Report

Cross Metathesis on Solid Support. Novel Strategy for the Generation of β-Lactam Libraries Based on a Versatile and Multidetachable Olefin Linker

Andrés A. Poeylaut-Palena and Ernesto G. Mata*

Instituto de Química Rosario, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, CONICET, Suipacha 531, S2002LRK Rosario, Argentina

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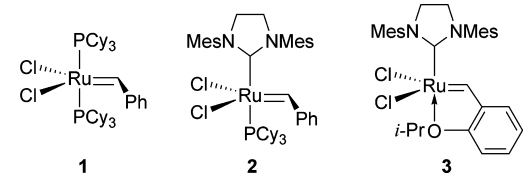
The recent development of structurally well-defined precatalysts for olefin metathesis has provided a great impulse to this field. Most outstanding, and commercially available, are ruthenium−carbene complexes like Grubbs' (**1**−**2**) and Hoveyda-Grubbs' (**3**) precatalysts (Figure 1).[1,2] Olefin metathesis is well developed in a number of methodologies like ring closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP). Nevertheless, in comparison with those methodologies, application of olefin cross metathesis (CM) to organic synthesis is not yet in a mature state. Grubbs and collaborators have established guidelines for an efficient selectivity in homogeneous-phase cross metathesis.[3] The major problem is concerned with the generation of olefin homodimers as derived byproducts. Conversely, cross metathesis on immobilized olefins provides a great advantage in purification since the product is linked to a solid support and all impurities are just filtered. However, cross metathesis on the solid phase has not been fully exploited.[4] Recently, we and others have pointed out some guidelines for help in development of this field.[5−7]

Olefin linkers have been introduced by Seeberger and collaborators during their solid-phase synthesis of glycosides.[8,9] They reported the release of the immobilized glycosides from the olefin resin by cross metathesis reactions with ethylene and 1-pentene in the presence of a variety of ruthenium precatalysts. Metathesis-cleaved linkers have the potential of carrying out cleavage and introduction of structural variation into the library at the same time.

β-lactams are widely recognized as one of the most important skeleton in organic chemistry, not only by their biological interest[10−12] but also by their use as intermediates in synthesis.[13,14] As part of our synthetic effort dealing with the application of solid-phase methodologies toward the development of biologically promising compounds, we are interested in the generation of β-lactam libraries and particularly those with structures resembling cholesterol absorption inhibitors (Figure 2).[15] Research in this area has recently received increasing attention due to the discover that ezetimibe (**4b**) blocks cholesterol absorption by interaction with Niemann-Pick C1 Like 1 (NPC1L1) protein.[16]

The Staudinger reaction between imines and ketenes is the most frequently used methodology for the construction of the β-lactam ring not only in solution but also in solid-phase chemistry.[17,18] Usually, the solid-phase version of the Staudinger reaction starts from polymer-bound imines, and only one case of an immobilized ketene has been reported.[19] We envisaged that metathesis-cleaved linkers would be useful for achieving high molecular diversity in β-lactam scaffolds using a strategy that involves an aldehyde as immobilized component in the Staudinger reaction. Accordingly, we have developed a novel synthetic pathway for the generation of highly diverse β-lactam libraries based on a new and versatile, multidetachable olefin linker that can be assembled and disassembled in a very simple way by olefin cross metathesis. In order to obtain the olefin linker **7** (Scheme 1), 4-pentenoic acid was attached to Wang resin by standard DIC/DMAP coupling, to give the corresponding immobilized olefin **5**. Resin **5** was subjected to the solid-phase cross metathesis[5] by treating with 5 equiv of 4-vinylbenzyl chloride in presence of 5 mol % of precatalyst **2** in DCM at reflux for 20 h. Resin **6** contained the expected polymer-bound benzyl chloride in addition to the intrasite cross metathesis product which remained as a passive bystander throughout the entire synthetic sequence.[20] Benzyl chloride functional group was then oxidized to its corresponding aldehyde (**7**) by treatment with DMSO at high temperature in presence of $NaHCO_3$.[21,22] This transformation was clearly visible by ^{13}C NMR gel-phase experiments where the signal assigned to the methylene carbon disappears and a signal of the aldehyde carbon arises, indicating the formation of resin **7**. Under our hypothesis, this resin contains the expected moieties to act as a multidetachable linker, i.e. it has an aldehyde to perform β-lactam synthesis and not only an



1 **2** **3**

Figure 1

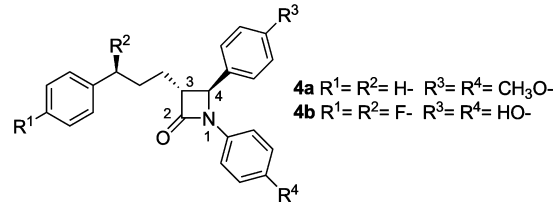


Figure 2

* To whom correspondence should be addressed. E-mail: mata@iquir-conicet.gov.ar. Fax: +54 341 4370477.

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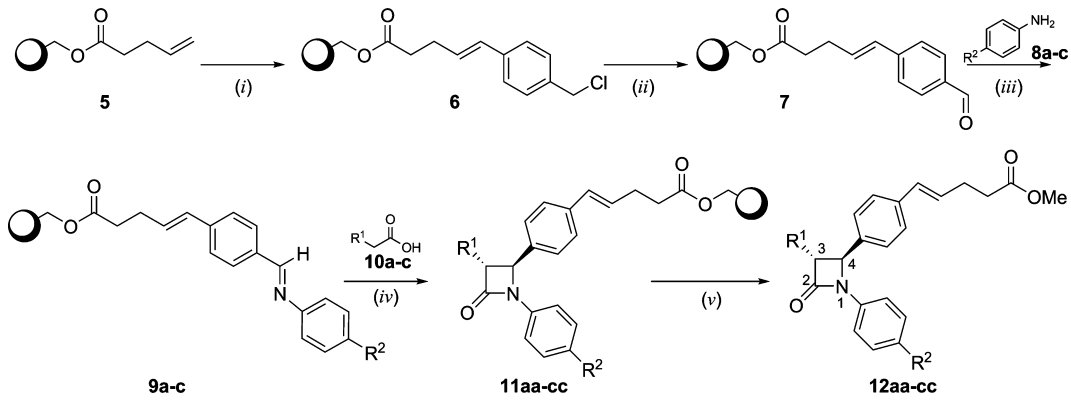
Scheme 1[a]



[a] Reagents and Conditions: (i) 4-vinylbenzyl chloride (5 equiv), precatalyst **2** (5 mol %), DCM, reflux 20 h; (ii) $NaHCO_3$ (1 equiv), DMSO, 155 °C, 5.5 h; (iii) amine **8a**−**c** (10 equiv), 4 Å molecular sieves, Dean−Stark trap, benzene, reflux, 14 h; (iv) carboxylic acid **10a**−**c** (2.5 equiv), Et_3N (6 equiv), Mukaiyama's reagent (3 equiv), $CHCl_3$, reflux, 2 h; (v) 10% TFA in DCM, rt, 1 h; then diazomethane, DCM, 0 °C, 30 min.

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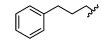
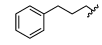
internal olefin to release the final product by olefin cross metathesis, but also an acid-labile functionality to increase the molecular diversity of the library.

Once linker **7** was obtained, attempts to synthesize β-lactams were performed. In previous works, we have synthesized imines by treatment of amines and aldehydes with 1% AcOH in DMF.[7,23] In our hands, these conditions worked well with aldehyde **7** and benzylamine but failed to give the desired product when anilines were employed as amines. Thus, solid-supported imines **9a**−**c** were synthetized by refluxing resin **7** in benzene with the respective amine (**8a**−**c**) using a 4 Å molecular sieves-loaded Dean−Stark trap (Scheme 1).[24] To construct β-lactam ring, imines **9a**−**c** were subjected to Staudinger reaction conditions with different carboxylic acids (**10a**−**c**) activated by Mukaiyama's reagent.[7] Formation of the resin-bound β-lactams **11aa**−**cc** was evidenced by IR spectroscopy and ^{13}C NMR gel-phase experiments. An initial library was achieved when solid-supported β-lactams (**11aa**−**cc**) were treated with 10% TFA in DCM and subsequently methylated with diazomethane. The corresponding resin-free β-lactam methyl esters **12aa**−**cc** were furnished in good overall isolated yields (Table 1).[25] Stereoselectivity at C3−C4 carbons is predominately controlled by the nature of the substituents rather than reaction conditions.[26] In agreement with previous reports, β-lactams **12aa**−**cc** were obtained with completely 3,4-trans selectivity.[7,26,27]

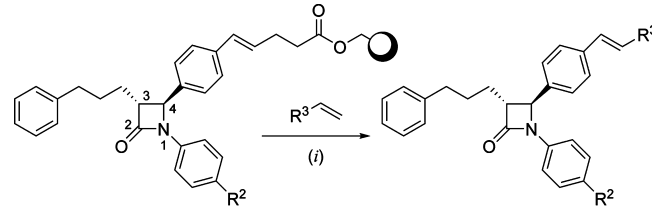
With the aim of increasing the structural diversity among the library, we carried out an alternative cleavage of resin-bound β-lactams **11aa**−**cc** by olefin cross metathesis allowing a new point of diversity at C4 position (Scheme 2). In the case of β-lactams **11aa**−**ac**, where the substitutent at C3 position was a 3-phenylpropyl moiety, different olefins were employed in the cross metathesis cleavage to achieve structural variation at C4 position. Thus, a library of novel 4-(4-vinyl-phenyl) β-lactams **11aaa**−**aca** was generated (Table 2). Cleavage by ruthenium precatalyst **2** gave good yields of the corresponding β-lactam **13aab** and **13abb** when using a type I olefin,[3] such as allylbenzene (entries 2 and 4), while yields for the cleavage by the sterically hindered 2-bromostyrene were poorer (entries 3 and 5). In contrast, another type II olefin such as crotonic acid, gave high yields of the corresponding β-lactams (entries 1 and 6). These

Table 1. Library of β-Lactams after TFA Cleavage[a]

Entry	Compound	R^1	R^2	Yield (%)[b]
1	**12aa**		MeO–	53%
2	**12ab**		F–	38%
3	**12ac**		H–	28%
4	**12ba**		MeO–	60%
5	**12bb**		F–	42%
6	**12bc**		H–	26%
7	**12ca**		MeO–	33%
8	**12cb**		F–	52%
9	**12cc**		H–	55%

[a] See Scheme *1*. [b] Overall isolated yield after flash column chromatography (five steps, based on loading of resin **6**).

Scheme 2[a]



[a] Reagents and Conditions: (i) free olefin (5 equiv), precatalyst **2** (5 mol %), DCM, reflux 20 h.

results were in agreement with the reactivity already reported for cross metathesis in solid-phase synthesis.[5]

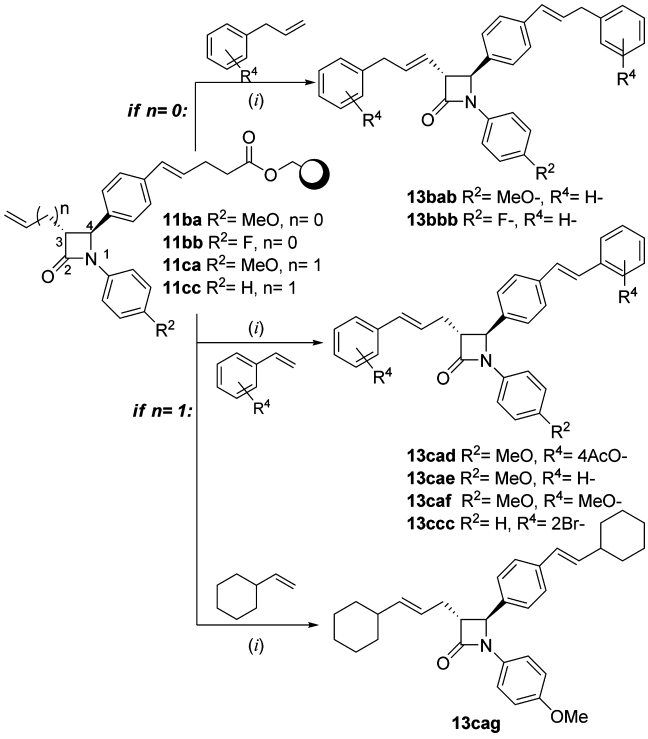
On the other hand, for vinyl and allyl substitutent at C3 position, cleavage from the resin must proceed by a double cross metathesis event: one at the linker cleavage point and the other in the C3 side chain (Scheme 3). Thus, for 3-vinyl-β-lactams **11ba** and **11bb**, allylbenzene was employed to assemble a C3 side chain with the requiered length for

Table 2. Library of β-Lactams after Cross Metathesis Cleavage by Ruthenium Precatalyst **2**[a]

entry	starting material	R^2	R^3	product	yield [%][b]	CM yield [%][c]
1	**11aa**	MeO−	MeO_2C−[d]	**13aaa**	47%	88%
2	**11aa**	MeO−	Bn−	**13aab**	49%	92%
3	**11aa**	MeO−	2-BrPh−	**13aac**	27%	50%
4	**11ab**	F−	Bn−	**13abb**	31%	81%
5	**11ab**	F−	2-BrPh−	**13abc**	16%	41%
6	**11ac**	H−	MeO_2C−[d]	**13aca**	25%	87%

[a] See Scheme *2*. [b] Overall isolated yield after flash column chromatography (four steps, based on loading of resin **6**). [c] Cross metathesis step yields were calculated from the ratio between product yield and the yield of the corresponding β-lactam **12aa**−**ac**. [d] Crotonic acid was the olefin used, and prior to purification, the obtained product was esterified by treatment with diazomethane.

Scheme 3[a]



[a] Reagents and Conditions: (i) free olefin (5 equiv), precatalyst **2** (5 mol %), DCM, reflux 20 h.

cholesterol absorption activity.[28] Whereas, when an allyl side chain is the C3 substitutent (i.e.: **11ca** and **11cc**), substituted styrenes were used with the same purpose. These two strategies led to a series of unsaturated cholesterol absorption inhibitors analogs varying the double bond position in the C3 side chain (Scheme 3 and Table 3). Interestingly, we found that nonaromatic olefins such as vinylcyclohexane, were also an attractive substrate for the doble cross metathesis, giving the bis(cyclohexane)-substituted β-lactam **13cag** in 27% overall yield (82% yield for the cleavage and functionalization step) (entry 7).

In summary, the multidetachable linker **7** covers all the requirements to accomplish the solid-phase synthesis of β-lactam analogues of cholesterol absorption inhibitors. This linker can be assembled/disassembled in a very simple way by olefin cross metathesis. Given that in the cleavage step it is possible to alternate within different olefins, this strategy allows to increase the structural variation among the library in the same reaction. A remarkable hint is the double event of cross metathesis during releasing allyl and vinyl β-lactams, which gives the desired product, in some cases in very high yield. On the other hand, acid cleavage allows the generation of an alternative library. We also think that this approach could facilitate the development of solid-phase libraries of biologically promising compounds thanks to the versatility of the benzyl chloride/benzaldehyde linker that could be applied to different solid-phase synthesis areas.

Table 3. Library of β-Lactams after by Ruthenium Precatalyst **2** with a Double Event of Cross Metathesis[a]

entry	starting material	*n*	R^2	R^4	product	yield [%][b]	CM yield [%][c]
1	**11ba**	0	MeO−	H−	**13bab**	58%	97%
2	**11bb**	0	F−	H−	**13bbb**[d]	52%	100%
3	**11ca**	1	MeO−	4-AcO−	**13cad**	24%	73%
4	**11ca**	1	MeO−	H−	**13cae**	33%	100%
5	**11ca**	1	MeO−	4-MeO−	**13caf**	21%	64%
6	**11cc**	1	H−	2-Br−	**13ccc**	18%	33%
7	**11ca**	1	MeO−	cyclohexyl[e]	**13cag**	27%	82%

[a] See Scheme *3*. [b] Overall isolated yield after flash column chromatography (four steps, based on loading of resin **6**). [c] Cross metathesis step yields were calculated from the ratio between product yield and the yield of the corresponding β-lactam **12aa**−**cc**. [d] A mixture trans/*cis* (85:15) at the arylalkenyl side chain double bound was obtained. See the *Supporting Information*. [e] Vinylcyclohexane was used as substrate.

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Supporting Information Available. Detailed experimental procedures, spectroscopic data, and ^{1}H NMR and ^{13}C NMR spectra of new compounds. This material is available free of change via the Internet at http://pubs.acs.org.

References and Notes

(1) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.
(2) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
(3) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
(4) Testero, S. A.; Mata, E. G. *J. Comb. Chem.* **2008**, *10*, 487–497.
(5) Poeylaut-Palena, A. A.; Testero, S. A.; Mata, E. G. *J. Org. Chem.* **2008**, *73*, 2024–2027.
(6) Garner, A. L.; Koide, K. *Org. Lett.* **2007**, *9*, 5235–5238.
(7) Testero, S. A.; Mata, E. G. *Org. Lett.* **2006**, *8*, 4783–4786.
(8) Kanemitsu, T.; Seeberger, P. H. *Org. Lett.* **2003**, *5*, 4541–4544.
(9) Andrade, R. B.; Plante, O. J.; Melean, L. G.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 1811–1814.
(10) Mascaretti, O. A.; Danelon, G. O.; Setti, E. L.; Laborde, M.; Mata, E. G. *Curr. Pharm. Des.* **1999**, *5*, 939–953.
(11) Singh, G. S. *Mini Rev. Med. Chem.* **2004**, *4*, 69–92.
(12) Singh, G. S. *Mini Rev. Med. Chem.* **2004**, *4*, 93–109.
(13) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, 4437–4492.
(14) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921–1949.
(15) (a) Ritter, T.; Kværnø, L.; Werder, M.; Hauser, H.; Carreira, E. M. *Org. Biomol. Chem.* **2005**, *3*, 3514–3523. (b) Tiwari, D. K.; Shaikh, A. Y.; Pavase, L. S.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Tetrahedron* **2007**, *63*, 2524–2534. (c) Burnett, D. A. *Curr. Med. Chem.* **2004**, *11*, 1873–1887.

Downloaded by UNIV MAASTRICHT on November 1, 2009 | http://pubs.acs.org
Publication Date (Web): July 2, 2009 | doi: 10.1021/cc900072z

(16) Garcia-Calvo, M.; Lisnock, J.; Bull, H. G.; Hawes, B. E.; Burnett, D. A.; Braun, M. P.; Crona, J. H.; Davis, H. R.; Dean, D. C.; Detmers, P. A.; Graziano, M. P.; Hughes, M.; MacIntyre, D. E.; Ogawa, A.; O'Neill, K. A.; Iyer, S. P. N.; Shevell, D. E.; Smith, M. M.; Tang, Y. S.; Makarewicz, A. M.; Ujjainwalla, F.; Altmann, S. W.; Chapman, K. T.; Thornberry, N. A. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8132–8137.
(17) Laborde, M. A.; Mata, E. G. *Mini Rev. Med. Chem.* **2006**, *6*, 109–120.
(18) Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465–10496.
(19) Méndez, L.; Testero, S. A.; Mata, E. G. *J. Comb. Chem.* **2007**, *9*, 189–192.
(20) Vinylbenzyl chloride loading in resin **6** was determined by measurement of chloride content through elemental analysis. According to this, cross metathesis coupling was carried out in 45% yield, giving a loading of 0.40 mmol/g for resin **6**.
(21) Nace, H.; Monagle, J. *J. Org. Chem.* **1959**, *24*, 1792–1793.
(22) Ayres, J. T.; Mann, C. K. *J. Polym. Sci., Polym. Lett. Ed.* **1965**, *3*, 505–508.
(23) Delpiccolo, C. M. L.; Mendez, L.; Fraga, M. A.; Mata, E. G. *J. Comb. Chem* **2005**, *7*, 331–344.
(24) Singh, R.; Nuss, J. M. *Tetrahedron Lett.* **1999**, *40*, 1249–1252.
(25) As expected, a small amount of the intrasite cross metathesis product, 4-octenedioic acid dimethyl ester, was also isolated.
(26) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060–6069.
(27) (a) Decazes, J.; Luche, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1970**, *11*, 3661–3664. (b) Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron Lett.* **2004**, *45*, 4085–4088.
(28) Wang, Y.; Zhang, H.; Huang, W.; Kong, J.; Zhou, J.; Zhang, B. *Eur. J. Med. Chem.* **2009**, *44*, 1638–1643.

CC900072Z

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