr[c]
1	(+)-**7ea**	3,4-$(MeO)_2$Ph	A	45	>25/1
2	(+)-**7ec**	4-MeOPh	A	78	>25/1
3	(+)-**7ed**	(*E*)-Ph-CH=CH	A	36	n.d.[d]
4	(+)-**7ee**	2-furyl	A	46	>25/1
5	(−)-**7ej**	Ph_2C=CH	A	42	8/1
6	(+)-**7ea**	3,4-$(MeO)_2$Ph	B	83	>25/1
7	(+)-**7eb**	Ph	B	79	>25/1
8	(+)-**7ec**	4-MeOPh	B	77	>25/1
9	(+)-**7ed**	(*E*)-Ph-CH=CH	B	42	>25/1
10	(+)-**7ee**	2-furyl	B	59	>25/1

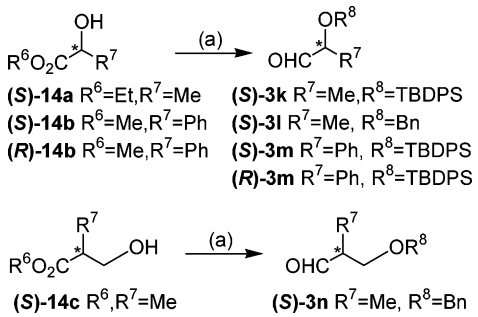
[a] For conditions, see Scheme 5: A: path b. B: path c. [b] Overall isolated yield of major diastereomer after flash chromatography [on the basis of the initial loading level of Fmoc−Gly−Wang resin (**1**)]. [c] Determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures prior to purification. [d] Not determined.

configured product detected at all. This stereochemical outcome has been explained by the absence of electrostatic repulsion between the lone pair of the carbonyl oxygen and the phenyl of the oxazolidinone in the transition state that lead to the major *cis*-(3*R*)-*β*-lactam diastereomers (**7ea**−**ej**).[43]

This synthetic sequence represents a useful procedure for the generation of chiral *β*-lactams as intermediates for the synthesis of biologically interesting compounds, such as the preparation of enantiomerically pure α-amino acids[44] or, in **7ed** and **7ej**, as precursors of novel carbacephems antibiotics.[45]

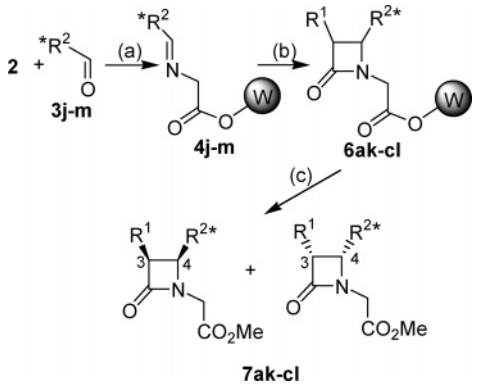
Asymmetric induction from the imine component is another way of preparing optically active *β*-lactams. In solution chemistry, the use of chiral imines derived from homochiral aldehydes and achiral amines has been the most effective in terms of asymmetric induction, since the use of those derived from achiral aldehydes and chiral amines usually yield low levels of diastereoselectivity on the *β*-lactam product.[22] To investigate the former strategy in solid phase, five homochiral aldehydes were synthesized (Scheme 6). Aldehydes (***S***)-**3k** and (***S***)-**3l** were obtained from (*S*)-ethyl lactate (**14a**) by a sequence including hydroxy group protection and DIBAL reduction, following Terashima's procedure.[46] Enantiomeric (*tert*-butyldiphenylsilyloxy)-phenyl-acetaldehydes (***S***)/(***R***)-**3m** were derived from (*S*) and (*R*)-methyl mandelate (**14b**) respectively, although, in these cases, direct reduction of the ester to the aldehyde proved to be

Scheme 6[a]



[a] Reagents and conditions: (a) for (***S***)-**3k**: (i) TBDPSCl, imidazole, DMF (ii) DIBAL, −78 °C; for (***S***)-**3l**: (i) $CCl_3C(NH)OBn$, TfOH, cyclohexane-CH_2Cl_2 (ii) DIBAL, −78 °C; for (***S***)/(***R***)-**3m**: (i) TBDPSCl, imidazole, DMF (ii) DIBAL, −45 °C (iii) Swern; for (***S***)-**3n**: (i) $CCl_3C(NH)OBn$, TfOH, cyclohexane-CH_2Cl_2 (ii) DIBAL, −45 °C (iii) Swern.

Scheme 7[a]



[a] Reagents and conditions: (a) molec. sieves 4Å, CH_2Cl_2, reflux, 8 h. (b) NEt_3, R^1CH_2COCl (**5a/5c**) in CH_2Cl_2, 0 °C to r.t., overnight. (c) (i) 10% TFA in CH_2Cl_2. (ii) CH_2N_2.

less effective and, interestingly, reduction of the protected methyl mandelate with lithium aluminum hydride provided an extensive deprotection of the hydroxy group.[47] Finally, aldehydes (***S***)/(***R***)-**3m** were efficiently prepared by reduction of methyl mandelate with DIBAL at −45 °C and the corresponding alcohol reoxidized by Swern procedure (53% overall yield). A similar approach was used for the synthesis of (*S*)-3-benzyloxy-2-methylpropionaldehyde (**14c**) from the readily available (*S*)-methyl-3-hydroxy-2-methylpropionate (**3n**): hydroxy group protection, DIBAL reduction at −45 °C, and Swern oxidation.

For the solid-phase asymmetric synthesis, these homochiral aldehydes were condensed with the Wang resin-bound glycine (**2**) using very mild conditions: a suspension of resin **2** and the corresponding aldehydes were refluxed in dichloromethane in the presence of 4 Å molecular sieves for 8 h (Scheme 7). These resin-bound homochiral aldimines (**4k**−**m**) were then subjected to the asymmetric Staudinger reaction with the ketenes derived from phenoxyacetyl chloride (**5a**) and methoxyacetyl chloride (**5c**) to give the corresponding β-lactams **6ak**−**6cl** which, after cleavage and esterification, led to products **7ak**−**7cm**. Good overall isolated yields were observed with high to excellent diastereoselectivity in most of the cases (Table 5, entries 1−6). This asymmetric induction has been rationalized on the basis of stereoelectronic effects.[43] The formation of the major diasteromer was explained by a better two-electron interaction between the C−O σ* orbital (being C the stereogenic carbon atom) and the p atomic orbital of the C-3 atom of the β-lactam. The absence of an electronegative atom directly attached to the stereogenic carbon significantly reduced diastereoselectivity as can be noticed in β-lactam **7an**, obtained with only a 2:1 diastereoisomeric ratio (Table 5, entry 7). Asymmetric induction from the imine component of the Staudinger cycloadition provides versatile intermediates for the syntheses of novel forms of important carbapenems, carbacephems, isooxacephems, and other multicyclic β-lactams.[22,48]

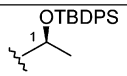
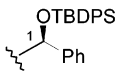
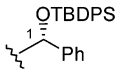
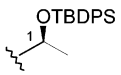
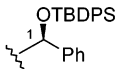
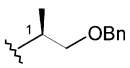
Conclusions

We have carried out a comprehensive study on the solid-phase synthesis β-lactams compounds. The use of reliable methodologies for solid-phase synthesis of polisubstituted β-lactams using different approaches is included. We have found that the Staudinger reaction proceeded efficiently giving good to very good overall yields with excellent cis-selectivity. Reactions could be easily monitored by FT-IR and gel-phase ^{13}C NMR using conventional equipment. Asymmetric versions using either homochiral acid chlorides or homochiral aldimines led to the corresponding optically active β-lactams in good to very good overall yields and high diastereoselectivity in most cases. The Staudinger cycloaddition using Mukaiyama's salt as dehydrating agent is a practical alternative that facilitates the development of manual solid-phase parallel libraries of biologically interesting β-lactam compounds, requiring less sophisticated equipment. The cost-effective Wang resin is clearly the appropriate solid support for this chemistry. In principle, PAM resin was an interesting alternative because of acid stability; however, final cleavage proved to be difficult. The recent discovery of new active β-lactam compounds, together with the permanent need for new drugs with broader antibacterial activity, ensures renewed interest in the synthesis of azetidinones. Thus, the present procedures for the solid-phase Staudinger cycloaddition would be quite useful for the synthesis of the precursors of various antibiotics and other biologically interesting molecules. Our main objective in the future will be to expand our knowledge in this area by developing the solid-phase synthesis of multicyclic β-lactams.

Experimental Section

General. Chemical reagents were purchased from commercial sources and were used without further purification unless noted otherwise. Solvents were analytical grade or were purified by standard procedures prior to use. Resins were purchased from Novabiochem (San Diego, CA). Melting points were taken on a Ernst Leitz melting point apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature using a 1-mL capacity cell, on a JASCO DIP-1000 polarimeter. Infrared spectra (IR) were recorded on a Bruker IFS25 or a Shimadzu FT-IR 8101 spectrophotometers and only partial spectral data are listed. ^1H NMR spectra were recorded on a Bruker AC200 at 200 MHz in $CDCl_3$ unless otherwise stated, in the presence of TMS (0.00 ppm) as the internal standard. ^{13}C NMR spectra were recorded on the same apparatus at 50 MHz with $CDCl_3$ as solvent and reference (76.9 ppm), unless otherwise stated. ^{13}C NMR assignments were made

Table 5. Asymmetric Solid-Phase Synthesis of β-Lactams Using Homochiral Aldehydes

Entry	Comp.	R^1	R^2	configuration[a]	Yield (%)[b]	dr[c]
1	(-)-**7ak**	PhO		3*S*, 4*S*, 1*S*	67	10/1
2	(-)-**7al**	PhO		3*S*, 4*R*, 1*S*	65	10/2
3	(-)-**7am**	PhO		3*S*, 4*S*, 1*S*	61	> 25:1
4	(+)-**7am**	PhO		3*R*, 4*R*, 1*R*	70	> 25/1
5	(-)-**7ck**	MeO		3*S*, 4*S*, 1*S*	41	> 25/1
6	(+)-**7cm**	MeO		3*S*, 4*S*, 1*S*	57	8/1
7	**7an**	PhO		3*S*, 4*R*, 1*R*	25[d]	2/1

[a] Major diastereomer. [b] Overall isolated yield of major diastereomer after flash chromatography [on the basis of the initial loading level of Fmoc−Gly−Wang resin (**1**)]. [c] Determined by ^{1}H NMR from crude material. [d] Inseparable mixture with its (3*R*, 4*S*, 1*R*)-diastereomer.

on the basis of chemical shifts and proton multiplicities (from DEPT spectra). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Mass spectra were performed at the University of California Riverside Mass Spectrometry Facility, using a Micromass VG7070EHF Spectrometer, and GC-MS analyses were carried out on a Hewlett-Packard 5898A apparatus. Analytical thin-layer chromatography (TLC) was carried out with silica gel 60 F_{254} precoated aluminum sheets (Merck). Flash column chromatography was performed using Merck silica gel 60 (230−400 mesh), according to the procedure reported by Still.[49] Acid chlorides were commercially available except **5b** and **5e**,[42] which were prepared by treating the corresponding acids with oxalyl chloride in dry toluene at 60 °C for 3 h and were used in crude form after solvent evaporation. Compound **7ab**[50] and **7ae**[51] have been already described in the literature.

General for Solid-Phase Chemistry. Solid-phase reactions were carried out in polypropylene cartridges equipped with a frit (Supleco, Bellefonte, PA), unless reflux conditions were required, in that cases standard glassware was used. All solid-phase reaction mixtures were stirred at the slowest rate. Although it is a common practice to preswell the polymer in the reaction solvent for 30 min prior to adding other reagents, we have noticed that this procedure does not affect yields or efficiency. For solid-phase IR, KBr pellets were formed from about 3 mg of the resin and 100 mg of KBr. For gel-phase ^{13}C NMR, 50−80 mg of resin was placed in a conventional NMR tube and about 0.5 mL of $CDCl_3$ was added to obtain a gel that was finally homogenized by sonication. Spectra were recorded according to parameters described in the literature,[28] only partial spectral data were listed.

Representative Procedure for the Solid-Phase Synthesis of 3,4-Disubstituted β-Lactam Using Achiral and Homochiral Acid Chlorides: 1-(Methoxycarbonyl)methyl-4-(3,4-dimethoxyphenyl)-3-phenoxy-2-azetidinone (7aa). Fmoc−Gly Wang resin **1** (100 mg, loading 0.78 mmol/g, 0.078 mmol) was suspended in 30% piperidine in DMF (3 mL). After stirring for 50 min at room temperature, the mixture was filtered and washed successively with DMF (3 × 4 mL), CH_2Cl_2 (3 × 4 mL), MeOH (3 × 4 mL), CH_2Cl_2 (1 × 4 mL), and dried under high vacuum to afford H-Gly Wang resin **2** which was taken immediately onto the next step. Resin **2** (0.078 mmol) was suspended in a 1% solution of AcOH in DMF (ca. 2.5 mL) and 3,4-dimethoxybenzaldehyde (**3a**) (65 mg, 0.30 mmol, 5 equiv) was added. The reaction was stirred for 45 min at room temperature, after which the resin was filtered, washed with DMF (3 × 3 mL), and resubjected to the same reaction conditions. After that, the resin was filtered, washed successively with DMF (3 × 4 mL), CH_2Cl_2 (3 × 4 mL), AcOEt (3 × 4 mL), MeOH (3 × 4 mL), and CH_2Cl_2 (1 × 4 mL), and dried under high vacuum affording the support-bound aldimine **4a**: IR: 1650 cm^{-1} (C═N); ^{13}C NMR gel phase (50 MHz, $CDCl_3$) δ 164.9 (C═N, C═O), 149.2, 144.9 (arom. *O-ipso*), 110.2, 108.8 (arom. *O-orto*), 55.8 (CH_3O). To a suspension of support-bound aldimine **4a** (0.078 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C, triethylamine (0.217 mL, 1.56 mmol, 20 equiv) and phenoxyacetyl chloride **5a** (0.162 mL, 1.17 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 × 4 mL), AcOEt (3 × 4 mL), MeOH (3 × 4 mL), and CH_2Cl_2 (1 × 4 mL), and dried under high vacuum affording the support-bound β-lactam **6aa**: IR: 1772 cm^{-1} (β-lactam); ^{13}C NMR gel phase (50 MHz, $CDCl_3$) δ 165.9 (C═O), 156.7, 148.8, 145.0 (arom. *O-ipso*), 115.3, 110.7 (arom. *O-orto*), 82.5 (C-3), 62.5(C-4), 55.7 (CH_3O). A 10% solution of TFA in CH_2Cl_2 (5 mL) was added to the polymer-bound β-lactam **6aa** (95 mg, theoretical loading 0.74 mmol/g, 0.07 mmol). The reaction mixture was stirred for 50 min at room temperature, filtered, and washed with CH_2Cl_2 (2 × 3 mL) and the filtrate was evaporated under reduced pressure. Esterification with diazomethane afforded the crude product that was then purified by column chromatography (hexane-

AcOEt, 80:20) to give 20 mg of **7aa** (78% overall yield, on the basis of the initial loading level of the Fmoc−Gly Wang resin): IR (film) 1772 (β-lactam), 1746 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.56 (d, $J = 18.0$ Hz, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.46 (d, $J = 18.0$ Hz, 1H), 5.17 (d, $J = 4.5$ Hz, 1H), 5.56 (d, $J = 4.5$ Hz, 1H), 6.74−7.15 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.75, 52.36, 55.71, 55.90, 62.54, 82.52, 110.61, 111.23, 115.35, 121.42, 121.95, 124.51, 129.15, 148.81, 149.41, 156.74, 165.99, 168.11; GC/MS *m*/*z* (%): 371 (M^+, 12), 277 (100), 256 (90), 241 (27), 178 (22), 151 (10); anal. HRMS calcd for $C_{20}H_{21}NO_6$ (M^+, *m*/*z*): 371.1369; found: 371.1370.

1-(Methoxycarbonyl)methyl-4-(4-methoxy-phenyl)-3-phenoxy-2-azetidinone (7ac). IR (film) 1770 (β-lactam), 1746 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.52 (d, $J = 18.0$ Hz, 1H), 3.73 (s, 3H), 3.76 (s, 3H), 4.47 (d, $J = 18.0$ Hz, 1H), 5.19 (d, $J = 4.45$ Hz, 1H), 5.54 (d, $J = 4.45$ Hz, 1H), 6.73−7.28 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.60, 52.31, 55.09, 62.28, 82.53, 113.69, 115.41, 121.88, 123.95, 129.10, 129.82, 156.77, 159.90, 166.04, 168.11; GC/MS *m*/*z* (%): 341 (M^+, 2), 247 (100), 226 (62), 208 (27), 148 (15), 121 (13); anal. HRMS calcd for $C_{19}H_{19}NO_5$ (M^+, *m*/*z*): 341.1263; found: 341.1269.

1-(Methoxycarbonyl)methyl-3-phenoxy-4-styryl-2-azetidinone (7ad). IR (film) 1770 (β-lactam), 1740 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.72 (d, $J = 18.0$ Hz, 1H), 3.76 (s, 3H), 4.37 (d, $J = 18.0$ Hz, 1H), 4.79 (dd, $J = 4.6$, 9.0 Hz, 1H), 5.48 (d, $J = 4.6$ Hz, 1H), 6.22 (dd, $J = 15.9$, 9.0 Hz, 1H), 6.72 (d, $J = 15.9$ Hz, 1H), 6.96−7.34 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.76, 52.38, 61.58, 82.54, 115.54, 121.57, 122.19, 126.66, 128.38, 128.55, 129.41, 135.67, 137.50, 157.21, 165.55, 168.38; GC/MS *m*/*z* (%): 337 (M^+, 14), 243 (100), 212 (39), 184 (31), 156 (16), 129 (23); anal. HRMS calcd for $C_{20}H_{19}NO_4$ (M^+, *m*/*z*): 337.1314; found: 337.1325.

4-(4-Bromophenyl)-1-(methoxycarbonyl)methyl-3-phenoxy-2-azetidinone (7af). IR (film) 1780 (β-lactam), 1754 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.52 (d, $J = 18.0$ Hz, 1H), 3.73 (s, 3H), 4.47 (d, $J = 18.0$ Hz, 1H), 5.19 (d, $J = 4.6$ Hz, 1H), 5.56 (d, $J = 4.6$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 2H), 6.87−6.95 (m, 1H), 7.12−7.25 (m, 4H), 7.44 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.78, 52.35, 62.08, 82.50, 115.35, 122.13, 122.90, 129.19, 130.10, 131.44, 131.49, 156.55, 165.78, 167.91; MS (DCI) *m*/*z* (%): 390 (MH^+, 100), 362 (21), 312 (54), 297 (49), 276 (68), 196 (44), 105 (48); HRMS calcd for $C_{18}H_{16}BrNO_4$ (MH^+, *m*/*z*): 390.0341; found: 390.0351.

1-(Methoxycarbonyl)methyl-3-phenoxy-4-(4-*p*-tolyl)-2-azetidinone (7ag). mp 98−99 °C; IR (KBr) 1777 (β-lactam), 1754.(ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.52 (d, $J = 17.9$ Hz, 1H), 3.72 (s, 3H), 4.47 (d, $J = 17.9$ Hz, 1H), 5.18 (d, 4.5 Hz, 1H), 5.54 (d, $J = 4.6$ Hz, 1H), 6.74−6.88 (m, 3H), 7.08−7.25 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.05, 40.66, 52.30, 62.56, 82.65, 115.52, 121.91, 128.45, 128.99, 129.09, 138.62, 156.87, 166.08, 168.12; MS (EI) *m*/*z* (%): 325 (M^+, 2), 231 (100), 210 (91), 192 (46), 105 (85); anal calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31; found: C, 70.02; H, 5.90; N, 4.24.

4-(4-Clorophenyl)-1-(methoxycarbonyl)methyl-3-phenoxy-2-azetidinone (7ah). IR (film) 1779 (β-lactam), 1754 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.52 (d, $J = 17.9$ Hz, 1H), 3.74 (s, 3H), 4.47 (d, $J = 17.9$ Hz, 1H), 5.21 (d, $J = 4.7$ Hz, 1H), 5.56 (d, $J = 4.7$ Hz, 1H), 6.73−6.77 (m, 2H), 6.87−6.94 (m, 1H), 7.11−7.28 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.82, 52.40, 62.05, 82.55, 115.36, 122.15, 128.53, 129.22, 129.84, 130.96, 134.74, 156.58, 165.84, 167.97; MS (DCI) *m*/*z* (%): 346 (MH^+, 100), 254 (34), 230 (59), 212 (28), 165 (20), 105 (22); HRMS calcd for $C_{18}H_{16}ClNO_4$ (MH^+, *m*/*z*): 346.0846; found: 346.0852.

4-(2-Bromophenyl)-1-(methoxycarbonyl)methyl-3-phenoxy-2-azetidinone (7ai). IR (film) 1783 (β-lactam), 1754 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.63 (d, $J = 18.0$ Hz, 1H), 3.76 (s, 3H), 4.54 (d, $J = 18.0$ Hz, 1H), 5.62 (d, $J = 4.7$ Hz, 1H), 5.68 (d, $J = 4.7$ Hz, 1H), 6.81−6.95 (m, 3H), 7.12−7.52 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.46, 52.45, 61.82, 83.04, 115.94, 122.24, 124.19, 127.26, 128.66, 129.17, 129.85, 132.39, 132.93, 156.93, 166.42, 167.83; MS (DCI) *m*/*z* (%): 407 (MNH_4^+, 20), 392 (100), 390 (MH^+, 97), 362 (54), 274 (65), 194 (25); HRMS calcd for $C_{18}H_{16}BrNO_4$ (MH^+, *m*/*z*): 390.0341; found: 390.0327.

1-(Methoxycarbonyl)methyl-4-(3,4-dimethoxyphenyl)-3-phthalimido-2-azetidinone (7ba). IR (film) 1770 (β-lactam), 1742 (ester), 1722 (imides) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.76 (d, $J = 18.0$ Hz, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 4.67 (d, $J = 18.0$ Hz, 1H), 5.27 (d, $J = 5.2$ Hz, 1H), 5.64 (d, $J = 5.2$ Hz, 1H), 6.70−7.72 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.94, 52.41, 55.64, 55.79, 60.45, 61.75, 109.86, 110.95, 120.07, 123.32, 124.59, 128.20, 131.12, 134.18, 148.79, 148.96, 164.29, 166.71, 168.08; MS (DEI) *m*/*z* (%): 425 (MH^+, 2.3), 424 (2.4), 309 (10), 277 (100), 238 (28), 178 (52), 104 (55); anal. HRMS calcd for $C_{22}H_{20}N_2O_7$ (M^+, *m*/*z*): 424.1271; found: 424.1280.

1-(Methoxycarbonyl)methyl-4-(4-methoxyphenyl)-3-phthalimido-2-azetidinone (7bc). Mp 176.5−177.5 °C; IR (film) 1771 (β-lactam), 1742 (ester), 1720 (imides) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.75 (d, $J = 18.0$ Hz, 1H), 3.77 (s, 3H), 4.69 (d, $J = 18.0$ Hz, 1H), 5.29 (d, $J = 5.26$ Hz, 1H), 5.64 (d, $J = 5.26$ Hz, 1H), 6.73−7.70 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.85, 52.42, 55.05, 60.30, 61.53, 113.93, 123.31, 124.10, 128.47, 131.11, 134.08, 159.55, 164.37, 166.62, 168.11; anal calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.6; N, 7.1; found: C, 63.68; H, 4.74; N, 6.95.

1-(Methoxycarbonyl)methyl-3-phthalimido-4-styryl-2-azetidinone (7bd). IR (film) 1775 (β-lactam), 1742 (ester), 1722 (imides) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.80 (d, $J = 18.0$ Hz, 1H), 4.50 (d, $J = 18.0$ Hz, 1H), 4.87 (dd, $J = 5.25$, 9.0 Hz, 1H), 5.7 (d, $J = 5.25$ Hz, 1H), 6.21 (dd, $J = 15.9$, 9.0 Hz, 1H), 6.70 (d, $J = 15.9$ Hz, 1H), 7.27−7.88 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.46, 52.40, 58.58, 61.86, 121.63, 123.67, 126.64, 128.48, 128.55, 131.45, 134.39, 135.31, 138.33, 164.19, 167.19, 168.22; MS (DEI) *m*/*z* (%): 390 (M^+, 22), 243 (85), 204 (67), 160 (63), 132 (46), 128 (82), 104 (100); anal. HRMS calcd for $C_{22}H_{18}N_2O_5$ (M^+, *m*/*z*): 390.1216; found: 390.1224.

4-(Furan-2-yl)-1-(methoxycarbonyl)methyl-3-phthalimido-2-azetidinone (7be). mp 181.5−182.5 °C; IR (film) 1771 (β-lactam), 1750 (ester), 1720 (imides) cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$) δ; 3.77 (d, $J = 18.1$ Hz, 1H), 3.78 (s, 3H), 4.62 (d, $J = 18.1$ Hz, 1H), 5.36 (d, $J = 5.1$ Hz, 1H), 5.68 (d, $J = 5.1$ Hz, 1H), 6.22−7.82 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.61, 52.44, 55.84, 59.68, 110.31, 110.59, 123.50, 131.24, 134.22, 143.41, 146.96, 163.75, 166.45, 168.03; anal calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91; found: C, 60.52; H, 4.06; N, 7.88.

3-Methoxy-1-(methoxycarbonyl)methyl-4-phenyl-2-azetidinone (7cb). IR (film) 1780 (β-lactam), 1759 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.49 (d, $J =$ 18.0 Hz, 1H), 3.70 (s, 3H), 4.42 (d, $J = 18.0$ Hz, 1H), 4.82 (d, $J = 4.5$ Hz, 1H), 5.02 (d, $J = 4.5$ Hz, 1H), 7.35−7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.60, 52.22, 58.15, 62.37, 86.32, 128.31, 128.41, 128.67, 133.03, 167.18, 168.16; MS (EI) *m*/*z* (%): 249 (M^+, 3), 217 (3), 178 (24), 134 (100), 119 (13), 91 (63); anal. HRMS calcd for $C_{13}H_{15}NO_4$ (M^+, *m*/*z*): 249.1001; found: 249.1012.

3-Methoxy-1-(methoxycarbonyl)methyl-4-(4-methoxyphenyl)-2-azetidinone (7cc). IR (film) 1771 (β-lactam), 1740 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.46 (d, $J = 18.0$ Hz, 1H), 3.7 (s, 3H), 3.81 (s, 3H), 4.37 (d, $J = 18.0$ Hz, 1H), 4.78 (d, $J = 4.5$ Hz, 1H), 4.96 (d, $J =$ 4.5 Hz, 1H), 6.89−7.28 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.47, 52.18, 55.17, 58.11, 61.90, 86.21, 113.91, 124.74, 129.65, 160.00, 167.24, 168.19; GC/MS *m*/*z* (%): 279 (M^+, 35), 248 (88), 208 (56), 164 (100), 149 (35), 121 (42); anal. HRMS calcd for $C_{14}H_{17}NO_5$ (M^+, *m*/*z*): 279.1107; found: 279.1107.

4-(4-Bromophenyl)-3-methoxy-1-(methoxycarbonyl)methyl-2-azetidinone (7cf). IR (film) 1782 (β-lactam), 1754 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.46 (d, $J = 18.0$ Hz, 1H), 3.71 (s, 3H), 4.39 (d, $J = 18.0$ Hz, 1H), 4.81 (d, $J = 4.4$ Hz, 1H), 4.99 (d, $J = 4.4$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.63, 52.28, 58.30, 61.80, 86.24, 122.85, 130.01, 131.62, 132.17, 167.00, 168.02; MS (EI) *m*/*z* (%): 327 (M^+, 2), 256 (17), 212 (96), 169 (22), 118 (100); anal. HRMS calcd for $C_{13}H_{14}BrNO_4$ (M^+, *m*/*z*): 327.0106; found: 327.0115.

3-Methoxy-1-(Methoxycarbonyl)methyl-4-(4-*p*-tolyl)-2-azetidinone (7cg). IR (film) 1766 (β-lactam), 1748 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.16 (s, 3H), 3.47 (d, $J = 17.9$ Hz, 1H), 3.69 (s, 3H), 4.40 (d, $J =$ 17.9 Hz, 1H), 4.80 (d, $J = 4.5$ Hz, 1H), 4.49 (d, $J = 4.5$ Hz, 1H), 7.20 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.09, 40.50, 52.20, 58.17, 64.15, 86.24, 128.26, 129.14, 129.86, 138.66, 167.26, 169.19; MS (EI) *m*/*z* (%): 263 (M^+, 6), 192 (31), 148 (100), 132 (20), 105 (75); anal. HRMS calcd for $C_{14}H_{17}NO_4$ (M^+, *m*/*z*): 263.1158; found: 263.1163.

(3*S*, 4*R*)-1-(Methoxycarbonyl)methyl-4-(3,4-dimethoxyphenyl)-3-[(4*S*)-4-phenyl-2-oxooxazolidin-3-yl]-2-azetidinone (7ea). $[\alpha]^{31}_D = +51.1$ (*c* 0.66, $CHCl_3$); IR (film) 1776 (β-lactam), 1762 (ester and carbamate) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.57 (d, $J = 18.0$ Hz, 1H), 3.69 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 3.90−4.01 (m, 1H), 4.15−4.28 (m, 2H), 4.54 (d, $J = 18.0$ Hz, 1H), 4.54 (d, $J = 4.8$ Hz, 1H), 4.94 (d, $J = 4.8$ Hz, 1H), 6.8−7.42 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.6, 52.2, 55.8, 56.1, 59.7, 61.8, 64.0, 70.0, 110.4, 111.1, 120.3, 125.0, 127.3, 129.4, 136.0, 149.3, 156.7, 163.9, 168.2; MS (DEI) *m*/*z* (%): 441 (MH^+, 2.7), 326 (9), 277 (100), 238 (54), 178 (46), 151 (28), 104 (40); anal. HRMS calcd for $C_{23}H_{25}N_2O_7$ (MH^+, *m*/*z*): 441.1662; found: 441.1648.

(3*S*, 4*R*)-1-(Methoxycarbonyl)methyl-4-phenyl-3-[(4*S*)-4-phenyl-2-oxooxazolidin-3-yl]-2-azetidinone (7eb). mp 143.5−144.5 °C; $[\alpha]^{29}_D = +37.4$ (*c* 0.465, chloroform); IR (KBr) 1785 (β-lactam), 1755 (ester and carbamate) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.59 (d, $J = 18.0$ Hz, 1H), 3.66 (s, 3H), 3.92 (dd, $J = 7.2$, 8.4 Hz, 1H), 4.17 (t, $J = 8.4$ Hz, 2H), 4.32 (dd, $J = 7.2$, 8.4 Hz, 1H), 4.55 (d, $J = 18.0$ Hz, 1H), 4.63 (d, $J = 5.0$ Hz, 1H), 5.04 (d, $J = 5.0$ Hz, 1H), 7.18−7.39 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.6, 52.3, 59.6, 61.9, 64.0, 70.1, 127.3, 127.5, 128.7, 128.8, 129.3, 129.4, 132.8, 136.2, 156.6, 163.9, 168.2; anal calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36; found: C, 66.13; H, 5.30; N, 7.09.

(3*S*,4*R*)-1-(Methoxycarbonyl)methyl-4-(4-methoxy-phenyl)-3-[(4*S*)-4-phenyl-2-oxooxazolidin-3-yl]-2-azetidinone (7ec). Mp 146−147 °C; $[\alpha]^{25}_D = +52.9$ (*c* 1.46, $CHCl_3$); IR (film) 1772 (β-lactam), 1757 (ester and carbamate) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.56 (d, $J = 18.0$ Hz, 1H), 3.67 (s, 3H), 3.82 (s, 3H), 3.94 (dd, $J = 6.4$, 7.6 Hz, 1H), 4.17−4.33 (m, 2H), 4.51 (d, $J = 18.0$ Hz, 1H), 4.55 (d, $J =$ 5.0 Hz, 1H), 4.98 (d, $J = 5.0$ Hz, 1H), 6.90−7.40 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.49, 52.17, 55.17, 59.63, 61.66, 64.04, 70.04, 114.23, 124.44, 127.27, 128.94, 129.25, 129.34, 136. 30, 156.66, 159.87, 163.88, 168.17; anal calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83; found: C, 64.39; H, 5.63; N, 6.67.

(3*S*, 4*R*)-1-(Methoxycarbonyl)methyl-3-[(4*S*)-4-phenyl-2-oxooxazolidin-3-yl]-4-styryl-2-azetidinone (7ed). $[\alpha]^{25}_D = +76.5$ (*c* 0.31, $CHCl_3$); IR (film) 1778 (β-lactam), 1749 (ester and carbamate) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.59 (d, $J = 18.0$ Hz, 1H), 3.68 (s, 3H), 4.17 (dd, $J = 8.8$, 7.3 Hz, 1H), 4.35 (d, $J = 18.0$ Hz, 1H), 4.56−4.66 (m, 3H), 4.84 (dd, $J = 7.3$, 8.8 Hz, 1H), 6.16 (m, 1H), 6.66 (d, $J =$ 15.82 Hz, 1H), 7.34−7.41 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.24, 52.21, 60.17, 61.88, 63.19, 70.04, 122.45, 126.79, 127.53, 128.62, 129.45, 129.34, 135.49, 136.84, 137.70, 157.52, 163.87, 168.20; MS (DEI) *m*/*z* (%): 406 (M^+, 3.6), 243 (73), 204 (70), 164 (22), 115 (49), 104 (100); anal. HRMS calcd for $C_{23}H_{22}N_2O_5$ (M^+, *m*/*z*): 406.1529; found: 406.1560.

(3*S*, 4*S*)-4-(Furan-2-yl)-1-(methoxycarbonyl)methyl-3-[(4*S*)-4-phenyl-2-oxooxazolidin-3-yl]-2-azetidinone (7ee). $[\alpha]^{25}_D = +48.3$ (*c* 0.85, $CHCl_3$); IR (film) 1771 (β-lactam), 1759 (ester and carbamate) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.62 (d, $J = 18.0$ Hz, 1H), 3.69 (s, 3H), 4.02 (dd, $J = 12.5$, 11.75 Hz, 1H), 4.31−4.37 (m, 2H), 4.48 (d, $J =$ 18.0 Hz, 1H), 4.52 (d, $J = 4.7$ Hz, 1H), 5.06 (d, $J = 4.7$ Hz, 1H), 6.45−6.48 (m, 2 H), 7.26−7.48 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.30, 52.33, 55.74, 59.93, 63.81, 70.07, 110.91, 111.29, 127.29, 129.40, 135.90, 143.14, 147.27, 156.61, 163.53, 168.17; GCMS *m*/*z* (%): 371 (MH^+, 1), 255 (51), 207 (100), 168 (94), 120 (12), 104 (26); anal. HRMS calcd for $C_{19}H_{19}N_2O_6$ (MH^+, *m*/*z*): 371.1243; found: 371.1239.

(3*S*, 4*R*)-1-(Methoxycarbonyl)methyl-3-[(4*S*)-4-phenyl-2-oxooxazolidin-3-yl]-4-(2,2-diphenyl-vinyl)-2-azetidinone (7ej). $[\alpha]^{25}_D = -42.9$ (*c* 0.48, $CHCl_3$); IR (film) 1771 (β-lactam), 1750 (ester and carbamate) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.64 (d, $J = 17.8$ Hz, 1H), 4.22 (d, $J = 17.8$ Hz, 1H), 4.22 (dd, $J = 8.7$, 7.2 Hz, 1H), 4.53−4.70 (m, 3H), 4.84 (dd, $J = 8.7$, 7.2 Hz, 1H), 5.59 (d, $J = 9.1$ Hz, 1H), 7.13−7.38 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.55, 52.17, 58.75, 59.89, 61.88, 63.94, 70.63, 121.68, 127.70, 127.94, 128.15, 128.46, 129.30, 129.47, 136.99, 138.36, 140.94, 149.42, 157.72, 163.97, 167.90; MS (DEI) *m*/*z* (%): 482 (M^+, 28), 366 (12), 319 (99), 280 (100), 204 (52), 191 (98), 104 (96); anal. HRMS calcd for $C_{29}H_{26}N_2O_5$ (M^+, *m*/*z*): 482.1842; found: 482.1858.

Representative Procedure for the Solid-Phase Synthesis of 3,4-Disubstituted β-Lactams Using Mukaiyama's Reagent: 1-(Methoxycarbonyl)methyl-4-phenyl-3-phthalimido-2-azetidinone (7bb). Resin **2** (0.084 mmol) was suspended in a 1% solution of AcOH in DMF (ca. 3 mL) and benzaldehyde (**3b**) (0.043 mL, 44.7 mg, 0.42 mmol, 5 equiv) was added. The reaction was stirred for 45 min at room temperature, after which the resin was filtered, washed with DMF (3 × 3 mL), and resubjected to the same reaction conditions. After that, the resin was filtered, washed successively with DMF (3 × 4 mL), CH_2Cl_2 (3 × 4 mL), AcOEt (3 × 4 mL), MeOH (3 × 4 mL), and CH_2Cl_2 (1 × 4 mL), and dried under high vacuum affording the polymer-bound imine **4b** which was taken immediately onto the next step. *N*-Phthaloylglycine **11b** (43 mg, 0.21 mmol, 2.5 equiv) and Et_3N (0.070 mL, 0.51 mmol, 6 equiv) were dissolved in anhydrous chloroform (4 mL) and added to a suspension of imine **4b** (0.084 mmol) in anhydrous chloroform (1.2 mL) under a nitrogen atmosphere. After a minute, 2-chloro-1-methylpyridinium iodide (**12**) (65 mg, 0.252 mmol, 3 equiv) was added and the suspension was stirred at room temperature for 24 h. Then, the reaction mixture was filtered and the resin was washed successively with CH_2Cl_2 (3 × 5 mL), AcOEt (3 × 5 mL), MeOH (3 × 5 mL), and CH_2Cl_2 (1 × 5 mL). After drying in vacuo overnight, a portion of support-bound β-lactam **6bb** (84 mg, theoretical loading: 0.943 mmol/g, 0.079 mmol) was treated with 3 mL of 10% TFA in CH_2Cl_2 for 50 min. The mixture was filtered and the filtrate was evaporated under reduced pressure. Esterification of the residue with diazomethane gave a crude compound as a 20:1 mixture of cis:trans isomers. This crude was purified by column chromatography (hexane−AcOEt, 55:45) to provide 21.1 mg of the compound **7bb** as a white solid (72% overall yield, on the basis of the initial loading level of the Fmoc−Gly Wang resin): mp 174−175 °C; IR (KBr) 1776 (β-lactam), 1755 (ester), 1722 (imides) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.79 (d, $J = 18.0$ Hz, 1H), 4.71 (d, $J = 18.0$ Hz, 1H), 5.34 (d, $J = 5.4$ Hz, 1H), 5.68 (d, $J = 5.4$ Hz, 1H), 7.21−7.67 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.0, 52.4, 60.2, 61.7, 123.3, 126.9, 128.4, 128.5, 131.0, 132.4, 134.1, 164.3, 166.5, 168.1; anal calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69; found: C, 65.84; H, 4.41; N, 7.66.

(3*SR*,4*RS*)-1-(Methoxycarbonyl)methyl-4-phenyl-3-vinyl-2-azetidinone (7db-*trans*). IR (film) 1779 (β-lactam), 1750 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.48 (d, $J = 18.0$ Hz, 1H), 3.69 (m, 1H), 3.71 (s, 3H), 4.39 (d, $J = 18.0$ Hz, 1H), 4.67 (d, $J = 2.2$ Hz, 1H), 5.26−5.39 (m, 2H), 5.96−6.13 (m, 1H), 7.31−7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.3, 52.2, 62.0, 64.6, 119.5, 126.3, 128.6, 129.0, 130.6, 136.6, 168.4, 168.5; anal. MS (DCI) *m*/*z* (%): 246 (MH^+, 100), 178 (36), 131 (48), 116 (15); HRMS calcd for $C_{14}H_{16}NO_3$ (MH^+, *m*/*z*): 246.1130; found: 246.1121. The corresponding cis isomer (**7db**-*cis*) could not be isolated.

(3*SR*,4*RS*)-1-(Methoxycarbonyl)methyl-4-(4-methoxyphenyl)-3-vinyl-2-azetidinone (7dc-*trans*). IR (film) 1770 (β-lactam), 1748 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.45 (d, $J = 18.0$ Hz, 1H), 3.67 (m, 1H), 3.71 (s, 3H), 3.81 (s, 3H), 4.35 (d, $J = 18.0$ Hz, 1H), 4.62 (d, $J = 2.3$ Hz, 1H), 5.28−5.37 (m, 2H), 5.94−6.12 (m, 1H), 6.91 (d, 2H), 7.23 (d, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.1, 52.2, 55.2, 61.5, 64.6, 114.3, 119.5, 127.7, 128.4, 130.6, 159.9, 168.4, 168.6; GCMS *m*/*z* (%): 275 (M^+, 20), 244 (8), 208 (76), 202 (40), 160 (73), 148 (100), 121 (92); anal. HRMS calcd for $C_{15}H_{17}NO_4$ (M^+, *m*/*z*): 275.1158; found: 275.1152.

(3*SR*,4*SR*)-1-(Methoxycarbonyl)methyl-4-(4-methoxyphenyl-3-vinyl-2-azetidinone (7dc-*cis*). IR (film) 1770 (β-lactam), 1748 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.55 (d, $J = 18.0$ Hz, 1H), 3.72 (s, 3H), 3.82 (s, 3H), 4.21−4.28 (1H, m), 4.45 (d, $J = 18.0$ Hz, 1H), 5.05−5.11 (2H, m), 5.29−5.35 (m, 2H), 6.89−6.95 (m, 2H), 7.12−7.27 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.0, 52.3, 55.2, 59.2, 59.6, 114.0, 120.2, 126.3, 128.6, 128.7, 159.5, 168.5, 168.6; GCMS *m*/*z* (%): 275 (M^+, 18), 244 (5), 208 (78), 202 (40), 160 (35), 148 (100), 121 (94); anal. HRMS calcd for $C_{15}H_{17}NO_4$ (M^+, *m*/*z*): 275.1158; found: 275.1158.

Representative Procedure for the Solid-Phase Synthesis of 3,4-Disubstituted β-Lactams Using Homochiral Aldehydes: (3*S*, 4*S*)-4-[(1*S*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-1-(methoxycarbonyl)methyl-3-phenoxy-2-azetidinone (7ak). To a solution of (*S*)-ethyl lactate (**14a**) (930 mg, 7.9 mmol) in DMF (7.7 mL) was added imidazole (752 mg, 11 mmol) and *tert*-butyldiphenylchlorosilane (2.42 mL, 9.5 mmol). After 2 h at room temperature, the mixture was diluted with hexane (45 mL) and water (6 mL). The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane:AcOEt, 95:5) to give (*S*)-ethyl-2-(*tert*-butyl-diphenyl-silanyloxy)propionate (2.6 g, 92%): $[\alpha]^{32}_D = -44.5$ (*c* 6.28, $CHCl_3$); IR (film) 1750 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.11 (t, $J = 7.1$ Hz, 3H), 1.37 (d, $J = 6.7$ Hz, 3H), 4.02 (q, $J = 7.1$ Hz, 2H), 4.26 (q, $J = 6.7$ Hz, 1H), 7.35−7.70 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.90, 19.12, 21.12, 26.70, 60.41, 68.86, 127.41, 127.49, 129.61, 133.14, 133.51, 134.68, 135.62, 135.78, 173.59. To a solution of the ester (1.6 g, 4.7 mmol) in anhydrous THF (30 mL) was added a solution of DIBAL in toluene (0.65 M, 13.8 mL, 9 mmol) dropwise at −78 °C. After 1 h, MeOH (0.79 mL) and water (2.1 mL) were added and the mixture was allowed to reach room temperature and was stirred for an additional hour. The suspension was then filtered through a pad of Celite and washed with ether. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure. The residue was subjected to column chromatography (hexane−AcOEt, 95:5) to give (*S*)-2-(*tert*-butyldiphenyl-silanyloxy)propionaldehyde **3k** (767 mg, 53%): $[\alpha]^{29}_D = -17.32$ (*c* 17.9, $CHCl_3$); IR (film) 1750 (ester) 1735 (aldehyde) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.22 (d, $J = 6.8$ Hz, 3H), 4.08 (dq, $J = 1.3$, 6.8 Hz, 1H), 7.38−7.65 (m, 10H), 9.64 (d, $J = 1.3$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.18, 19.02, 26.67, 74.23, 127.57, 127.64, 129.77, 129.84, 132.76, 133.151, 135.53, 203.58. To a suspension of resin **2** (0.13 mmol) and 4 Å molecular sieves (six beads) in CH_2Cl_2 (5 mL) was added **3k** (304 mg, 0.98 mmol, 7.5 equiv). The reaction mixture was refluxed for 8 h, after which the resin was filtered, washed with CH_2Cl_2 (3 × 4 mL), and dried under high vacuum affording the support-bound imine **4k**, which was taken immediately onto the next step. To a suspension of resin **4k** (0.013 mmol) in CH_2Cl_2 (5 mL) at 0 °C, triethylamine (0.362 mL, 2.6 mmol, 20 equiv) and phenoxyacetyl chloride **5a** (0.276 mL, 1.95 mmol, 15 equiv) were successively added dropwise. After 5 min at the same temperature, the mixture was stirred overnight at room temperature, filtered, and washed successively with CH_2Cl_2 (3 × 4 mL), AcOEt (3 × 4 mL), MeOH (3 × 4 mL), and CH_2Cl_2 (1 × 4 mL). After drying in vacuo overnight, the support-bound β-lactam **6ak** (149 mg, theoretical loading: 0.83 mmol/g, 0.123 mmol) was treated with 5 mL of 10% TFA in CH_2Cl_2 for 50 min at room temperature. The mixture was then filtered and the filtrate was evaporated under reduced pressure. Esterification of the residue with diazomethane gave a crude compound as a 10:1 mixture of diastereoisomers [(3*S*, 4*S*, 1*S*)/(3*R*, 4*R*, 1*S*)], which was purified by column chromatography (hexane−AcOEt, 80:20) to provide 43 mg of the compound **7ak** (67% overall yield, on the basis of the initial loading level of the Fmoc−Gly Wang resin): $[\alpha]^{25}_D = -62.1$ (*c* 0.53, $CHCl_3$); IR (film) 1779 (β-lactam), 1744 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (d, $J = 6.2$ Hz, 3H), 1.04 (s, 9H), 3.75 (s, 3H), 4.01 (d, $J = 18.0$ Hz, 1H), 4.10 (dd, $J = 5.3$, 7.7 Hz, 1H), 4.43 (d, $J = 18.0$ Hz, 1H), 4.42−4.49 (m, 1H), 5.29 (d, $J = 5.3$ Hz, 1H), 6.98−7.70 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.06, 20.94, 26.90, 42.84, 52.40, 63.22, 70.44, 80.39, 115.87, 122.21, 127.51, 127.70, 129.41, 129.66, 129.74, 133.41, 134.40, 135.49, 135.72, 157.61, 167.30, 168.48; MS (DEI) *m*/*z* (%): 518 (MH^+, 6.5), 460 (100), 432 (22), 388 (58), 360 (63), 275 (95), 213 (85), 135 (63); anal. HRMS calcd for $C_{30}H_{36}NO_5Si$ (MH^+, *m*/*z*): 518.2363; found: 518.2370.

(3*S*,4*R*)-4-[(1*S*)-1-Benzyloxyethyl]-1-(methoxycarbonyl-)methyl-3-phenoxy-2-azeti Dinone (7al). mp 73−74 °C; $[\alpha]^{25}_D = -69.2$ (*c* 0.27, $CHCl_3$); IR (film) 1771 (β-lactam), 1750 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, $J = 5.5$ Hz, 3H), 3.61 (s, 3H), 4.03 (d, $J = 17.8$ Hz, 1H), 3.99−4.08 (m, 2H), 4.29 (d, $J = 17.8$ Hz, 1H), 4.4 (d, $J = 1.3$ Hz, 1H), 4.68 (d, $J = 11.3$ Hz, 1H), 5.34 (d, $J = 4.8$, 1H), 7.02−7.36 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.13, 42.88, 52.01, 61.81, 70.34, 76.01, 80.35, 115.84, 122.30, 127.44, 127.60, 128.34, 129.50, 138.04, 157.63, 166.62, 168.32; anal calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79; found: C, 68.65; H, 6.72; N, 3.56.

(3*S*, 4*S*)-4-[(1*S*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-phenyl-methyl]-1-(methoxycarbonyl)methyl-3-phenoxy-2-azetidinone (−) (7am). $[\alpha]^{25}_D = -41.8$ (*c* 1.31, $CHCl_3$); IR (film) 1774 (β-lactam), 1746 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 9H), 3.76 (s, 3H), 3.97 (d, $J = 18.0$ Hz, 1H), 4.28 (d, $J = 18.0$ Hz, 1H), 5.53 (dd, $J = 5.3$, 9.2 Hz, 1H), 5.07 (d, $J = 5.3$ Hz, 1H), 5.26 (d, $J = 9.2$ Hz, 1H), 6.71−7.63 (m, 20H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.08, 26.90, 42.90, 52.20, 63.59, 80.55, 115.58, 121.85, 127.23, 127.62, 127.73, 127.91, 128.06, 129.09, 129.49, 129.65, 132.66, 133.61, 135.34, 135.80, 139.76, 157.63, 167.56, 168.56; MS (FAB^+) *m*/*z* (%): 580 (MH^+, 11), 522 (35), 345 (63), 296 (34), 213 (32), 197 (78), 135 (100); anal. HRMS calcd for $C_{35}H_{37}NO_5Si$ (MH^+, *m*/*z*): 580.2519; found: 580.2501.

(3*R*, 4*R*)-4-[(1*R*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-phenyl-methyl]-1-(methoxycarbonyl)methyl-3-phenoxy-2-azetidinone (+) (7am). $[\alpha]^{25}_D = +45.2$ (*c* 0.64, $CHCl_3$).

(3*S*, 4*S*)-4-[(1*S*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-1-(methoxycarbonyl)meth yl-3-methoxy-2-azetidinone (7ck). $[\alpha]^{25}_D = -49.0$ (c 0.67, $CHCl_3$); IR (film) 1771 (β-lactam), 1749 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (d, $J = 6.1$ Hz, 3H), 1.01 (s, 9H), 3.48 (s, 3H), 3.71 (s, 3H), 3.88 (dd, $J = 8.08$, 5.2 Hz, 1H), 3.93 (d, $J = 18.0$ Hz, 1H), 4.28 (dq, $J = 8.1$, 6.1 Hz, 1H), 4.33 (d, $J = 18.0$ Hz, 1H), 4.5 (d, $J = 5.2$ Hz, 1H), 7.71−7.36 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.02, 20.60, 26.90, 42.52, 52.05, 59.04, 63.25, 70.68, 83.36, 127.46, 127.65, 129.60, 129.66, 133.63, 134.49, 135.44, 135.71, 168.52, 168.73; MS (DEI) *m*/*z* (%): 456 (MH^+, 6), 398 (36), 370 (42), 326 (40), 283 (43), 213 (100), 183 (33), 135 (35); anal. HRMS calcd for $C_{25}H_{33}NO_5Si$ (MH^+, *m*/*z*): 456.2206; found: 456.2199.

(3*S*, 4*S*)-4-[(1*S*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-phenyl-methyl]-1-(methoxycarb onyl)methyl-3-methoxy-2-azetidinone (7cm). $[\alpha]^{25}_D = +35.6$ (*c* 0.34, $CHCl_3$) IR (film) 1771 (β-lactam), 1750 (ester) cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 0.95 (s, 9H), 2.83 (s, 3H), 3.23 (s, 3H), 4.00 (d, $J = 18.0$ Hz, 1H), 4.03 (d, $J = 5.2$ Hz, 1H), 4.33 (d, $J = 18.0$ Hz, 1H), 4.42 (dd, $J = 5.2$, 9.0 Hz, 1H), 5.37 (d, $J = 9.0$ Hz, 1H), 6.95−7.77(m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.97, 26.81, 42.54, 51.93, 59.33, 63.93, 76.77, 83.78, 127.09, 127.45, 129.70, 127.84, 129.31, 129.48, 132.75, 133.62, 135.27, 135.71, 140.30, 168.49, 168.69.

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