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Application of tandem Ugi reaction/ring-closing metathesis in multicomponent synthesis of unsaturated nine-membered lactams

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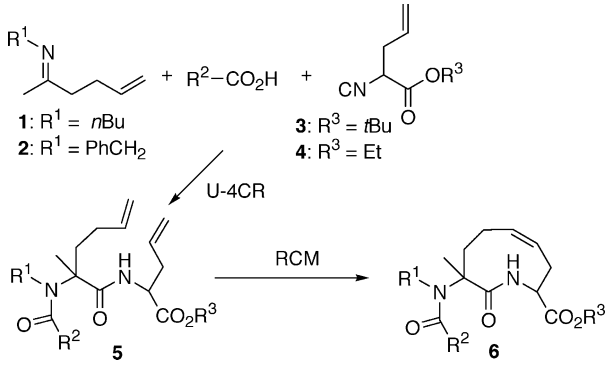
Abstract—A new straightforward entry into unsaturated nine-membered lactams of potential use as external reverse turn inducers was developed. It is based on an Ugi multicomponent reaction using two unsaturated substrates, followed by highly stereoselective ring-closing metathesis (RCM). The synthesis of a nine-membered secondary lactam by RCM is reported for the first time.

The conformational restriction of peptide chains by attaching them to semirigid scaffolds is an important strategy toward the development of receptor antagonists endowed with higher affinity and selectivity.[1] Moreover, this approach leads to valuable information on the real conformation of the natural ligand. The scaffolds capable of inducing a reverse-turn in a peptide backbone attached to it are of particular interest. These have been referred to as 'external reverse turn scaffolds'.[2] Bicyclic lactams[3] or monocyclic five- to seven-membered monocyclic 'Freidinger' lactams[4] have been extensively used in the past as external reverse turn inducers. On the other hand, there are very few examples in the literature involving mesocyclic lactams.[5,6] Due to their higher flexibility, mesocyclic compounds are expected to be useful as external reverse turn inducers only if some other kind of conformational restriction is present, such as an unsaturation. At the outset of this work we could only find very few examples concerning the synthesis of unsaturated nine-membered lactams in the literature.[7,8] None of them, however, were suited for acting as reverse-turn scaffolds, since they were lacking the necessary amino and carboxylic functionalities. Only very recently has Gmeiner reported the synthesis of potential reverse turn inducers based on a nine-membered unsaturated tertiary lactam.[9]

This prompted us to report our results in this area. Through preliminary computer-aided conformational analyses[10–15] we devised hexahydroazoninones of general formula **6** as highly promising external reverse turn inducers and decided to explore a new straightforward entry into these scaffolds by coupling a multicomponent reaction (Ugi-4CR)[16] with a ring-closing metathesis (RCM).[17] In this way, libraries of compounds of this type could be accessed in a few steps, introducing three diversity factors (R^1, R^2 plus groups different from methyl in the starting ketone) following the general strategy depicted in Scheme 1.

In this study, we used, as in situ source of the imine **1** or **2**, a model ketone, namely 5-hexen-2-one. In the course of preliminary experiments we found out that by simply mixing this ketone with an amine, various acids, and ethyl or *t*-butyl isocyanoacetate, the desired Ugi reaction took place, but with very long reaction times and in some cases in unsatisfactory yields. On the other hand, the analogous reactions employing preformed imines **1** or **2** were complete in 1–2 days affording excellent yields.



Scheme 1.

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Table 1. Results of the tandem Ugi 4-component (U-4CR)/RCM reactions

Entry	R^1	R^2	R^3	U-4CR[a]		RCM[b]	
				Product	Yield (%)	Product	Yield (%)
1	$PhCH_2$	$PhCONHCH_2$	*t*Bu	**5a**	80[c]	**6a**	69
2	$PhCH_2$	$PhCONHCH_2$	Et	**5b**	93[c]	**6b**	58
3	*n*Bu	$(Boc)NHCH_2$	Et	**5c**	79[d]	**6c**	42 (55)
4	$PhCH_2$	$(Boc)NHCH_2$	Et	**5d**	82[d]	**6d**	45 (65)
5	*n*Bu	$PhCH_2$	Et	**5e**	76[d]	**6e**	26 (39)
6	$PhCH_2$	CH_3	Et	**5f**	85[d]	**6f**	43 (51)
7	$PhCH_2$	$(Boc)NHCH_2CONHCH_2$	Et	**5g**	63[d]	**6g**	40 (52)
8	$PhCH_2$	$(Fmoc)NHCH_2$	*t*Bu	**5h**	86[c]	**6h**	46
9	$PhCH_2$	$(Fmoc)NHCH_2CONHCH_2$	*t*Bu	**5i**	69[c]	**6i**	50

[a] Reactions were carried out for 48–72 h in MeOH or EtOH at room temperature and at 1 M reactant concentration. Yields are of pure isolated products (50:50 diastereoisomeric mixture).

[b] Reactions were carried out for 48 h in CH_2Cl_2 at reflux under Ar at 4 mM concentration, using 0.2 equiv. of Grubbs' catalyst [benzylidene–bis(tricyclohexylphosphine)ruthenium dichloride]. Overall yields of the two pure isolated diastereoisomers are reported. Yields in brackets are calculated taking into account the recovered substrate.

[c] Reaction carried out in MeOH.

[d] Reaction carried out in EtOH.

Thus, allyl substituted racemic isocyanoacetates **3**[18] or **4**[19,20] were reacted in MeOH or EtOH[21] with two preformed imines **1** or **2** and various carboxylic acids to give Ugi adducts **5** in excellent yields.[22] The results are listed in Table 1. It is worth noting that some of the carboxylic acids employed were protected amino acids or peptides. No diastereoselection was observed in all the cases tested so far. The diastereoisomeric ratio was always 50:50 as determined by NMR. The isomers were not easily separable at this stage and therefore we carried out all the subsequent cyclization reactions on the diastereomeric mixture.

By treating these Ugi adducts with Grubbs' first generation catalyst in refluxing CH_2Cl_2, the nine-membered lactams **6a–i** were isolated[23] in yields that could be considered quite good for the closure of a mesocyclic ring. The isolated by-products were all acyclic compounds derived from intermolecular reactions as indicated by the presence of terminal $CH{=}CH_2$ carbons in the ^{13}C NMR (DEPT) spectrum. Further lowering the concentration below 4 mM did not suppress the formation of these by-products and resulted in lower yields. These results represent the first examples of cyclization under RCM conditions of secondary amides to nine-membered lactams. It is worth noting that the similar cyclization of secondary amides to afford eight-membered rings by RCM is reported to be unfeasible.[6] An explanation for this different behavior may be the preference for *anti* amide bond conformations in hexahydroazoninones,[8] as foreseen by computer-aided conformational analysis[11] and demonstrated by NOE experiments.[24]

These RCMs were found to be highly stereoselective with regard to double bond configuration. In the crude mixtures we could detect only two cyclic products, diastereoisomeric at the two stereogenic centers. The double bond configuration was unambiguously established as *Z* in several instances by the C*H*=C*H* coupling constants (9–10 Hz). This result was not fully expected: the analogous RCM reaction leading to ten-membered rings affords *E* or *Z* isomers depending on the substituents and on the double bond position.[5,9]

At this stage, the two diastereoisomers (*cis* and *trans*) resulting from the nonstereoselective Ugi reaction could be easily isolated by chromatography[23] in nearly all the cases, the exceptions being Fmoc-containing adducts **6h** and **6i**. NOE experiments,[24] carried out on the two diastereoisomers of **6f**, demonstrated that the compound with the lower R_f value (petroleum ether/AcOEt eluents) had the *trans* configuration. A series of NMR analogies (^1H and ^{13}C)[25] indicated that for **6a–e** and **6g**, the compounds with lower R_f were *trans* as well.

In conclusion, we have demonstrated for the first time the preparation of nine-membered secondary lactams in moderate to good yields by RCM and that this cyclization is highly stereoselective with regard to the double bond configuration. We have also developed a highly convergent approach to these promising scaffolds, amenable to the introduction of three diversity factors, by coupling the Ugi four-component reaction with an RCM.

At present our research is focussed on the use of enantiomerically pure **3** and **4** and optically active protected amino acids or peptides in order to obtain, in a few convergent steps, scaffolds well suited for the synthesis of constrained cyclic peptides.

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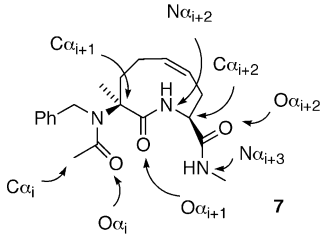
10. Conformational analysis[11] carried out on compound **7** (*cis* isomer) in chloroform showed that in 70% of the conformations not exceeding 12.57 kJ/mol from the global minimum, a hydrogen bond between $O\alpha_i$ and $N\alpha_{i+3}$, typical of a reverse turn, was present. The remaining conformations had either a hydrogen bond between $O\alpha_i$ and $N\alpha_{i+2}$ (10%) or between $O\alpha_{i+1}$ and $N\alpha_{i+3}$ (20%). In water the percentage of considered conformations characterized by a hydrogen bond decreased from 100 to 55%, but 44% of them still had the H-bond between $O\alpha_i$ and $N\alpha_{i+3}$. The β virtual dihedral angle ($C\alpha_i$–$C\alpha_{i+1}$–$C\alpha_{i+2}$–N_{i+3}) was optimal for a reverse turn in 67 or 60% of the conformations considered, respectively, in water and chloroform. For the *trans* epimer of **7** the situation was far less favorable. No considered conformation possessing a H-bond between $O\alpha_i$ and $N\alpha_{i+3}$ was found. The epimer of **7** also turned out to be generally less stable and more flexible than **7**.



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11. Conformational analyses were carried out at the Institute of Molecular Pharmacy, Pharmacenter of the University of Basel, and would have not been possible without the precious collaboration of Professor Beat Ernst and Samuel Schmid. They have been performed on a Silicon Graphics O_2 console, using the program MacroModel,[12] version 5.0. TNCG (Truncated Newton Conjugate Gradient)[13] and Amber* force field (Amber all-atom force field) have been used for the minimization steps, while unconstrained Monte Carlo/energy minimisation (MC/EM)[14] has been applied for the conformational search (ring closures have been defined for each ring, when these were not automatically defined). At least 2,000 conformations were generated for each analysis, only those with energy not exceeding 50 kJ/mol from the global minimum being taken into consideration. Each conformation was minimized (500 iterations) and only those having a gradient ≤ 0.01 kJ/Å mol were considered. Analyses in water and chloroform were carried out using the solvation model by Still (GB/SA, Generalised Born/Solvent Accessible Surface Area).[15]
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18. Isocyanide **3** was prepared from commercially available diethyl formamido malonate: (a) NaH, DMF, rt, 95%; (b) 0.13 M NaOH in EtOH, rt; (c) dioxane, reflux, 79%; (d) $POCl_3$, Et_3N, CH_2Cl_2, −30°C, 92%.
19. Isocyanide **4** was prepared from *t*-butyl isocyanoacetate as described.[20] In our hands the yields were not higher than 40%.
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21. In some cases by using MeOH and isocyanide **3** we observed various degrees of transesterification. Thus we now prefer to use EtOH for reactions involving **3**.
22. All new compounds were fully characterized by ^1H and ^{13}C NMR, IR, GC–MS (when possible) and elemental analysis.
23. While the two diastereoisomers were usually well separated by silica gel chromatography using petroleum ether/AcOEt eluents (with the exceptions of **6h** and **6i**), complete removal of intermolecular products was in some cases troublesome and required 2–3 subsequent chromatographies with different eluents.
24. The *trans* isomer of **6f** showed a remarkable 20% NOE on the N*H* when irradiating the CH_3 bonded at C-3. This is clearly possible only for this diastereoisomer and only if the cyclic amide is in an *anti* conformation. On the

other hand, the *cis* epimer of **6f** showed a 10% NOE on one of the two *H*-4 (irradiating the same methyl), as well as a 3% NOE on the N*H* by irradiating the aromatic protons and a 2% NOE on CH_3CO irradiating the N*H*. Also these latter NOEs seem possible only if the amide conformation is *anti*. The CO_2R^4 group prefers a *pseudo*-equatorial position in both epimers, as demonstrated by the high *J* (9–10 Hz) between N*H* and C*H*–N. Thus in the *cis* compound the methyl group is *pseudo*-axial and lies at a close distance with one of the *H*-4. All these results fit well with the expected (Macromodel and Chem3D) preferred conformations.

25. In the ^{1}H NMR spectra, the CH_3 bonded at C-3 resonates at 1.43–1.49 in *trans* isomers and at 1.65–1.70 in the *cis* counterparts. In the ^{13}C *C*-5: *trans*: 32.91–33.68; *cis*: 29.60–30.92. *C*-6: *trans*: 124.02–124.19; *cis*: 122.55–122.85. *C*-7: *trans*: 134.21–134.46; *cis*: 134.90–135.35. The methyl at C-3 is always upfield for *trans* isomers by 0.5–1.75 ppm. *C*-4 is always downfield for *trans* isomers. *C*-8 is always upfield for *trans* isomers by 0.60–0.93 ppm. *C*-9 is always downfield for *trans* isomers by 0.42–0.55 ppm.