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Facile synthesis of versatile functionalized amino caprolactams using RCM reactions of α-amino acrylamide

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Abstract—We report an efficient synthetic methodology allowing access to functionalized α-amino caprolactams using ring-closing metathesis (RCM). A very high tolerance of α-amino acrylamide RCM precursors toward functional groups is demonstrated. The synthetic pathway is facile, and can be extended to prepare a variety of substituted amino caprolactams in good to excellent yields. These compounds serve as versatile building blocks for the synthesis of some important natural products and their analogues.

Medium-sized lactams, especially the seven-membered ones, are of considerable interest in drug discovery and pharmaceutical research, as some natural products (or their analogues) and small molecules bearing such units show potent biological activity. As shown in Figure 1, bengamide B and one of its analogues LAF389 display an activity with IC_{50} values at the nanomolar level for in vitro growth inhibition.[1] New vasopeptidase inhibitors containing hydroxamic acid-derived azepinones (caprolactams) have been found to have selective angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) inhibition.[2] Lately, BN 83253 compounds have been shown to act as powerful anti-inflammatory agents in vivo at the doses of 1 mg/kg.[3] Another novel class of orally active factor Xa (FXa) inhibitors has also been developed.[4] On the other hand, the development of small molecular weight scaffolds containing a high degree of diversity has become a focus in modern drug discovery.[5] In this regard, the efficient synthesis of multiply substituted amino caprolactams is of great importance. However, the synthetic methods that have been used seem to be either too long (usually involving complex transformation[6]), or lack flexibility (where limited functional groups are modified at the amide nitrogen[7] or are difficult to functionalize at position 7). Following our successful construction methodology for the ring-closing metathesis (RCM) reaction of α-amino acrylamide[8] to substituted amino caprolactams, in this work, we extend the scope of this methodology to diverse substitution at the amide nitrogen, and have constructed 1-, 6-, 7-position functionalized α-amino caprolactams **3** (Scheme 1), which can be easily transformed to caprolactams by hydrogenation.

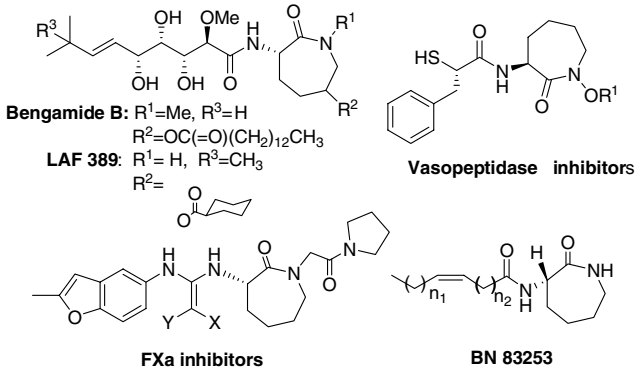

Figure 1. Some bioactive natural products (or analogues) and small molecules containing amino caprolactam units.

Our method therefore provides an easy access to all of the above-mentioned natural products and their versatile analogues with potentially interesting properties.

Keywords: Ring-closing metathesis; Functionalized lactams; Natural products; α-Amino acrylamide; α-Amino α,β-unsaturated caprolactams.
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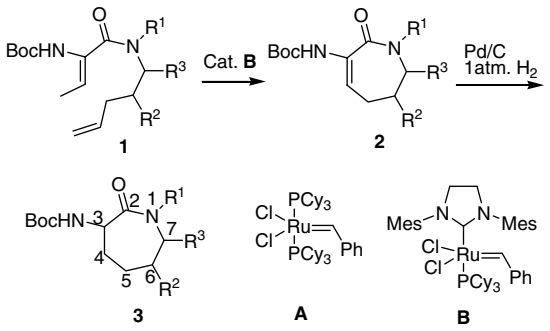


Scheme 1. General procedure for the synthesis of 1,6,7-position functionalized α-amino caprolactams.

The general procedure for the synthesis of functionalized α-amino caprolactam **3** is shown in Scheme 1. The key intermediate is compound **2** (α-amino α,β-unsaturated caprolactam), and this was achieved from **1** by the RCM of α-amino acrylamide as a key step using Grubbs' second-generation catalyst **B** (**B** was selected here, as it is generally considered to be more reactive than **A** in olefin metathesis reactions in the conversion of electron-deficient C–C double bonds[9]). Compound **1** can be readily produced by α,β-unsaturated amino acid or its active ester with a substituted secondary amine. Later on, we found out that R^1, R^2, and R^3 in compound **1** were able to accommodate diverse functional groups for successful ring closure, which extends the scope of our former RCM methodology.

The R^1 group can be either a benzyl, 2,4-dimethoxylbenzyl (DMB), phenylethyl, benzyloxy, furfuryl, pyridin-2-yl, or a $–CH_2COOEt$ group. This was introduced by using a conventional reductive amination of various aldehydes with amine **5**, or amino acid ester with pent-4-enal **8** (Scheme 2, **2a**, **2b**, **2d**–**2g**). Examples of the synthetic pathway are shown in **2d** and **2g**, and typical experimental procedure for RCM is illustrated with **2d**.[11] Cyclization yields of these compounds were generally high, with the amount of catalyst used below 10 mol % (Table 1). Compound **2e**, with a nucleophilic nitrogen in its pyridine ring, which is usually thought to coordinate to the Ru complex, was also synthesized in a yield up to 88% after the addition of a little more catalyst. Compounds **2d**, **2e**, and **2f** are very interesting lactams, which provide an additional reactive group to construct N-functionalized caprolactam-containing molecules.

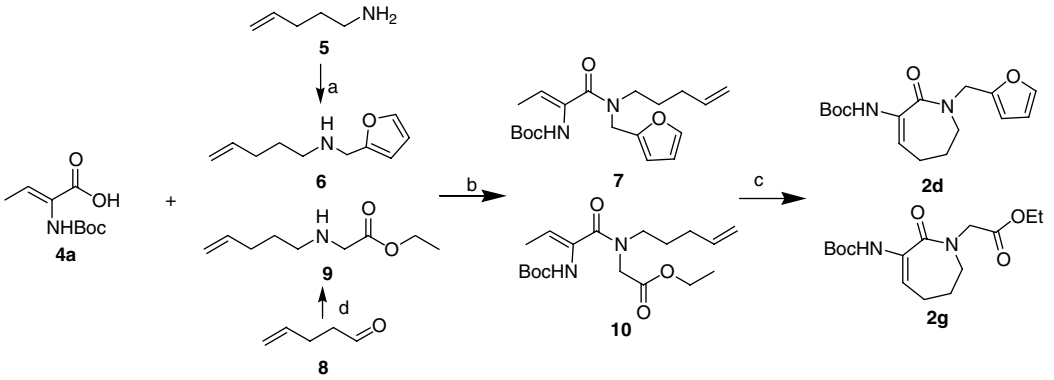
The R^2 group can be either an H or acyloxyl group. The intermediate was produced by the addition of ally magnesium bromide to a range of aldehydes, followed by N-protection with DMB to afford the substituted secondary amine. A representative pathway is shown in Scheme 3. The ring closure of the precursor **14** afforded **2h** in a near quantitative yield, while the amount of catalyst used was much less. A number of such 6-position hydroxy-derived caprolactams have been documented. The advantage of our strategy resides in the stereo configuration of the 6-position, which can be effectively controlled in the early stage (step a) by the stereoselective addition of a metalloorganic reagent to the chiral α-amino aldehyde, along with the short reaction path and the high yield. Using this procedure, we produced **2i** in 97% yield (Table 1).

The R^3 group can be either an H or a benzyl group, and it can also be diversified by using an amino acid as the starting material to produce a chiral α-amino aldehyde, and following the procedure shown in Scheme 4, generates a stereo (6,7-position)-controlled caprolactam.

In a previous work,[8] we have reported that the dimethoxybenzyl group can be used as an amide N-protecting group for further cyclization. Here, we extend the substitution group to the N atom of caprolactam, and phenylalkyl **2b**, **2f**, alkoxyl **2c**, **2l**, heterocycloalkyl **2d**, **2e** and alkoxycarbonylalkyl **2g** were introduced on the N atom and underwent successful cyclization. These results further demonstrate the high tolerance of our RCM precursors toward functional groups.

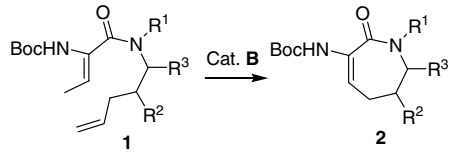
Hydrogenation of all the RCM products (α-amino α,β-unsaturated caprolactams **2a**–**2l**) gave α-amino caprolactams **3** in near quantitative yields.

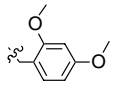
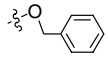
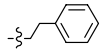
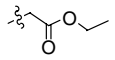
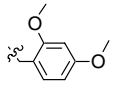
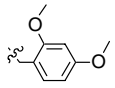
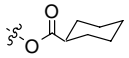
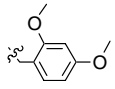
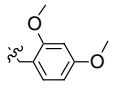
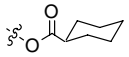
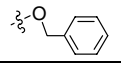
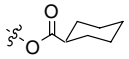
The reason for the surprising reaction facility of this type of RCM precursor is not clear, N-substitution of



Scheme 2. An illustrative synthesis of **2d** and **2g**. Reagents and conditions: (a) 2-furaldehyde, Et_3N, EtOH, then $NaBH_4$, rt, 50%; (b) EDC·HCl, HOBT, CH_2Cl_2, 4 Å M.S., rt, 66% (**4a** was prepared according to the literature procedure[10]); (c) see Table 1; (d) H-Gly-OEt·HCl, Et_3N, EtOH, then $NaBH_4$, rt, 70% from **8**.

Table 1. RCM reaction conditions[a] of α-amino α,β-unsaturated caprolactams



Entry	R^1	R^2	R^3	Cat. B (mol %)	Yields[b] (%)
2a		H	H	5	86
2b		H	H	10	78
2c		H	H	10	45
2d		H	H	5	90
2e		H	H	10	88
2f		H	H	10	92
2g		H	H	5	86
2h		OAc	H	5	95
2i			H	5	97
2j[c]		OAc		5	70
2k[c]				10	85
2l			H	5	90

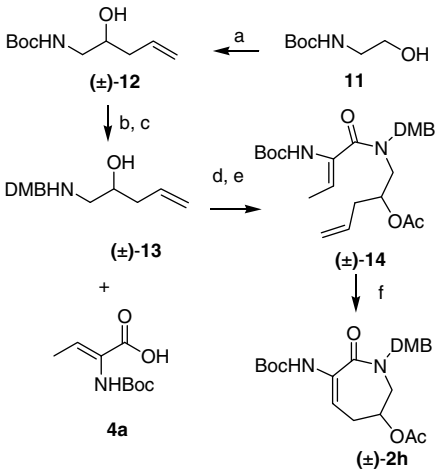
[a] Other conditions: substrate = 1.0–2.0 mM, reaction time = 10–28 h, solvent 1,2-dichloroethane (DCE) for **2c** and dichloromethane (DCM) for the others, reaction temperature = 90 °C for **2c**, rt for **2h**, **2i** and 40 °C for the others.

[b] Isolated yields.

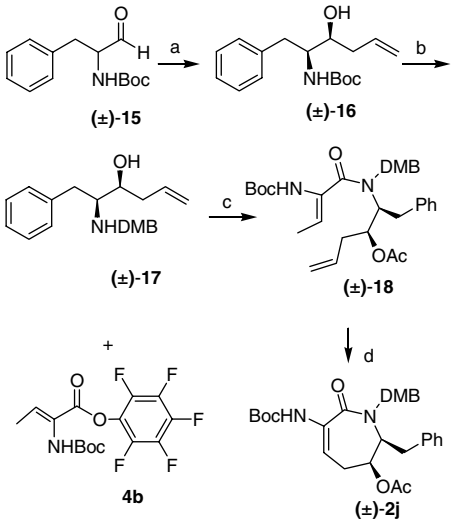
[c] The stereo configuration of **2j** and **2k** was determined as *syns* based on NOESY data, and the reported diastereoselectivity results of **16**.[13]

the lactam amide induces a conformation change, which may serve as a factor, as it ensures a sufficient proportion of the *cis* amide rotamer, which, according to Miller et al.,[14] is necessary for cyclization.

In conclusion, a variety of α-amino caprolactams **3** were conveniently synthesized in generally good to excellent yields using RCM of α-amino acrylamide as key step. The resulting versatile amino caprolactams may serve as advantageous structural moieties for the construction of small-molecule libraries with structural features of some natural products. At the same time, our former RCM methodology was extended to obtain diverse sub-



Scheme 3. An illustrative synthesis of **2h**. Reagents and conditions: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, then ally magnesium bromide, Et_2O, 0 °C to rt, 48% from **11**; (b) HCl/dioxane, rt; (c) Et_3N, EtOH, 2,4-dimethoxybenzaldehyde, then $NaBH_4$, rt, 73%; (d) EDC·HCl, HOBT, DMAP, 4 Å MS, rt, 62%; (e) Ac_2O/pyridine (v/v = 1/1), rt, 95%; (f) see Table 1.



Scheme 4. An illustrative synthesis of **2j**. Reagents and conditions: (a) and (b): the same as Scheme 3, 50% from **15**, (dr = 5/1); (c) K_2CO_3, CH_3COCH_3, rt, 60% from **17** (**4b** was used, as it is more selective than **4a**[12]), then Ac_2O/pyridine (v/v = 1/1), rt; (d) see Table 1.

stitution at amide nitrogen sites. Compared to other RCM methodologies, the tolerance of the R^1, R^2, and R^3 groups toward functional groups is high. We are now using this amino caprolactam scaffold in the synthesis of some natural product analogues, and are further extending our RCM methodology to six and eight-membered rings. The results of these works will be presented in due course.

Acknowledgements

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Shanghai Commission of Science and Technology (Grant 03dz19228).

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11. Typical experimental procedure for RCM (Table 1, substrate **2d**):
    To a 250 mL flask (dry) equipped with a condenser was added a solution of 0.14 mmol α-amino acrylamide **7** in 80 mL of dry DCM, the solution was deaerated by bubbling argon through the mixture for 5 min. Second-generation Grubbs catalyst **B** (5 mol %) in 30 mL of dry, degassed DCM was added to the mixture under argon atmosphere, and the argon bubbling was continued for an additional 5 min. The mixture was heated and stirred at 40 °C for 10 h until TLC showed the reaction was complete. The solvent was removed in vacuo and the residue was purified by silica gel chromatography to give *tert*-butyl (*E*)-1-((furan-2-yl) methyl)-2,5,6,7-tetrahydro-2-oxo-1*H*-azepin-3-ylcarbamate (**2d**, 39.0 mg, 90% yield) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (9H, s), 1.74 (2H, quin, $J = 6.9$ Hz), 2.18 (2H, q, $J = 6.9$ Hz), 3.40 (2H, t, $J = 6.3$ Hz), 4.63 (2H, s), 6.28–6.29 (1H, m), 6.31–6.33 (1H, m), 6.64 (1H, t, $J = 6.0$ Hz), 6.76 (1H, br s, NH), 7.35 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.0, 29.0, 29.9, 43.7, 46.6, 80.3, 108.9, 110.7, 116.4, 131.3, 142.6, 150.9, 153.5, 167.9. HRMS (EI): calcd for $C_{16}H_{22}N_2O_4$ [M+] 306.1580, found 306.1577.
12. Compound **4b** coupled high selectively with **17** to obtain the target products, when **4a** was employed, hydroxy-acylated byproducts were produced.
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