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Stereoselective, solid phase-based synthesis of *trans* 3-alkyl-substituted β-lactams as analogues of cholesterol absorption inhibitors

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ABSTRACT

A straightforward solid phase-based strategy for the rapid generation of two small libraries of *trans* 3-alkyl-substituted β-lactams is described. For the glycine-derived library, a controlled excess of non-activated acid chlorides was used to prevent oxazinone formation. The second library involved the attachment of Fmoc-protected *p*-aminophenol to Wang resin for the preparation of structurally-closed analogues of known cholesterol absorption inhibitors. This strategy allowed us to introduce diversity in the three variable positions of the β-lactam ring.

1. Introduction

Solid-phase organic synthesis (SPOS) has experienced a spectacular growth since its beginning in the early nineties. With the advent of the small-molecule combinatorial chemistry, the potential of SPOS for the generation of molecular diversity was immediately recognized and this methodology was successfully applied in the field of drug discovery.[1] The advantage of SPOS is the purification step, a simple filtration avoids tiresome and time-consuming separation techniques. Consequently, reagents can be added in excess in order to force the reactions to completion. Moreover, solid-phase methodologies tolerate the use of high-boiling solvents, since their elimination by evaporation is not necessary. More recently, SPOS has gained interest in some particular areas of organic synthesis in view of the effect of the spatial separation of substrates achieved by immobilization on a polystyrene resin. This is remarkably useful in cross coupling reactions to avoid undesired homocoupling products,[2] and in intramolecular macrocyclization due to the 'pseudo-dilution effect'.[3] Therefore, there is a clear need to expand the synthetic transformations and organic structures that can be accomplished through solid-phase techniques.

β-Lactam skeleton has been widely recognized as one the most significant heterocyclic structure in organic chemistry. It is present in a variety of clinically relevant antibiotics, such as penicillins, cephalosporins, carbapenems, carbacephems and monobactam.[4] The usefulness of β-lactam derivatives has been also demonstrated in other important therapeutic areas like inhibition of cholesterol absorption, prostate specific antigen, human tryptase, thrombin and chymase, cysteine protease, human leukocyte elastase and human cytomegalovirus protease.[5] The therapeutic importance of this structure is also clear from reports about β-lactams related to the treatment of cancer,[6] Parkinson[7] and other neurological diseases.[8] Furthermore, β-lactam compounds are very useful as synthetic building blocks.[9]

Excluding antibacterial activity, the use of β-lactams in the treatment of hypercholesterolaemia is their most significant application. Dietary cholesterol consumption and intestinal cholesterol absorption contribute to plasma cholesterol levels, and high serum cholesterol level is the main risk factor for coronary heart disease. In 1994, Burnett et al. reported the synthesis of several β-lactams that were tested for their cholesterol absorption inhibitory activity.[10] They found that the compound (−)-SCH48461 (**A**, Fig. 1) reduces cholesterol levels both in vivo and in vitro assays. The design of these compounds was based on conformationally constrained variants of known ACAT (acyl-coenzime A cholesterol acyltransferase) inhibitors.

Based on the structure of active metabolites of **A**, Van Heek et al.[11] found (−)-SCH58235 (Ezetimibe, **B**, Fig. 1), which was approved as drug by FDA in 2002.[12] The mechanism of action of these β-lactam derivatives does not appear to be similar to that of previous hypolipidemic agents.[13] In fact, it was recently established

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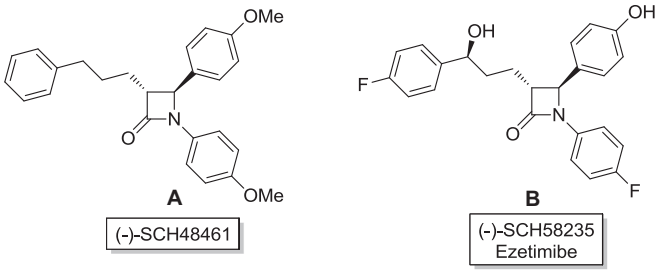
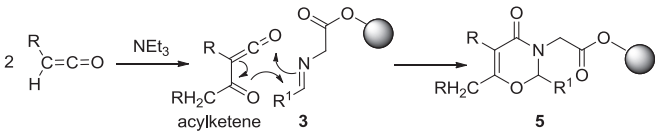


Fig. 1. Cholesterol absorption inhibitors.



Scheme 2. Formation of oxazinone from acylketene and imine.

that Ezetimibe (**B**) blocks cholesterol absorption by interaction with Niemann–Pick C1 Like 1 (NPC1L1) protein.[14] While some recent attempts to improve the activity of ezetimibe through the preparation of new analogues were unsuccessful, it is clear that this field has not yet been thoroughly explored.[15,16]

In continuation to our interest on new strategies for the preparation of biologically promising compounds, we envisaged that the development of a reliable solid phase-based synthesis of *trans* 3-alkyl-substituted β-lactams could be useful for the generation of libraries for biological analysis, as well as mechanistic studies. Our results are summarized in this paper.[17]

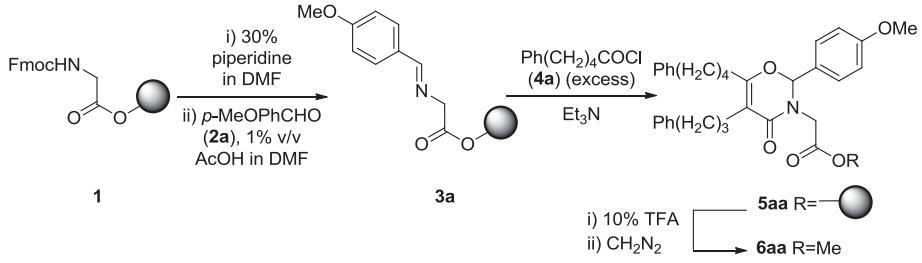
2. Results and discussion

Among a large number of synthetic methods for the synthesis of β-lactam compounds, one of the most used is the [2+2] cycloaddition of imines with in situ-generated ketenes.[18] This annulation of activated carboxylic acids with imines in the presence of base is called Staudinger reaction.[19] Our first synthetic approach for the preparation of a model 3-alkyl-β-lactam was the application of the solid-phase version of the Staudinger reaction.[20] Starting from commercial Fmoc-Gly-Wang resin (**1**), the amine group was deprotected by standard conditions using 30% piperidine in DMF (Scheme 1). This amine tethered to the solid support was condensed with *p*-anisaldehyde (**2a**), giving the imine **3a**. For the Staudinger reaction on solid phase, and in order to drive the reaction to completion, a large excess of 5-phenylvaleroyl chloride (**4a**) (15 equiv) and triethylamine (20 equiv) was added to a dichloromethane suspension of the immobilized imine **3a** at 0 °C. Surprisingly, after stirring for 12 h at room temperature, the oxazinone **5aa** was obtained, instead of the expected β-lactam. Formation of the oxazinone was confirmed after releasing into solution with 10% TFA/DCM followed by esterification with diazomethane, to give **6aa** that was spectroscopically characterized.[21] This compound was isolated in 40% overall yield, based on the initial loading of the Fmoc-Gly-Wang resin.

To prevent the formation of the oxazinone, we decided to decrease the amount of the alkanoyl chloride. For example, when the reaction was performed using 2 equiv of 5-phenylvaleroyl chloride (**4a**) and 4 equiv of triethylamine at reflux of toluene overnight, the expected β-lactam **8aa** (Table 1, entry 1) was isolated but only in 26% overall yield. Due to the presence of the starting aldehyde in the crude mixture, we assumed that the reaction was incomplete. After several attempts, the best conditions were found when a controlled excess of **4a** (4 equiv) and triethylamine (8 equiv) were added to the immobilized imine **3a** and refluxed in toluene for 12 h. After resin cleavage, esterification and purification by flash column chromatography, β-lactam **8aa** was obtained in 57% overall isolated yield (based on initial loading level of Fmoc-Gly-Wang resin). The resultant product was obtained with excellent selectivity, only the 3,4-*trans* stereoisomer was detected (based on analysis of ^{1}H NMR of the crude material). The stereochemistry of the β-lactam was determined from the coupling constants of the protons attached at C-3 and C-4 (≅2 Hz).

After establishing the optimal conditions, we developed a library of different 3-alkyl-β-lactams. As can be seen in Table 1, good overall yields of the β-lactams were obtained and only the trans isomers were observed in all cases. While the 5-phenylvaleroyl chloride (**4a**) was generated in situ from the corresponding acid, propionyl and butyryl chlorides were prepared and used after distillation (entries 6–10); in these cases, 3 equiv of the acid chloride were the optimum conditions to achieve the best performance.

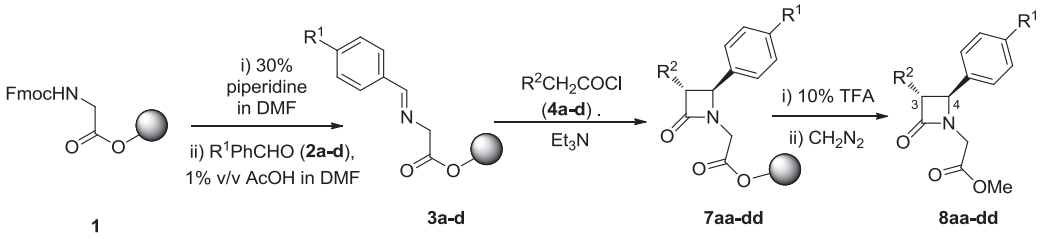
The high stereoselectivity observed can be ascribed to the effect of the substituents at the β-lactam ring. According to the ketene-imine mechanism,[22,23] a zwiterionic intermediate **III** is initially formed through the attack of the imine nitrogen at the carbonyl carbon of the ketene, followed by a direct ring closure (leading to the *cis* β-lactam) or an isomerization-ring closure (leading to the *trans* β-lactam) (Scheme 3). Electron-donating groups in the ketene component (R) accelerate the conrotatory ring closure due to the increase in nucleophilicity of the enolate, yielding the thermodynamically less stable



Scheme 1. Synthesis of the unexpected oxazinone.

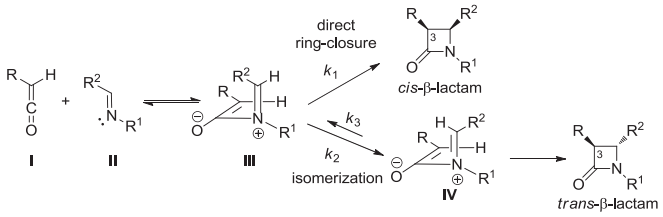
This result could be explained by the tendency of ketenes to suffer dimerization to acylketenes, which is favoured by the excess of alkanoyl chloride used in our strategy. It is known that *cis* β-lactam (increase k_1). In our case, a nonactivated aliphatic ketene is formed, so the tendency to the direct ring closure is diminished and the zwitterionic intermediate **III** could rotate to the sterically less

Table 1
Solid-phase synthetic sequence for the preparation of 3-alkyl-β-lactams



Entry	β-Lactam	R^1	R^2	Yield[a] %
1	**8aa**	4-MeO	$Ph(CH_2)_3$	26[b]
2	**8aa**	4-MeO	$Ph(CH_2)_3$	57[c]
3	**8ba**	H	$Ph(CH_2)_3$	57[c]
4	**8ca**	4-Me	$Ph(CH_2)_3$	56[c]
5	**8da**	4-Br	$Ph(CH_2)_3$	43[c]
6	**8ab**	4-MeO	CH_3	52[d]
7	**8cb**	4-Me	CH_3	54[d]
8	**8ac**	4-MeO	CH_3CH_2	51[d]
9	**8ad**	4-MeO	$CH_3(CH_2)_3$	48[d]
10	**8dd**	4-Br	$CH_3(CH_2)_3$	50[d]

[a] Overall isolated yield after flash column chromatography (based on initial loading of Fmoc-Gly-Wang resin, five reaction steps).
[b] Performed using 2 equiv of acid chloride and 4 equiv of Et_3N.
[c] Performed using 4 equiv of acid chloride and 8 equiv of Et_3N.
[d] Performed using 3 equiv of acid chloride and 6 equiv of Et_3N.



Scheme 3. Proposed mechanism for the Staudinger Reaction.[22]

congested iminiun ion **IV**, leading to the *trans* β-lactam (k_2). It is clear that the substituent at position 3 rules the stereochemical outcome in our examples since no effect is observed when substituents in the imine component are changed.

At the next stage in the solid-phase synthesis of analogues of cholesterol absorption inhibitors, we decided to install the proper substituent at position 1 of the β-lactam ring. Thus, we planned a new strategy using a *p*-aminophenol moiety as the solid-phase linker. Fmoc-protected *p*-aminophenol (**9**, Scheme 4) was attached to Wang resin using tetramethylamine azodicarboxylate (TMAD) and tributylphosphine in THF/DCM (1/1). Optimal results were obtained when the mixture was stirred overnight at room temperature.[24] The Fmoc group in resin **10** was eliminated by treatment with 30% piperidine in DMF, and the resultant immobilized aniline was condensed with *p*-anisaldehyde (**2a**) to perform the imine **11a**. Two different conditions were tested for the β-lactam ring formation. In the first approach, the immobilized imine **11a** was refluxed in toluene in the presence of 5-phenylvaleroyl chloride (**4a**) and triethylamine, under the previously optimized conditions. After releasing into solution with 10% TFA/DCM, the corresponding *trans* β-lactam **15aa** was obtained in 9% isolated overall yield.[25] Further attempts to improve this yield were unsuccessful.

In the search for a more efficient procedure, the formation of the ketene from an in situ activated carboxylic acid was tested. Therefore, the resin-bound imine **11a** was treated with triethylamine (6 equiv), 5-phenylvaleric acid (**12a**) (2.5 equiv) and Mukaiyama's reagent (**13**) as acid-activating agent (3 equiv), followed by refluxing in chloroform for 2 h.[26] Then, the resin was resubjected to the same reaction conditions to ensure the complete formation of the product. After standard separation from the resin and purification, the desired β-lactam **15aa** was obtained in 15% isolated yield for the whole synthetic sequence (based on the initial loading level of the Wang resin).

Interestingly, compound **15aa** is a demethylated analogue of cholesterol absorption inhibitor SCH48461 (see Fig. 1). A small library of 3-alkyl-1-aryl-β-lactams was then generated using the activation by Mukaiyama's reagent (Table 2). After five reaction steps, different analogues of cholesterol absorption inhibitors were obtained. The lower yields compared with the glycine-derived library might be explained because of the lower activity of the aromatic imine in the Staudinger reaction. In all cases, trans-selectivity was excellent (the cis isomer was not identified by ^1H NMR). Besides, formation of the corresponding oxazinone was not detected under the optimized conditions.

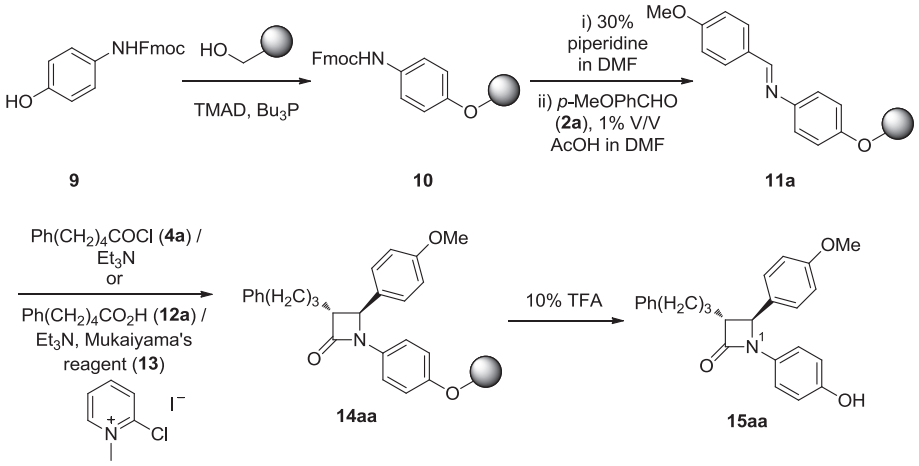
3. Conclusions

A renewed interest in the synthesis of monocyclic β-lactams has been sparked due to the outstanding antihypercholesterolemic activity of some of their derivatives. Herein, we report a solid-phase synthetic sequence for the rapid generation of *trans* 3-alkyl-substituted β-lactams. Key step was the Staudinger reaction between immobilized imines and in situ-generated ketenes. For the glycine-derived library, acid chlorides were an efficient precursor of the ketenes, while a controlled excess of them was used to avoid the oxazinone by-product. On the other hand, activation of alkanoic acid by Mukaiyama's reagent was more effective for the preparation 3-alkyl-1-aryl-β-lactams. In this way, we have generated a small library where we have introduced diversity in the three variable positions of the β-lactam ring. In summary, we have demonstrated the usefulness of the solid-phase synthesis for the generation of structurally-closed analogues of known biologically interesting compounds.

4. Experimental section

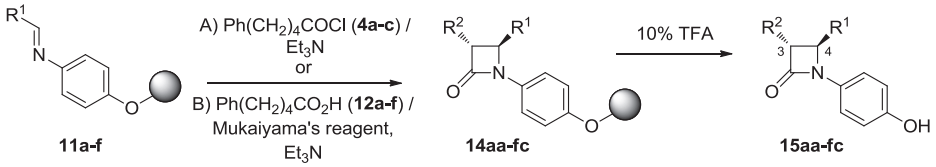
4.1. General

Chemical reagents were purchased from commercial sources and were used without further purification unless noted otherwise.



Scheme 4. Sequence for the solid-phase synthesis of 3-alkyl-1-aryl-β-lactams.

Table 2
Library of 3-alkyl-1-aryl-β-lactams



Entry	β-Lactam	R^1	R^2	Method	Yield[a] %
1	**15aa**	4-MeOPh	$Ph(CH_2)_3$	B	15
2	**15aa**	4-MeOPh	$Ph(CH_2)_3$	A	9
3	**15ba**	Ph	$Ph(CH_2)_3$	B	8
4	**15da**	4-BrPh	$Ph(CH_2)_3$	B	12
5	**15fa**	4-ClPh	$Ph(CH_2)_3$	B	10
6	**15ac**	4-MeOPh	CH_3CH_2	B	9
7	**15ac**	4-MeOPh	CH_3CH_2	A	—

[a] Overall isolated yield after flash column chromatography (based on initial loading of Fmoc-Gly-Wang resin, five reaction steps).

Solvents were analytical grade or were purified by standard procedures prior to use. Infrared spectra (IR) were recorded on a Shimadzu Prestige 21 spectrophotometer and only partial spectral data are listed. ^{1}H NMR spectra were recorded on a Bruker avance at 300 MHz and on a Bruker AC200 at 200 MHz for 1H in $CDCl_3$, in the presence of TMS (0.00 ppm) as the internal standard. Conventional and gel-phase ^{13}C NMR spectra were recorded on the same apparatus at 75 MHz and 50 MHz with $CDCl_3$ as solvent and reference (76.9 ppm), unless otherwise stated. ^{13}C NMR assignments were made on the basis of chemical shifts and proton multiplicities (from DEPT spectra). Mass spectra were performed at the University of California Riverside Mass Spectrometry Facility. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh).[27]

4.2. Typical procedures

Preparation of **4a**: A solution of 5-phenylvaleric acid (**12a**) (0.053 g, 0.3 mmol, 4 equiv) and oxalyl chloride (0.040 mL, 0.45 mmol) were stirred in anhydrous dichloromethane (1.9 mL) for 3 h, and then the mixture was evaporated in vacuo to afford the crude 5-phenylvaleroyl chloride (**4a**), which was used without further purification.

Preparation of β-lactam **7aa**: Fmoc-Gly-Wang resin (**1**) (100 mg, 0.075 mmol, loading 0.75 mmol/g) was suspended in 30% piperidine in DMF (3 mL). After stirring for 50 min at room temperature, the mixture was filtered and washed sequentially with DMF (3×4 mL), CH_2Cl_2 (3×4 mL), MeOH (3×4 mL) and CH_2Cl_2 (1×4 mL), and dried under high vacuum. Then, the resin was suspended in a 1% solution of AcOH in DMF and *p*-anisaldehyde (**2a**) (45 μL, 0.375 mmol, 5 equiv) was added. The reaction was stirred 45 min at room temperature, after that the resin was filtered, and reprocessed under the same conditions. The resin was filtered and washed successively with DMF (3×4 mL), CH_2Cl_2 (3×4 mL), MeOH (3×4 mL) and CH_2Cl_2 (1×4 mL), and dried to afford **3a**. To a suspension of resin-bound imine **3a** (0.075 mmol) in dry toluene (2.2 mL) was added dropwise triethylamine (0.084 mL, 0.6 mmol, 8 equiv) and a solution of **4a** (4 equiv) in toluene (0.8 mL). The mixture was stirred at reflux overnight. After that, the resin was filtered and washed with DMF (3×4 mL), CH_2Cl_2 (3×4 mL), MeOH (3×4 mL) and CH_2Cl_2 (1×4 mL), and finally dried in vacuo affording **7aa**. Resin-bound β-lactam **7aa** (0.097 g, 0.073 mmol, 0.75 mmol/g) was suspended in 10% TFA in dichloromethane (3 mL) and was stirred at room temperature for 50 min. The reaction was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in dichloromethane (3 mL), stirred at 0 °C, and a solution of diazomethane in ether were added. After the reaction was completed, the solvent was evaporated and the crude product was purified by flash chromatography using hexane/ethyl acetate (70:30) to afford **8aa** (15.3 mg, 57%).

Preparation of β-lactam **15aa**: Wang resin (500 mg, 0.55 mmol, 1.1 mmol/g) was swelled by gentle stirring in a 1:1 mixture of anhydrous THF/CH_2Cl_2 (8 mL) under a nitrogen atmosphere. Solid TMAD (472 mg, 2.75 mmol, 5 equiv) was added with stirring until

dissolution occurs. Phenol **9** (909 mg, 2.75 mmol, 5 equiv) was added and the reaction mixture was stirred until complete dissolution occurs. Then, neat Bu_3P (0.674 mL, 2.4 mmol, 5 equiv) was added via syringe. The mixture was stirred overnight at room temperature. After filtration, the resin **10** was sequentially washed with THF (3×4 mL), CH_2Cl_2 (3×4 mL), MeOH (3×4 mL) and CH_2Cl_2 (4 mL), and finally dried under high vacuum. This Resin **10** (0.55 mmol) was suspended in 30% piperidine in DMF (5 mL) and stirred for 50 min at room temperature. Then, 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 (4 mL) and dried under high vacuum. The resulting resin-bound aniline (0.55 mmol) was suspended in a 1% solution of AcOH in anhydrous DMF (ca. 5 mL) and *p*-anisaldehyde (**2a**) (0.33 mL, 2.75 mmol, 5 equiv) was added. The reaction was stirred for 45 min at room temperature, after which the resin was filtered, washed with anhydrous DMF (3×4 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), MeOH (3×4 mL) and CH_2Cl_2 (1×4 mL), and dried under high vacuum affording the support-bound aldimine **11a**, which was taken immediately to the next step.

5-phenylvaleric acid (**12a**) (245 mg, 1.37 mmol, 2.5 equiv) and Et_3N (0.46 mL, 3.3 mmol, 6 equiv) were dissolved in anhydrous chloroform (6 mL) and added to a suspension of imine **11a** (0.55 mmol) in anhydrous chloroform (2 mL) under a nitrogen atmosphere. After a minute, 2-chloro-1-methylpyridinium iodide (**13**) (Mukaiyama's reagent, 421 mg, 1.65 mmol, 3 equiv) was added and the suspension was refluxed for 2 h. Then, the reaction mixture was filtered and the resin was washed successively with CH_2Cl_2 (3×5 mL), MeOH (3×5 mL) and CH_2Cl_2 (1×5 mL). After drying in vacuo, the resin was resubjected to the same reaction conditions. A portion of the immobilized β-lactam **14aa** (98 mg, 0.862 mmol/g, 0.084 mmol) was treated with 5 mL of 10% TFA in CH_2Cl_2 for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give 24 mg of a crude β-lactam **14aa**. This crude material was purified by column chromatography (hexane/AcOEt) to provide 9.3 mg (0.034 mmol) of the compound **15aa** (15% overall yield, on the basis of the initial loading level of the Wang resin).

Preparation of oxazinone **6aa**: To the resin **3a** (0.092 mmol) suspended in anhydrous dichlorometane (2.7 mL) at 0 °C was added dropwise triethylamine (0.26 mL, 1.8 mmol, 20 equiv) and the solution of crude 5-phenylvaleroyl chloride (**4a**) (15 equiv) in dichloromethane (1.8 mL). The reaction was stirred at room temperature overnight. Then, the resin was filtered and washed with DMF (3×4 mL), CH_2Cl_2 (3×4 mL), MeOH (3×4 mL) and CH_2Cl_2 (1×4 mL), and dried in vacuo affording **5aa**. Resin-bound oxazinone **5aa** (0.133 g, 0.089 mmol, 0.67 mmol/g) was suspended in 10% TFA in dichloromethane (3.5 mL) and stirred at room temperature for 50 min. After that, the reaction was filtered and the filtrate evaporated in vacuo. The residue was dissolved in dichloromethane (3.5 mL) at 0 °C, and a solution of diazomethane in ether was added. After the reaction was completed, the solvent was evaporated and the crude product was purified by flash chromatography using hexane/ethyl acetate (80:20) to give **6aa** (18.6 mg, 40%).

*4.2.1. 6-(4-Phenylbutyl)-5-(3-phenylpropyl)-2,3-dihydro-3-methoxycarbonylmethyl-2-(4-methoxyphenyl)-[1,3]oxazin-4-one (**6aa**).* ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52–1.80 (m, 6H), 1.82–2.69 (m, 8H), 3.26 (d, *J*=17.6 Hz, 1H), 3.64 (s, 3H), 4.47 (d, *J*=17.6 Hz, 1H), 6.10 (s, 1H), 6.90–7.38 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.97, 165.70, 164.82, 160.83, 141.97, 142.27, 129.22, 128.33, 128.18, 126.66, 125.62, 125.51, 109.89, 88.57, 55.22, 51.87, 44.21, 35.62, 35.39, 31.54, 30.75, 30.28, 26.33, 24.73.

*4.2.2. 6-Ethyl-2,3-dihydro-3-methoxycarbonylmethyl-2-(4-methoxyphenyl)-5-methyl-[1,3]oxazin-4-one (**6ab**).* IR (film): 1750 (ester), 1660 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, *J*=7.4 Hz), 1.85 (s, 3H), 2.25–2.38 (m, *J*=7.4 Hz, 2H), 3.25 (d, *J*=18 Hz, 1H), 3.64 (s, 3H), 3.83 (s, 3H), 4.46 (d, *J*=18 Hz, 1H), 6.14 (s, 1H), 6.93 (d, *J*=8.8 Hz, 2H), 7.39 (d, *J*=8.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.13, 166.38, 165.98, 160.83, 129.26, 126.58, 114.102, 104.06, 88.74, 55.24, 51.92, 44.13, 24.15, 10.91, 9.95. MS (EI) *m*/*z* (%): 319 (M^+, 4.5), 262 (72), 192 (11), 148 (100), 134 (26), 121 (68).

*4.2.3. (3SR,4RS)-3-(3-Phenylpropyl)-4-(4-methoxyphenyl)-1-methoxycarbonylmethyl-azetidin-2-one (**8aa**).* IR (film): 1768 (β-lactam), 1747 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60–1.95 (m, 4H), 2.62 (t, *J*=6.8 Hz, 2H), 3.05 (br t, *J*=5.6 Hz, 1H), 3.40 (d, *J*=18 Hz, 1H), 3.68 (s, 3H), 3.80 (s, 3H), 4.31 (d, *J*=18 Hz, 1H), 4.45 (d, *J*=2 Hz, 1H), 6.87–7.26 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.77, 168.59, 159.77, 141.73, 129.18, 128.27, 128.22, 127.64, 125.71, 114.36, 61.32, 61.00, 55.23, 52.10, 40.90, 35.60, 28.80, 28.00. MS *m*/*z* (%): 367 (M^+, 6), 259 (40), 250 (100), 224 (20), 208 (60), 148 (72), 121 (78), 91 (11); HRMS calcd for $C_{22}H_{25}NO_4$ (M^+, *m*/*z*): 367.1784; found, 367.1796.

*4.2.4. (3SR, 4RS)-3-(3-Phenylpropyl)-4-(4-methylphenyl)-1-methoxycarbonylmethyl-azetidin-2-one (**8ca**).* IR (film): 1774 (β-lactam), 1754 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72–1.93 (m, 4H), 2.35 (s, 3H), 2.62 (t, *J*=7.3 Hz, 2H), 3.01 (br t, *J*=6, 2 Hz, 1H), 3.41 (d, *J*=18 Hz, 1H), 3.68 (s, 3H), 4.35 (d, *J*=18 Hz, 1H), 4.48 (d, *J*=2 Hz, 1H), 7.12–7.26 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.73, 168.61, 141.70, 138.32, 134.31, 129.60, 128.26, 128.19, 126.24, 125.68, 61.44, 61.02, 52.11, 40.89, 35.58, 28.81, 28.00, 21.01. MS *m*/*z* (%): 351 (M^+, 20), 292 (10), 259 (10), 234 (100), 208 (25), 192 (48), 145 (56), 131 (65), 105 (80), 91 (56), 43 (13); HRMS calcd for $C_{22}H_{25}NO_3$ (M^+, *m*/*z*): 351.1834; found, 351.1837.

*4.2.5. (3SR,4RS)-4-(4-Bromophenyl)-3-(3-phenylpropyl)-1-methoxycarbonylmethyl-azetidin-2-one (**8da**).* IR (film): 1778 (β-lactam), 1760 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78–1.90 (m, 4H), 2.63 (t, *J*=7.3 Hz, 2H), 3.03 (br t, *J*=6.7, 2.2 Hz, 1H), 3.41 (d, *J*=18 Hz, 1H), 3.69 (s, 3H), 4.33 (d, *J*=18 Hz, 1H), 4.48 (d, *J*=2.2 Hz, 1H), 7.11–7.26 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.37, 168.44, 141.57, 136.64, 132.14, 128.25, 127.98, 126.24, 125.77, 122.37, 61.33, 61.10, 52.17, 41.06, 35.56, 28.76, 27.97. MS (DEI) *m*/*z* (%): 415 (M^+, 4), 256 (15), 182 (10), 169 (15), 144 (43), 116 (53), 104 (60), 91 (100), 79 (16), 65 (18), 55 (29); HRMS calcd for $C_{21}H_{22}BrNO_3$ (M^+, *m*/*z*): 415.0783; found, 415.0788.

*4.2.6. (3SR,4RS)-3-Methyl-4-(4-methoxyphenyl)-1-methoxycarbonylmethyl-azetidin-2-one (**8ab**).* IR (film): 1765 (β-lactam), 1747 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (d, *J*=7.4 Hz, 3H), 3.01–3.14 (qd, *J*=2, 7.4 Hz, 1H), 3.42 (d, *J*=18 Hz, 1H), 3.71 (s, 3H), 3.81 (s, 3H), 4.32 (d, *J*=18 Hz, 1H), 4.39 (d, *J*=2 Hz, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.23 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.44, 168.61, 159.78, 129.08, 127.67, 114.28, 62.87, 55.76, 52.23, 52.12, 40.94, 12.66. MS *m*/*z* (%): 263 (M^+, 20), 248 (36), 232 (55), 148 (100), 121 (50), 91 (14), 77 (12); HRMS calcd for $C_{14}H_{17}NO_4$ (M^+, *m*/*z*): 263.1158; found, 263.1158.

*4.2.7. (3SR,4RS)-3-Methyl-4-(4-methylphenyl)-1-methoxycarbonylmethyl-azetidin-2-one (**8cb**).* IR (film): 1775 (β-lactam), 1754 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (d, *J*=7.3 Hz, 3H), 2.36 (s, 3H), 3.02–3.14 (dq, *J*=2, 7.3 Hz, 1H), 3.43 (d, *J*=18 Hz, 1H), 3.71 (s, 3H), 4.35 (d, *J*=18 Hz, 1H), 4.41 (d, *J*=2 Hz, 1H), 7.19 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.39, 168.58, 138.36, 134.27, 129.56, 126.29, 63.10, 55.84, 52.10, 41.01, 21.00, 12.67. MS *m*/*z* (%): 247 (M^+, 2), 232 (17), 219 (24), 192 (13), 132 (100), 117 (80), 105 (28), 91 (15); HRMS calcd for $C_{14}H_{17}NO_3$ (M^+, *m*/*z*): 247.1208; found, 247.1207.

*4.2.8. (3SR,4RS)-3-(3-Phenylpropyl)-4-(phenyl)-1-methoxycarbonylmethyl-azetidin-2-one (**8ba**).* IR (film): 1775 (β-lactam),

1754 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–1.91 (m, 4H), 2.62 (t, J=7.3 Hz, 2H), 3.07 (br t, J=6, 2 Hz, 1H), 3.42 (d, J=18 Hz, 1H), 3.68 (s, 3H), 4.36 (d, J=18 Hz, 1H), 4.51 (d, J=2 Hz, 1H), 7.12–7.38 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.64, 168.659, 141.71, 137.52, 128.96, 128.45, 128.24, 126.30, 125.73, 77.54, 76.90, 76.27, 61.68, 61.21, 52.12, 41.05, 35.62, 28.82, 28.06. HRMS calcd for $C_{21}H_{23}NO_3$ (M^+, m/z): 337.1678; found, 337.1686.

*4.2.9. (3SR,4RS)-3-Ethyl-1-methoxycarbonylmethyl-4-(4-methoxyphenyl)-azetidin-2-one (**8ac**).* IR (film): 1773 (β-lactam), 1754 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.06 (t, J=7.4 Hz, 3H), 1.79–2.00 (m, 2H), 3.01 (ddd, J=2, 6.2 and 8.2 Hz, 1H), 3.41 (d, J=18 Hz, 1H), 3.71(s, 3H), 3.81 (s, 3H), 4.34 (d, J=18 Hz, 1H), 4.49 (d, J=2 Hz, 1H), 6.91 (d, J=8.6 Hz, 2H), 7.23 (d, J=8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.79, 168.66, 159.69, 129.40, 127.60, 114.31, 62.52, 60.77, 55.23, 52.11, 40.81, 21.44, 11.27. MS m/z (%): 277 (M^+, 20), 248 (100), 208 (32), 192 (16), 162 (31), 148 (90), 134 (22), 121 (70), 91 (30), 77 (12); HRMS calcd for $C_{15}H_{19}NO_4$ (M^+, m/z): 277.1314; found, 277.1307.

*4.2.10. (3SR,4RS)-3-Butyl-4-(4-methoxyphenyl)-1-methoxycarbonylmethyl-azetidin-2-one (**8ad**).* IR (film): 1770 (β-lactam), 1752 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, J=7 Hz, 3H), 1.44–1.26 (m, 4H), 1.90–1.75 (m, 2H), 3.03 (dt, J=2, 6.2 Hz, 1H), 3.40 (d, J=18 Hz, 1H), 3.70 (s, 3H), 3.81 (s, 3H), 4.33 (d, J=18 Hz, 1H), 4.46 (d, J=2 Hz, 1H), 6.90 (d, J=8.7 Hz, 2H), 7.22 (d, J=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.96, 168.65, 159.72, 129.41, 127.62, 114.32, 61.39, 61.22, 55.22, 52.08, 40.85, 29.22, 28.08, 22.43, 13.71. MS m/z (%): 305 (M^+, 12), 274 (24), 248 (82), 208 (54), 192 (36), 148 (100); 134 (26), 121 (74), 91 (32), 77 (14), 55 (24); HRMS calcd for $C_{17}H_{23}NO_4$ (M^+, m/z): 305.1627; found, 305.1639.

*4.2.11. (3SR, 4RS)-4-(4-Bromophenyl)-3-butyl-1-methoxycarbonylmethyl-azetidin-2-one (**8dd**).* IR (film): 1777 (β-lactam), 1754 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, J=7 Hz, 3H), 1.26–1.44 (m, 4H), 1.71–1.97 (m, 2H), 3.02 (dt, J=2, 6.5 Hz, 1H), 3.41 (d, J=18 Hz, 1H), 3.71 (s, 3H), 4.35 (d, J=18 Hz, 1H), 4.49 (d, J=2 Hz, 1H), 7.18 (d, J=8.4 Hz, 2H), 7.51 (d, J=8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.65, 168.49, 136.81, 132.13, 127.99, 122.30, 61.56, 61.22, 52.18, 41.02, 29.22, 28.07, 22.41, 13.70. MS (DEI) m/z (%): 353 (M^+, 5), 324 (6), 255 (19), 237 (81), 181 (52), 116 (100), 55 (15); HRMS calcd for $C_{16}H_{20}BrNO_3$ (M^+, m/z): 353.0627; found, 353.0637.

*4.2.12. (3SR, 4RS)-1-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-3-(3-phenylpropyl)-azetidin-2-one (**15aa**).* IR (film): 2926, 1720 (β-lactam) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.12 (m, 9H), 6.87 (d, J=8.8 Hz, 2H), 6.69 (d, J=8.8 Hz, 2H), 4.54 (d, J=2.3 Hz, 1H), 3.79 (s, 3H), 3.08–3.03 (m, 1H), 2.62 (t, J=7.3 Hz, 2H), 1.96–1.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 159.5, 152.1, 141.6, 131.0, 129.7, 128.3, 127.1, 125.8, 118.4, 115.6, 114.5, 60.9, 60.2, 55.2, 35.6, 28.8, 28.2; HRMS calcd for $C_{25}H_{26}NO_3$ (MH^+, m/z): 388.1913; found, 388.1911.

*4.2.13. (3SR, 4RS)-1-(4-Hydroxyphenyl)-4-phenyl-3-(3-phenylpropyl)-azetidin-2-one (**15ba**).* IR (film): 2925, 1714 (β-lactam) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.14 (m, 12H), 6.71 (d, J=8.8 Hz, 2H), 4.58 (d, J=2.3 Hz, 1H), 3.09–3.06 (m, 1H), 2.64 (t, J=7.3 Hz, 2H), 1.98–1.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 152.0, 141.7, 138.1, 131.4, 129.2, 128.4, 125.9, 118.4, 115.7, 61.3, 60.4, 35.7, 28.9, 28.4; HRMS calcd for $C_{24}H_{24}NO_2$ (MH^+, m/z): 358.1807; found, 358.1805.

*4.2.14. (3SR, 4RS)-1-(4-Hydroxyphenyl)-4-(4-bromophenyl)-3-(3-phenylpropyl)-azetidin-2-one (**15da**).* IR (film): 2925, 1714 (β-lactam) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J=8.3 Hz, 2H), 7.26–7.12 (m, 9H), 6.70 (d, J=8.6 Hz, 2H), 5.30 (br s, 1H), 4.54 (d, J=2.1 Hz, 1H), 3.04–3.01 (m, 1H), 2.63 (t, J=7.2 Hz, 2H), 1.92–1.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 152.3, 141.5, 137.1, 132.4, 130.9, 128.4, 127.6, 126.0, 122.3, 118.4, 115.9, 60.6, 60.5, 35.7, 28.9, 28.4; HRMS calcd for $C_{24}H_{23}BrNO_2$ (MH^+, m/z): 436.0912; found, 436.0915.

*4.2.15. (3SR, 4RS)-1-(4-Hydroxyphenyl)-4-(4-chlorophenyl)-3-(3-phenylpropyl)-azetidin-2-one (**15fa**).* IR (film): 2926, 1714 (β-lactam) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.11 (m, 11H), 6.70 (d, J=8.8 Hz, 2H), 4.56 (d, J=2.5 Hz, 1H), 3.07–3.02 (m, 1H), 2.63 (t, J=7.1 Hz, 2H), 1.89–1.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 152.2, 141.5, 136.6, 134.3, 131.0, 129.4, 128.4, 127.3, 126.0, 118.4, 115.8, 60.6, 60.5, 35.7, 28.9, 28.4; HRMS calcd for $C_{24}H_{23}ClNO_2$ (MH^+, m/z): 392.1417; found, 392.1424.

*4.2.16. (3SR, 4RS)-1-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-3-ethyl-azetidin-2-one (**15ac**).* IR (film): 2924, 1721 (β-lactam) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J=8.8 Hz, 2H), 7.16 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 6.71 (d, J=8.8 Hz, 2H), 4.57 (d, J=2.3 Hz, 1H), 3.80 (s, 3H), 3.04–2.98 (m, 1H), 2.00–1.79 (m, 2H), 1.08 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 159.6, 152.0, 131.3, 130.1, 127.2, 118.5, 115.7, 114.5, 61.9, 60.6, 55.3, 21.9, 11.5; HRMS calcd for $C_{18}H_{20}NO_3$ (MH^+, m/z): 298.1443; found, 298.1447.

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Supplementary data

^1H and ^{13}C NMR spectra for all new synthetic compounds are available in the Supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.072.

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