Synthesis of Novel Unsaturated Bicyclic Lactams by Ring-Closing Metathesis

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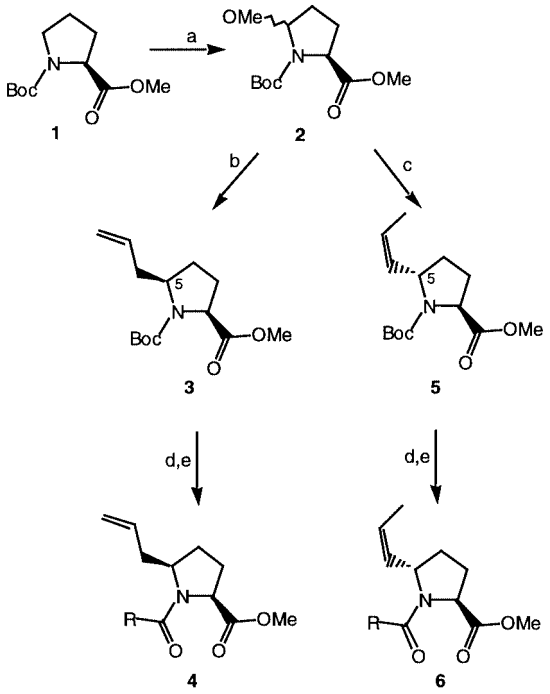
Abstract: An efficient and versatile synthetic method for the preparation of novel unsaturated fused bicyclic lactams is described. The crucial step of the stereoselective approach is the ring-closing metathesis reaction. The 6,5-, 7,5- and 8,5-fused 1-aza-2-oxobicycloalkenes can be obtained in five steps and good overall yield.

Key words: bicyclic compounds, metathesis, lactams, ruthenium

Fused bicyclic systems play a very important role in the field of drug discovery. They are often incorporated into linear bioactive molecules in order to reduce the conformational flexibility and/or to increase the metabolic stability of the parent substance.[2] Due to their rigid geometry, they are also useful tools to probe and elucidate the structure-activity relationships. In that regard, a particularly attractive class of compounds are the fused bicyclic lactams, or 1-aza-2-oxobicyclo[X.Y.0]alkanes. Several structures, possessing various ring sizes, have already been prepared and incorporated into pharmacologically relevant peptides.[3] However, very few efficient and versatile synthetic routes exist so far. Therefore, new methodologies for their preparation are still in high demand.

In this paper, we disclose the preparation of a series of novel unsaturated fused bicyclic lactams, which are of interest as a new type of potentially useful building blocks. The efficient stereoselective approach allows the synthesis of 6,5-, 7,5- and 8,5-fused bicycles in five steps from protected proline in good overall yield.

The dienyl precursors **4** and **6** were prepared from protected proline **1** (Scheme 1). The electrochemical oxidation of **1**, first described by Shono *et al*.,[4] provided the C_5-methoxylated intermediate **2** in large quantities. Without purification, **2** was converted with high diastereoselectivity (90%) into the allylproline derivative **3** using allyltrimethylsilane in the presence of $TiCl_4$.[5] The nucleophilic substitution proceeded best at low temperature (-20ºC) and gram quantities of intermediate **3** could be obtained as an oil in 46% yield from **1**. Alternatively, the vinylproline derivative **5** with the opposite configuration at C_5 could be prepared from **2** by boron trifluoride mediated cuprate addition as described by McClure *et al*.[6] Removal of the *tert*-butoxycarbonyl protecting group from **3** or **5** with HCl in Et_2O gave quantitatively the desired amines. The coupling of the hindered amines to various unsaturated carboxylic acids afforded the dienyl precursors **4a-f** and **6** in yields varying from 50 to 93%. The coupling reaction proceeded best by using either the acyl chloride or the mixed anhydride preactivation methods. Other conditions, like EDC/HOBT or DCC/DMAP, failed or gave lower yields.

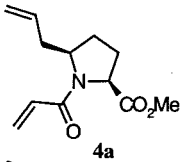
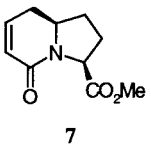
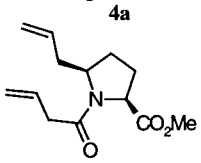
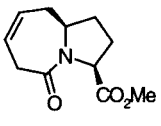
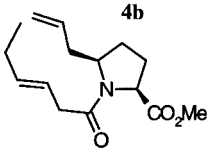
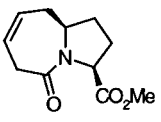
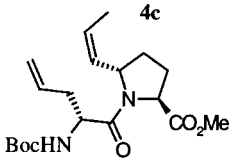
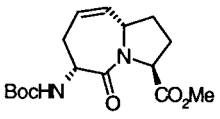
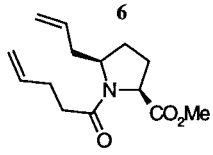
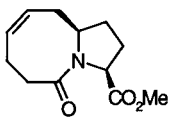
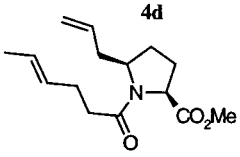
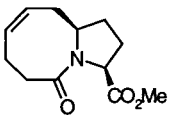
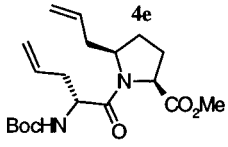
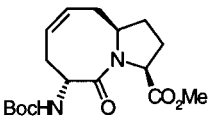


a) Electrolysis, 300 mA, MeOH, $Bu_4N^+BF_4^-$, b) Allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -20ºC, 46% from **1**, c) CuBr·DMS, (*Z*)-1-lithio-1-propene, $BF_3{\cdot}Et_2O$, Et_2O, 69% from **1**, d) HCl/Et_2O, quant., e) RCO_2H, THF, ^{i}BuOCOCl, NMM, 50-93%.

Scheme 1

The results of the ring-closing metathesis reaction on intermediates **4a-f** and **6** are summarized in Table 1.[7] The reactions were best carried out in refluxing CH_2Cl_2 using freshly prepared ruthenium catalyst ($Cl_2(PCy_3)_2Ru{=}CHPh$).[8] In comparison, identical reactions performed in C_6H_6 gave lower yields. In order to determine the scope of our approach, we prepared bicyclic lactams possessing three different ring sizes. The 6,5- and 7,5-fused bicyclic structures were obtained in excellent yields (entries 1-4). ^{1}H NMR analysis of the crude mixtures of these reactions indicated clean and quantitative formation of the products **7-9**. The substitution of one double bond by an additional alkyl group did not influence the yield of the reactions (entries 2 and 3, 5 and 6). The successful synthesis of lactam **9** showed that the approach is not limited to one stereochemistry at C_5 (entry

Table 1 Results of the ring-closing metathesis reaction of **4a-f** and **6**.

Entry	Diene	Bicycle	Yield[a]
1	 **4a**	 **7**	94%
2	 **4b**	 **8**	81%
3	 **4c**	 **8**	95%
4	 **6**	 **9**	75%
5	 **4d**	 **10**	35% (54%)[b]
6	 **4e**	 **10**	35% (29%)[b]
7	 **4f**	 **11**	41% (49%)[b]

[a] Conditions: $Cl_2(PCy_3)_2Ru{=}CHPh$ (10-15%), CH_2Cl_2, reflux, 16h.

[b] Recovered starting material

4). On the other hand, formation of the 8,5-fused bicyclic lactams proceeded at a slower rate and complete conversion could not be achieved. The difficulty of forming 8-membered rings by metathesis is well known.[9] Nevertheless, the presence of a rigid control element, the proline ring, allowed the reaction to proceed in good yield.

In summary, we have developed an efficient and versatile approach towards novel unsaturated fused bicyclic lactams.[10] The methodology described herein is of interest because it is suitable for the preparation of a large array of bicycles. Indeed, the 6,5-, 7,5- and 8,5-fused lactams can be obtained in good to excellent yields. In addition, the double bond can be located either in the C_6-C_7 or the C_7-C_8 position. Bicycles **7**, **9** and **11** are of particular interest. Compound **7** has been used previously as a crucial intermediate for the preparation of a tachykinin NK-2 receptor antagonist.[11] Bicycles **9** and **11** are potentially useful dipeptide analogues because they possess the required amino terminus. Finally, the double bond could be used to introduce additional functional groups. Further work is ongoing to determine the full potential of this methodology.

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(6) McClure, K.F.; Renold, P.; Kemp, D.S. *J. Org. Chem*. **1995**, *60*, 454.
(7) *Representative experimental procedure for the ring-closing metathesis reaction*: To a solution of **4** or **6** (0.2 mmol) in dry CH_2Cl_2 (5 mL) was added the freshly prepared ruthenium catalyst (10-15%) under nitrogen. The mixture was stirred under reflux overnight. The solvent was evaporated and the residue was purified by chromatography (SiO_2 or RP-18). All new compounds have been isolated in pure form and their spectral data (MS, IR and NMR) were consistent with the proposed structure.
Selected data for compound **7**: ^{1}H NMR (DMSO, 400 MHz) δ 6.70 (m, 1H), 5.82 (dd, *J* = 10.0, 4.5 Hz, 1H), 4.37 (d, *J* = 9.0 Hz, 1H), 3.75 (m, 1H), 3.64 (s, 3H), 2.57 (m, 1H), 2.10-2.20 (m, 3H), 1.95 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 30.9, 32.1, 52.7, 57.3, 57.4, 125.8, 140.1, 163.8, 173.3. EI-MS *m/z* 195 $(M)^+$, 136 $(M\text{-}CO_2CH_3)^+$.
Selected data for compound **8**: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.65 (m, 1H), 5.55 (m, 1H), 4.57 (dd, *J* = 7.0, 5.5 Hz, 1H), 4.30 (m, 1H), 3.72 (s, 3H), 3.50 (m, 1H), 2.88 (dd, *J* = 17.5, 9.0 Hz, 1H), 2.50 (m, 1H), 2.00-2.30 (m, 4H), 1.75 (m, 1H). ESI-MS *m/z* 210 $(M+H)^+$.
Selected data for compound **9**: ^{1}H NMR (DMSO, 400 MHz) δ 6.67 (d, *J* = 6.6 Hz, 1H), 5.68 (m, 1H), 5.60 (m, 1H), 4.88 (m, 1H), 4.72 (m, 1H), 4.42 (dd, *J* = 7.5, 3.0 Hz, 1H), 3.63 (s, 3H), 2.31-2.41 (m, 1H), 2.05-2.26 (m, 3H), 1.82-1.90 (m, 2H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 28.8, 32.9, 33.4, 51.3, 52.8, 56.1, 60.3, 79.9, 130.1, 130.5, 155.3, 171.0, 172.4. EI-MS *m/z* 324 $(M)^+$, 209.
Selected data for compound **10**: ^{1}H NMR (DMSO, 400 MHz) δ 5.67 (m, 1H), 5.53 (m, 1H), 4.45 (m, 1H), 4.23 (m, 1H), 3.58 (s, 3H), 2.80-2.89 (m, 1H), 2.52-2.66 (m, 2H), 1.97-2.30 (m, 5H), 1.70-1.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.8, 31.9, 32.9, 34.5, 51.0, 56.9, 59.1, 125.5, 128.7, 171.3, 172.0. ESI-MS *m/z* 224 $(M+H)^+$.

Selected data for compound **11**: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.74 (m, 1H), 5.59 (m, 1H), 4.98 (m, 1H), 4.34 (dd, *J* = 7.0, 6.5 Hz, 1H), 4.28 (m, 1H), 3.74 (s, 3H), 2.86-3.02 (m, 2H), 2.12-2.29 (m, 4H), 1.75-1.86 (m, 2H), 1.45 (s, 9H). FAB-MS *m/z* 339 $(M+H)^+$, 283 $(MH-C_4H_8)^+$, 239 $(MH-Boc)H^+$.

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