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The first example of ring-closing olefin metathesis of dehydroamino acids: an application to the synthesis of azabicyclo[X.Y.0]alkanes

Leonardo Manzoni,[a,*] Matteo Colombo[b] and Carlo Scolastico[b]

[a]*CNR-Istituto di Scienze e Tecnologie Molecolari (ISTM), Via Venezian 21, I-20133 Milano, Italy*
[b]*Dipartimento di Chimica Organica e Industriale and Centro Interdisciplinare Studi bio-molecolari e applicazioni Industriali (CISI), Università degli Studi di Milano, Via Venezian 21, I-20133 Milano, Italy*

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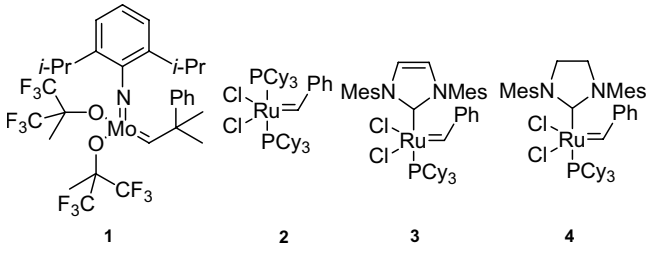
Abstract—The first example of ring-closing metathesis reaction of dehydroamino acids using ruthenium-based catalyst leading to the azabicyclo[X.Y.0]alkanes has been demonstrated. A preliminary investigation into the scope and limitations of the method will be presented.

The use of ring-closing metathesis strategies in organic synthesis has seen explosive growth over the past decade,[1] especially due to the advent of new improved catalysts with higher stability under more forcing conditions and a wider functional group tolerance.[2] RCM is routinely applied to construct cyclic olefins of virtually all ring sizes containing ether, ester, amide and/or amine functionalities[1] or heterocycles containing sulfur[3] and phosphorous.[4] In the majority of these synthesis, the first- and second-generation olefin metathesis catalyst **1**, **2** and **3**, **4**, respectively (Fig. 1) have been employed.

Although a wide number of examples of metathesis have been described, relatively few examples have been reported involving participation of heterosubstituted olefins. To date, enol ethers have been the most widely utilised partners of this class in RCM reactions.[5,6] Only recently examples such as fluoro-olefins,[7] vinyl chloro-olefins[8] and nitrogen substituted olefins such as enamides[9] have also been reported.



1 2 3 4

Figure 1. First and second generation olefin metathesis catalyst.

Our continuing interest in the synthesis of conformationally restricted peptidomimetics,[10] based on bicyclic lactam derivatives,[11] led us to consider new synthetic strategies for the preparation of such molecules.

Here we report on the synthesis of bicyclic lactams **5** and **6** that takes advantage of ring-closing metathesis reactions for constructing the fused bicyclic nucleus, as indicated in the retrosynthetic sequence depicted in Scheme 1.

RCM reactions have been already applied to the synthesis of bicyclic lactams like **5**–**6**,[12] but, to the best of our knowledge, no examples are known in which one component is a dehydroamino acid.

The RCM precursors **9**–**11** were prepared from the condensation between the known 5-allyl **7**[13] and 5-homoallylprolines **8**[†] and the commercially available 2-N-protected acrylic acids using DCC as a coupling reagent (Scheme 2).

Keywords: Peptidomimetics; Ring-closing metathesis (RCM); Dehydroamino acids.

* Corresponding author. Tel.: +39-0250314088; fax: +39-0250314072; e-mail: leonardo.manzoni@istm.cnr.it

[†] The homologous compound **8** was prepared from **7** by hydroboration followed by Swern oxidation and a Wittig reaction.

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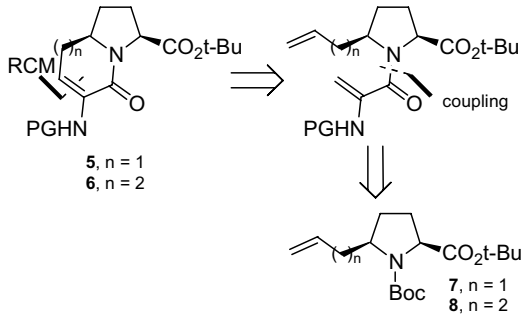
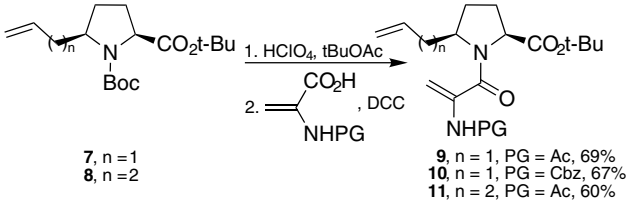


Scheme 1. Retrosynthetic scheme for the synthesis of azabicyclolactams.



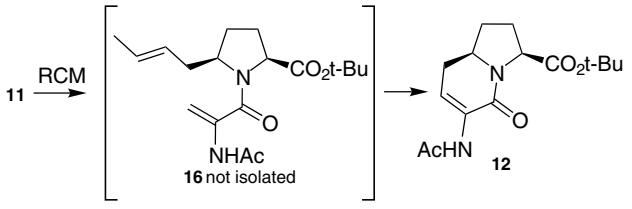
Scheme 2. Synthesis of RCM precursors.

With these precursors in hand, we began the ring-closing metathesis experiments (Table 1).

RCM was first carried out on the substrate **9**, which cyclised smoothly (5 h) at room temperature in DCM with 5 mol% of the second generation Grubbs catalyst **4** to afford the 6,5-fused bicyclic lactam **12** in good yield (89%, entry 2). On the contrary, only 4% yield was observed when the first generation of the Grubbs catalyst **2** was used and a consistent amount of precursor was recovered (entry 1). In contrast, when compound **10** (PG = Cbz) was submitted to the same reaction condition (catalyst 4) only the cross-metathesis product **15** was detected in high yields (entry 3), a behaviour that could be due both to steric and electronic factors of the N-protecting group. A similar trend has already been observed from amino acid substrates, low yields of metathesis were obtained when the sterically bulky amino acid moiety was hindering to the approach of the catalytic ruthenium species to the double bond of the substrate.[14]

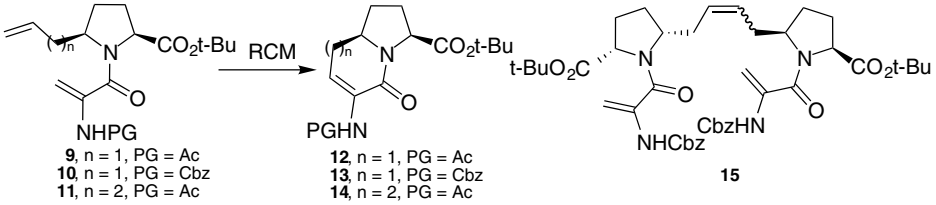
Inspired by the successful dehydroamino acid ring closure, we set out to explore ring-closing metathesis of homologous olefins like **11**.

Olefin **11** when subjected to ruthenium catalyst **4** at 40 °C afforded only a 12% of the cyclised product **14** after 24 h (entry 4). Increasing the catalyst loading to 15 mol% and rising the temperature to 80 °C, in toluene as solvent, an improved yield of 44% after 72 h was observed (entry 5). However, with catalyst **4** at higher temperature, 100 °C, and lower substrate concentration (4 mM) the starting material showed full conversion, leading to an isolated yield of 53% of **14** after column chromatography accompanied by 14% of the bicyclic lactam **12**. Probably, ruthenium-catalysed isomerisation to the more stable olefin **16** took place, followed by ring closure of the isomerised intermediates to the six-membered enamide **12** (Scheme 3).



Scheme 3. Seven-membered ring precursors **11** could lead to six-membered ring product **12**.

Table 1. RCM reaction



Entry	Precursors	Conditions[a]	Product	Yield (%)
1	**9**	**2**, 40 °C, 24 h, DCM	**12**	4[b]
2	**9**	**4**, 20 °C, 5 h, DCM	**12**	89
3	**10**	**4**, 40 °C, 24 h, DCM	**15**	81
4	**11**	**4**, 25 °C, 24 h, DCM	**14**	12[c]
5	**11**	**4**, 80 °C, 72 h, toluene	**14**	44
6	**11**	**4**, 100 °C, 72 h, toluene[d]	**14**	53[e]

[a] 40 mM substrate concentration; 5–10 mol% of catalyst.
[b] 50% of the starting material has been recovered.
[c] 55% of the starting material has been recovered.
[d] 4 mM substrate concentration.
[e] 14% of **12** has been detected.

In conclusion, we have shown the first successful examples of ring-closing metathesis of olefin-containing dehydroamino acids. We demonstrated also the possibility of constructing six- and seven-membered ring bicyclic lactam in good yields using this strategy. We are currently investigating further variations of this methodology, as well as applications to the synthesis of biological active compounds.

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