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Skeletal diversity by allylation/RCM on Ugi four-component coupling reaction products

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Abstract—Here, we report a diversity-oriented synthetic approach toward skeletally diverse, cyclized peptidomimetics with diverse appendages. Starting from α-(*N*-acylamino)amides with various appendages, 12 to 16-membered lactams with defined olefin geometry were synthesized by a common synthetic sequence. We also synthesized the macrocycle in a liquid phase directed toward a construction of the peptidomimetics library.

Biologically functional small molecules play a central role in the study of chemical biology and/or chemical genetics.[1] While useful molecules have been usually found in natural resources, efforts have been also paid in these studies to use a synthetic small molecules library, which is readily accessible by diversity-oriented organic synthesis (DOS).[2] The major concern in DOS, recently, is to develop an efficient methodology for acquisition of skeletal diversity in the library construction employing a split-pool technology to raise not only the quantity but also the quality of the small molecules library.[3–5]

One biologically important class of artificial small molecules is peptidomimetics which mimic unique secondary motifs of peptide, such as loop or turn structures, to modulate the interactions at protein/receptor or protein/protein.[6,7] Synthetic works on conformationally constrained, cyclized peptidomimetics for reverse turn motifs have been actively studied both in solution[8] and solid phases,[7] and ring-closing metathesis (RCM) reaction has been recently paid considerable attention for the cyclization of peptides.[9,10] However, there is no report describing the acquisition of skeletal diversity by DOS for these cyclized peptidomimetics. In this letter, we report our approach toward this by RCM as a key reaction starting from Ugi four-component coupling reaction products.[11] This is the first example for introduction of olefins, reactive in the cyclization step after the Ugi reaction, which produces only the appendage-based diversity; our approach thus enables realization of a small molecules library with both skeletal and appendage-based diversities.

The substrates used in this study were prepared by Ugi four-component coupling reaction between amine, aldehyde, carboxylic acid, and isocyanide.[12] As had been already reported, the reaction proceeded quite smoothly by employing 2,2,2-trifluoroethanol as a solvent,[13] to give α-(*N*-acylamino)amides in good to excellent yields (Fig. 1). Another advantage of this solvent is that the undesired transesterification between the ethyl ester and 2,2,2-trifluoroethanol, which frequently takes place when methanol is used as a solvent, was not observed at all and the Ugi products were obtained quite cleanly.

With the desired α-(*N*-acylamino)amides **1**–**6** in hand, we first explored the construction of 12-membered lactam triamide (Scheme 1). As expected from our previous study,[5] alkylation of the amide **1** with allyl iodide was smoothly effected by employing Cs_2CO_3 in DMF (86%). The use of allyl bromide was much less effective (70%). To the acrylamide moiety was then added allylamine at 40 °C (83%), and the resultant secondary amine was sulfonylated with TsCl in 100% yield to give the diallylated precursor for metathesis cyclization. Finally, by using 20 mol % of the second generation Hoveyda–Grubbs catalyst (Fig. 2)[14] at 80 °C in 1,2-dichloroethane, the desired lactam triamide **7** was obtained in 85% yield after 44 h with complete trans

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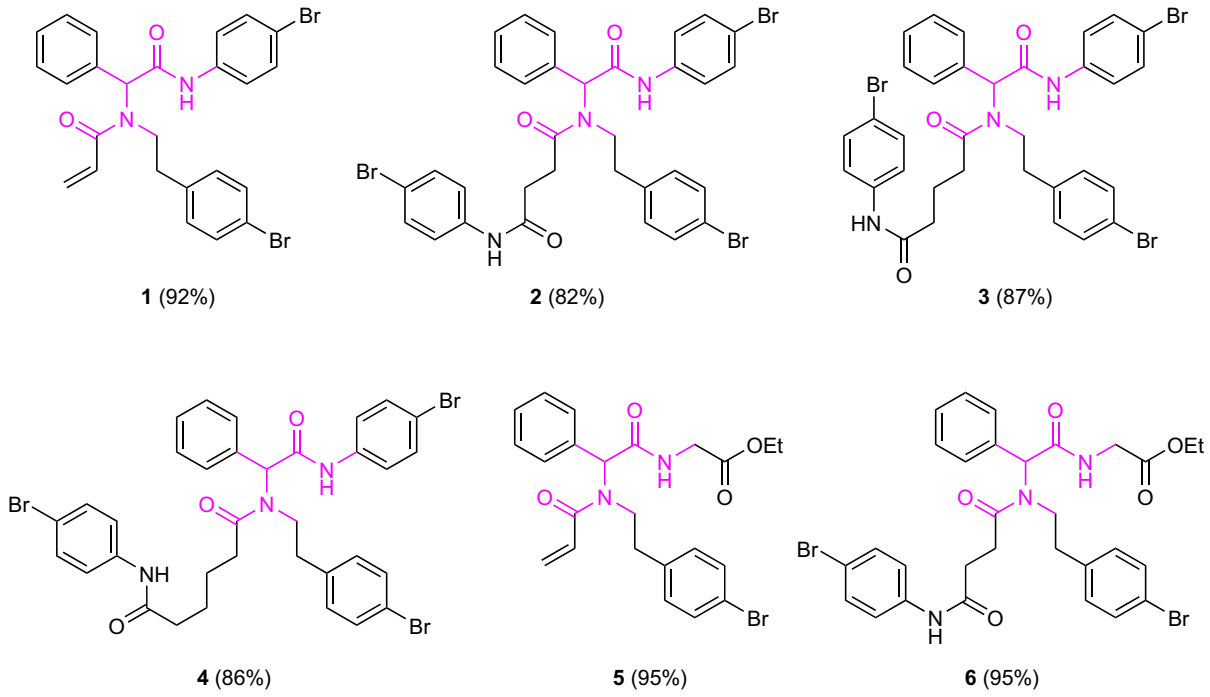
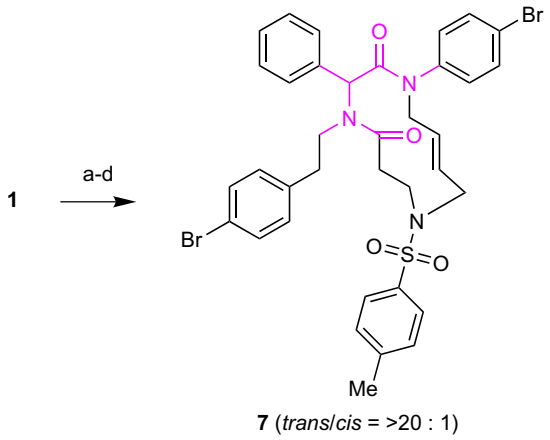


Figure 1. Ugi four-component coupling products used in the present study. In parentheses are yields, and the colored moieties are common skeleton for the Ugi product.



Scheme 1. Reagents and conditions: (a) allyl iodide, Cs_2CO_3, DMF, rt, 1 h, 86%, (b) allylamine, ethanol, 40 °C, 36 h, 83%, (c) TsCl, triethylamine, 1,2-dichloroethane, 0 °C, 30 min, 100%, (d) second generation Hoveyda–Grubbs catalyst (20 mol %), 1,2-dichloroethane, 80 °C, 44 h, 85%.

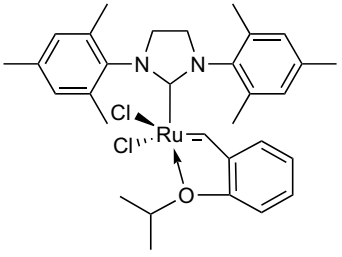
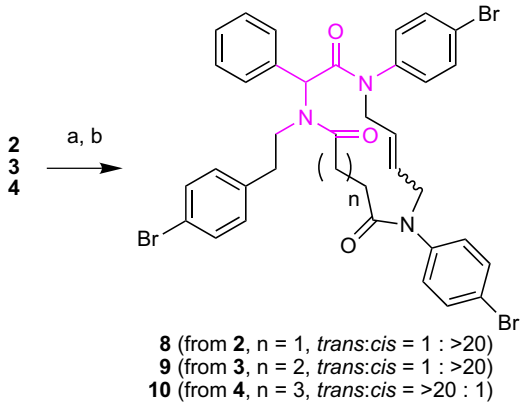


Figure 2. The second generation Hoveyda–Grubbs catalyst[14] used in the present study.

selectivity as judged from ^{1}H NMR and LC–MS analyses.[15] It should be noted that other acyl groups can be introduced to the intermediary secondary amines generated by the conjugate addition of allylamine to gain the appendage-based diversity.

Larger macrocycles were obtained by bisallylation strategy (Scheme 2). In these cases, the Ugi products **2**–**4** bearing two *p*-bromoanilides were treated with allyl iodide and Cs_2CO_3 in DMF at rt to afford the diallylated, metathesis precursors in 74–97% yields. Ring-closing metathesis of these precursors proceeded at 60–83 °C in moderate yields; 67% for 13-membered **8**, 74% for 14-membered **9**, and 71% for 15-membered **10**, lactam

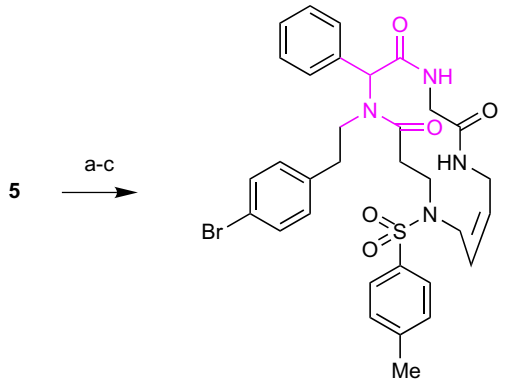


Scheme 2. Reagents and conditions: (a) allyl iodide, Cs_2CO_3, DMF, rt, 1.5 h, 86% from **2**, 74% from **3**, and 97% from **4**, (b) second generation Hoveyda–Grubbs catalyst (30 mol %), 1,2-dichloroethane, 67% for **8** (83 °C, 80 h), 74% for **9** (60 °C, 48 h), and 71% for **10** (60 °C, 42 h).

triamides with cis, cis, and trans geometries, respectively.[15] The size of the macrocycle with unique olefin geometry can be thus easily controlled by the choice of the dicarboxylic acid monoamide.

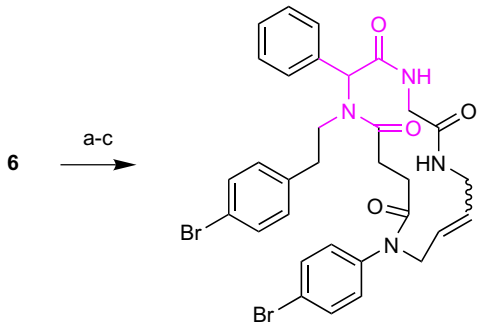
Fifteen-membered lactam tetramide was constructed from the Ugi product **5** bearing acrylamide and ethyl ester functionalities (Scheme 3). Treatment of **5** with allylamine in ethanol induced conjugate addition at rt, which was followed by amidation at the ester moiety at a higher temperature (50 °C) in one-pot operations, furnishing the diallylated product in 66% yield. After the secondary amine thus generated was again sulfonylated with TsCl (85%), the metathesis cyclization was realized quite smoothly by employing 25 mol % of the Hoveyda–Grubbs catalyst, to afford the 15-membered lactam tetramide **11** with *cis*-olefin in good yield (89%).[15] Because the reactivity of the acrylamide and ester functionalities toward allylamine is much different, different amines can be introduced to these positions by which different size of macrocycles would be accessible by these reaction sequences.

The last example is the construction of 16-membered tetramide from the Ugi product **6** (Scheme 4). Since **6** contains two amide protons, selective allylation of the anilide functionality over the alkyl amide should be achieved, and this was realized by the combination of allyl iodide and Cs_2CO_3, as used in other cases for **1**–**4**, in low yield (39%) but with complete selectivity. Other decomposed products were also detected but not characterized. After amidation of the ethyl ester with allylamine in 91% yield, the diallylated cyclization precursor was treated with 20 mol % of the Hoveyda–Grubbs catalyst at 60 °C to give the 16-membered tetramide **12** in acceptable yield (62%) and selectivity (trans/cis = 5:1).[15] It should be also noted here that the selective N-allylation of the anilide moiety in the presence of two other monoalkyl amides was also possible in the inversed-mode sequence, where amidation of the ester moiety was done (99%) prior to N-allylation (42%), for the synthesis of the metathesis substrate. This demonstration shows the usefulness of the incorporation of the anilide into a polyamide as a σ-element,[3,16] different appendages that pre-encode skeletal information, for the selective chemical modification in order to gain the skeletal diversity.



11 (*trans*/*cis* = 1 : >20)

Scheme 3. Reagents and conditions: (a) allylamine, ethanol, rt → 50 °C, 36 h, 66%, (b) TsCl, triethylamine, 1,2-dichloroethane, 0 °C, 30 min, 85%, (c) second generation Hoveyda–Grubbs catalyst (25 mol %), 1,2-dichloroethane, 60 °C, 20 h, 89%.

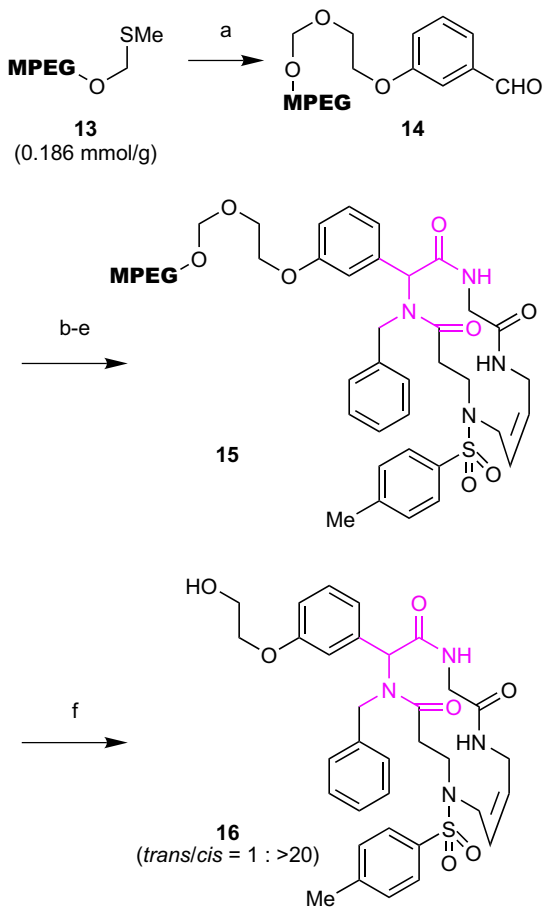


12 (*trans*/*cis* = 5 : 1)

Scheme 4. Reagents and conditions: (a) allyl iodide, Cs_2CO_3, DMF, rt, 24 h, 39%, (b) allylamine, ethanol, 40 °C, 36 h, 91%, (c) second generation Hoveyda–Grubbs catalyst (20 mol %), 1,2-dichloroethane, 60 °C, 8 h, 62%.

From the successful experiments shown above, the construction of the small molecules library comprising the skeletally diverse tri- and tetraamide macrocycles with appendage diversity was then expected by the common reaction sequence in the order of Ugi reaction, N-sulfonylation, 1,4-conjugate addition, amidation, N-acylation, and ring-closing metathesis. As a preliminary study toward this goal, we examined the liquid-phase synthesis of the 15-membered lactam tetramide on poly(ethylene glycol) monomethyl ether (MPEG-OH) of MW 5000.[17] Among three linkers developed by us for the high-throughput synthesis with the MPEG polymer,[18,19] a formylacetal linker[19] was employed in the present study because of the stability under alkaline conditions. At first, 3-(2-hydroxyethoxy)benzaldehyde was loaded onto the platform **13** (0.186 mmol/g) by using iodine monochloride (Scheme 5). The polymer was collected by the addition of diethyl ether in 100% (weight-based recovery), and the conversion yield for **14** was determined to be also 100% from ^{1}H NMR. To the aldehyde **14** was successively effected the reaction sequence including Ugi reaction, 1,4-conjugate addition, amidation, N-sulfonylation, and ring-closing metathesis to furnish the tetramide macrocycle **15** in 61% yield for four steps. Finally, the small molecule was released from the polymer on exposure to trifluoroacetic acid in CH_2Cl_2 to give the 15-membered lactam tetramide **16** in 98% isolated yield with excellent olefin geometrical selectivity (trans/cis = 1:>20).[15] The purity of **16** was found reasonable (44%) from LC–MS analysis.

In summary, we have developed a new DOS process, which features three types of introduction of allyl groups to the Ugi four-component coupling reaction products followed by RCM reaction, for skeletally diverse cyclized peptidomimetics with diverse appendages. We also demonstrated the synthesis of the macrocycle in liquid phase. Work is in progress to construct



Scheme 5. Reagents and conditions: (a) 3-(2-hydroxyethoxy)benzaldehyde, iodine monochloride, molecular sieves 4 Å, CH_2Cl_2, 0 °C → rt, 80 min, 100%, (b) ethyl isocyanoacetate, acrylic acid, benzylamine, CF_3CH_2OH, rt → 50 °C, 72 h, 100%, (c) allylamine, CF_3CH_2OH, ethanol, 50 °C, 20 h, 100%, (d) TsCl, triethylamine, CH_2Cl_2, 0 °C → rt, 90 min, 61%, (e) second generation Hoveyda–Grubbs catalyst (10 mol %), 1,2-dichloroethane, 60 °C, 35 h, 100%, (f) TFA/CH_2Cl_2 (3:7), rt, 4 h, 98% isolated yield, 44% purity. Yields were evaluated from ^1H spectra using a methyl group of the MPEG polymer as a reference except for the step f.

the skeletally diverse peptidomimetics library by these methodologies.

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