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Synthesis of 3-(Aryl)alkenyl-β-lactams by an Efficient Application of Olefin Cross-Metathesis on Solid Support

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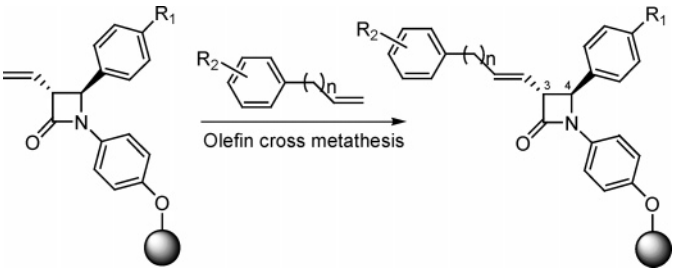
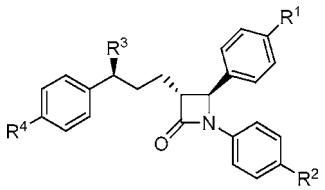
ABSTRACT



An efficient cross-metathesis on solid support for the synthesis of β-lactam analogues of cholesterol absorption inhibitors is described. The applied strategy allows the introduction of diversity in positions 3 and 4 of the β-lactam ring with excellent 3,4-trans selectivity and complete *E* selectivity at the C-3 side chain.

β-Lactams are widely recognized as highly efficient antibiotics and β-lactamase inhibitors.[1] Moreover, β-lactams (azetidin-2-ones) have recently been shown to possess completely different biological activities such as inhibitors of prostate-specific antigen,[2] thrombin,[3] human cytomegalovirus protein,[4] human leukocyte elastase,[5] and cysteine protease.[6] In particular, β-lactams **1** and **2** (ezetimibe) (Figure 1) have been described as potent hypocholesterolemic agents.[7]



1 R^1-R^2=OMe, R^3-R^4=H
2 R^1-R^2=OH, R^3-R^4=F

Figure 1. Representative cholesterol absorption inhibitors.

In the course of our research on the application of solid-phase methods for the generation of combinatorial libraries of biologically relevant compounds,[8] we became interested in the possibility of using a cross-metathesis reaction as a

(1) (a) Kidwai, M.; Sapra, P.; Bhushan, K. R. *Curr. Med. Chem.* **1999**, *6*, 195. (b) Mascaretti, O. A.; Boschetti, C. E.; Danelon, G. O.; Mata; E. G.; Roveri, O. A. *Curr. Med. Chem.* **1995**, *1*, 441. (c) Maiti, S. N.; Phillips, O. A.; Micetich, R. G.; Livermore, D. M. *Curr. Med. Chem.* **1998**, *5*, 441. (d) Mascaretti, O. A.; Danelon, G. O.; Setti, E. L.; Laborde, M.; Mata, E. G. *Curr. Pharm. Des.* **1999**, *5*, 939.

(2) (a) Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1689. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A. *Bioorg. Med. Chem.* **2002**, *10*, 1813.

(3) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Maggioni, F.; Puglisi, A. *J. Org. Chem.* **2003**, *68*, 2952.

(4) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jih, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365.

(5) Cvetovich, R. J.; Chartran, M.; Hartner, F. W.; Roberge, C.; Amato, J. S.; Grabowski, E. J. *J. Org. Chem.* **1996**, *61*, 6575.

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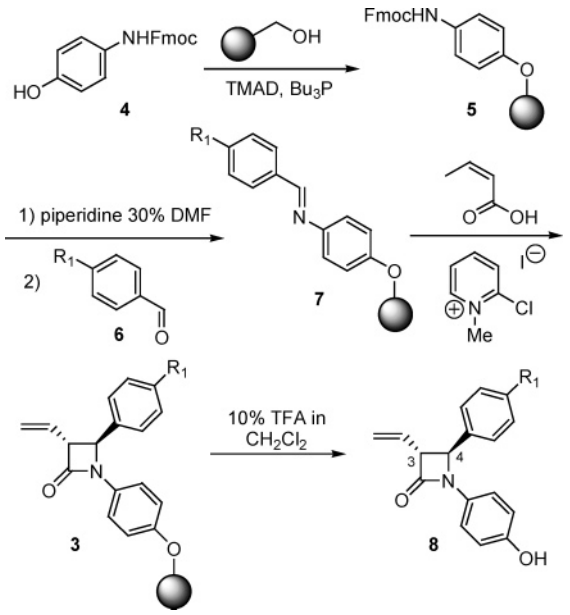
key step for the generation of cholesterol absorption inhibitor analogues. Ruthenium-catalyzed olefin metathesis, previously developed for solution chemistry, has emerged as a versatile tool for combinatorial and parallel synthesis on solid-phase;[9] however, while ring-closing metathesis (RCM) has been extensively used, reports on cross-metathesis (CM) on the solid phase are scarce.[10] The advantages of immobilizing one of the olefins during the cross-metathesis are clear: (i) The site isolation on the polymeric support makes homodimerization of the resin-bound olefin a considerably less favorable process. (ii) The olefin that remains in solution can be added in excess to drive the reaction to completion and its dimer can be eliminated easily by simple filtration, avoiding time-consuming separation techniques. (iii) Automation can be easily accomplished.

Herein we demonstrate the efficiency of cross-metathesis on the solid phase and its application to the generation of biologically interesting 3-(aryl)alkenyl-β-lactams. The key intermediate in our strategy was the resin-bound 3-vinyl-β-lactam (**3**) (Scheme 1). Although attachment of Fmoc-protected *p*-aminophenol (**4**) to Wang resin was unsuccessful under classical Mitsunobu conditions used in the solid phase (DEAD, Ph_3P),[11] immobilization was efficiently achieved by treatment with tetramethylamine azodicarboxylate (TMAD) and Bu_3P.[12] The resin-bound aniline **5** was deprotected following the standard procedure and converted to the aldimine **7** by condensation with aldehyde **6**. Then, synthesis of the β-lactam ring was carried out by a solid-supported Staudinger reaction using Mukaiyama's reagent as acid-activating agent.[8d] Thus, reaction between crotonic acid and the corresponding imine **7** effectively gave, after refluxing for 2 h in $CHCl_3$, the supported 3-vinyl-β-lactam (**3**). Formation of **3** was corroborated by FTIR and gel-phase ^{13}C NMR. At this point, we explored conditions for releasing the 3-vinyl-β-lactam from the support. Treatment of the resin with 10% trifluoroacetic acid in CH_2Cl_2 for 1 h at room temperature was found to be a very efficient procedure for the cleavage, affording the 3-vinyl-β-lactam (**8**) in 32% overall isolated yield (based on the manufacturer's loading of the Wang resin). FTIR spectroscopy of the cleaved resin indicated quantitative release of the β-lactam (disappearance of the β-lactam carbonyl peak at 1743 cm^{-1}).

Scheme 1. Solid-Phase Synthesis of 3-Vinyl-β-lactams



On the other hand, the Staudinger reaction proceeded with excellent trans selectivity (the cis isomer was not detected). This interesting result contrasts with our previous observation that solid-supported *N*-alkyl-substituted β-lactams gave a mixture of cis/trans isomers under similar conditions.[8d] We can presumably relate the preferential formation of trans isomer to the steric effect caused by the benzyloxyaniline linker and the polystyrene matrix.[13]

Subsequently, we focused our attention on the cross-metathesis reaction on solid-support. Olefin cross-metathesis is a convenient route to obtain functionalized and higher olefins from simple alkene precursors. The advantages of using olefin cross-metathesis include mild reaction conditions, tolerance to a wide range of functional groups, and availability of a wide variety of commercial olefin partners.

Therefore, resin-bound 3-vinyl-β-lactam (**3a**, R_1= methoxy) (Scheme 2) was heated at reflux in CH_2Cl_2 for 20 h in the presence of allylanisole and second-generation Grubbs precatalyst (**9**) (Figure 2),[14] which was initially tested considering its functional group tolerance, high activity, and stability. Then, the resin was resubjected to the same reaction conditions to ensure the formation of the coupled product (**10aa**, R_1= methoxy, R_2= 4-methoxy, n = 1). It should be noted that stability of the second-generation Grubbs precatalyst (**9**) made the process easier since no air-exclusion precautions were necessary.[15] Easy-to-handle reagents fa-

(6) (a) Setti, E. L.; Davis, D.; Chung, T.; McCarter, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2051. (b) Zhou, N. E.; Guo, D.; Thomas, G.; Reddy, A. V. N.; Kaleta, J.; Purisima, E.; Menard, R.; Micetich, R. G.; Singh R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 139.

(7) Burnett, D. A. *Curr. Med. Chem.* **2004**, *11*, 1873 and references therein.

(8) (a) Mata, E. G. *Tetrahedron Lett.* **1997**, *38*, 6335. (b) Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3893. (c) Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron: Asymmetry* **2002**, *13*, 905. (d) Delpiccolo, C. M. L.; Fraga, M. A.; Mata, E. G. *J. Comb. Chem.* **2003**, *5*, 208. (e) Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron Lett.*, **2004**, *45*, 4085. (f) Delpiccolo, C. M. L.; Méndez, L.; Fraga, M. A.; Mata, E. G. *J. Comb. Chem.* **2005**, *7*, 331. (g) Méndez, L.; Delpiccolo, C. M. L.; Mata, E. G. *Synlett* **2005**, *10*, 1563.

(9) Piscopio, A. D.; Robinson, J. E. *Curr. Opin. Chem. Biol.* **2004**, *8*, 245.

(10) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900 and references therein.

(11) Nam, N. H.; Sardari, S.; Parang, K. *J. Comb. Chem.* **2003**, *5*, 479.

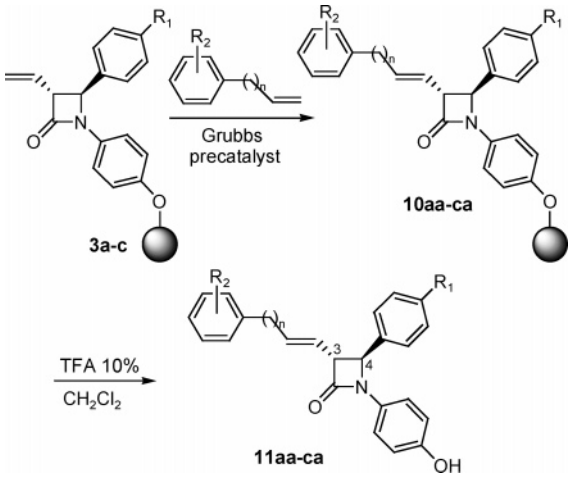
(12) Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.*, **1995**, *36*, 3789.

(13) The effect of *N*-aryl-substituted imines on the stereochemistry of the resulting β-lactam ring has been already observed in the homogeneous phase. See: Banik, B. K.; Becker, F. F. *Tetrahedron Lett.* **2000**, *41*, 6551.

(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(15) Strict exclusion of moisture and air was required in previous reports on cross-metathesis of polymer-supported olefins under first-generation Grubbs catalyst. See: (a) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed.* **1996**, *35*, 1979. (b) Breed, P. G.; Ramsden, J. A.; Brown, J. M. *Can. J. Chem.* **2001**, *79*, 1049.

Scheme 2. Synthesis of 3-(Aryl)alkenyl-β-lactams by Olefin Cross-Metathesis on Solid Support



cilitate manual parallel synthesis and require less sophisticated equipment.

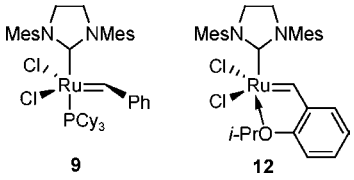


Figure 2. Grubbs **9** and Hoveyda−Grubbs **12** precatalysts.

Finally, cleavage of **10aa** from the resin was accomplished with 10% TFA/CH_2Cl_2. The resin filtrates were concentrated, and the residue was purified by flash chromatography to furnish the 3-(4-methoxyphenyl) propenyl β-lactam derivative (**11aa**) in 21% overall isolated yield for the six steps (based on the manufacturer's loading of the Wang resin) and 66% yield for the cross-metathesis step.

With the above encouraging results in hand, we decided to carry out the synthesis of an array of 3-(aryl)alkenyl β-lactams employing three aldehydes in combination with four different aromatic olefins (Table 1). This strategy allows the generation of libraries of analogues of cholesterol absorption inhibitors with a high level of diversity in position C-4 and, particularly, in position C-3 of the β-lactam ring.

The expected products were obtained in satisfactory overall isolated yields for the six reaction steps on the solid phase (11−25%).[16] We found that the metathesis can be performed using 5 mol % of Grubbs precatalyst **9**. In this way, we have reduced ruthenium metal byproducts to the minimum, obtaining a less ruthenium-contaminated resin and, therefore, a less contaminated product.[17]

Although some examples of "intra-site" olefin metathesis on solid support have been reported,[18] mainly with high capacity resins (1−2 mmol/g), no detectable amounts of homocoupled products were observed.

Table 1. Olefin Cross-Metathesis on Solid-Supported β-Lactams

entry	product	R_1	R_2	n	yield[a,b] (%)
1	**11aa**	MeO	4-MeO	1	21 (66)
2	**11ab**	MeO	H	1	21 (66)
3	**11ac**	MeO	4-Me	0	11 (35)
4	**11ad**	MeO	2-Br	0	23 (72)
5	**11ba**	H	4-MeO	1	13 (40)[c]
6	**11bb**	H	H	1	25 (78)
7	**11bc**	H	4-Me	0	13 (40)
8	**11ca**	Br	4-MeO	1	17 (53)[c]

[a] Overall isolated yield after flash column chromatography (based on the initial loading level of Wang resin, six reaction steps). [b] Data in parentheses are cross-metathesis step yields, calculated from the ratio between product yield and the yield of the 3-vinyl-β-lactam after release from the resin. [c] Obtained as a product/3-vinyl-β-lactam mixture.

It is also worth mentioning that the cross-metathesis proceeded with complete *E* selectivity as indicated by the coupling constant for the vinylic protons (J = 15.7 Hz). The reversible nature of the cross metathesis reaction is of synthetic importance because it generally ensures the preferential formation of the most thermodynamically stable product, in this case, the internal olefin with *E* configuration.

In the case of compounds **11ba** and **11ca** (entries 5 and 8), the cross-metathesis was incomplete and the starting 3-vinyl-β-lactam was detected in a ratio (product/3-vinyl-β-lactam) of 1:1.3 and 4:1, respectively. Alternatively, the reusable and more active Hoveyda−Grubbs precatalyst (**12**) (Figure 2)[19] was tested. In the case of compound **11ba**, the ratio of product/3-vinyl-β-lactam was slightly increased to 1.2:1. When this reaction was conducted in toluene at 80 °C, no product was obtained, presumably due to catalyst decomposition.[19] Finally, a complete metathesis was achieved by refluxing 20 mol % of Grubbs precatalyst **9** in CH_2Cl_2 for 20 h; however, the product **11ba** was isolated in low yield (6%).

With the optimized cross-methatesis in hand, we sought to apply our method to the preparation of the cholesterol absorption inhibitor **1** (Figure 1). To achieve this goal the 3-phenylpropenyl β-lactam **11ab** was subjected to catalytic

(16) **Representative Procedure for the Cross-Metathesis Reaction on Solid-Phase.** Support-bound vinyl β-lactam **3** (370 mg, 0.96 mmol/mg) was suspended in anhydrous CH_2Cl_2 (10 mL), and olefin (5 equiv) was added via syringe under a nitrogen atmosphere. Catalyst **9** (5 mol %) was added, and the flask was fitted with a condenser and refluxed for 20 h, after which time the resin was filtered, washed with CH_2Cl_2 (3 × 4 mL), MeOH (3 × 4 mL), and CH_2Cl_2 (1 × 4 mL), and dried under high vacuum. The resin was resubjected to the same reaction conditions. For releasing the product from the solid-phase, the resin 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. Finally, the crude material was purified by column chromatography.

(17) For different attempts to avoid contamination of products with ruthenium, see: McEleney, K.; Allen, D. P.; Holliday, A. E.; Crudden, C. M. *Org. Lett.* **2006**, *8*, 2663 and references therein.

(18) (a) Tang, Q.; Wareing, J. R. *Tetrahedron Lett.* **2001**, *42*, 1399. (b) Blackwell, H. E.; Clemons, P. A.; Schreiber, S. L. *Org. Lett.* **2001**, *3*, 1185.

(19) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8.

hydrogenation (Pd/C, ethyl acetate, 1 atm) and finally methylated with iodomethane and K_2CO_3 to give the desired inhibitor **1** in an 18% overall yield.

In summary, we report our work on the scarcely developed area of the application of second-generation Grubbs precatalyst to the olefin cross-metathesis on solid support. The simple experimental procedure did not require any air-exclusion precautions, and low catalyst loading (5 mol %) was used in order to reduce ruthenium-contaminated products. This method was employed to generate a library of analogues of cholesterol absorption inhibitors. The solid-phase reaction sequence proceeded efficiently giving good overall isolated yields, and the desired β-lactams were obtained with excellent 3,4-trans selectivity and complete *E* selectivity at the C-3 side chain. Furthermore, we found that 10% TFA in CH_2Cl_2 is an efficient and mild procedure for the cleavage of the benzyloxyaniline linker from Wang resin.

A general and comprehensive study on the solid-supported olefin cross-metathesis by ruthenium carbene complexes is underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectroscopic data, and ^{1}H NMR and ^{13}C NMR spectra of new compounds; ^{13}C NMR gel-phase spectra of β-lactam **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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