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SKELETAL DIVERSITY BY UGI FOUR-COMPONENT COUPLING REACTION AND POST-UGI REACTIONS

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Abstract – Here we report a strategy to alter the skeletal complexity of Ugi four-component coupling reaction products by using allylations followed by ring-closing metathesis. Principal component analysis is also performed for these compounds.

INTRODUCTION

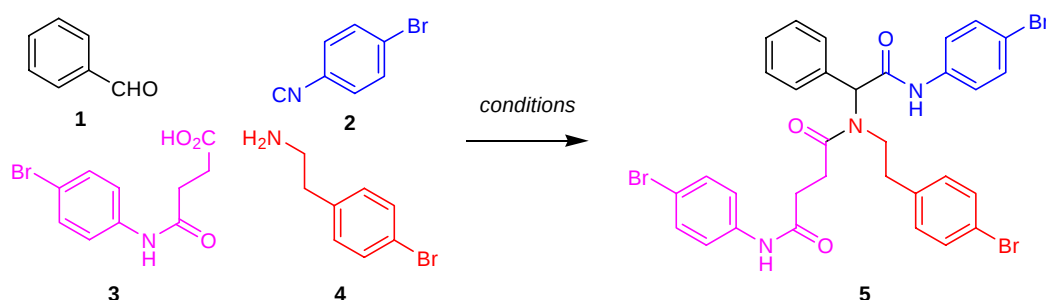
Molecular diversity is highly important for the de novo development of biologically functional small molecules for use in chemical genetics (or chemical biology), a research area of chemistry-driven biology.¹ One of the methods for rapidly obtaining a divergent, artificial molecular library is organic synthesis employing a multi-component coupling reaction (MCR).^{2,3} The MCR was first reported by Robinson in 1917,⁴ and various types of MCR have since been developed, including three-, four-, and five-component coupling reactions. However, MCRs basically yield a group of compounds sharing the same molecular skeleton, and hence are not the best way to acquire a library with truly broad molecular diversity. To solve this problem, other reactions are often applied to the MCR products. For these "post-MCRs", a simple derivatization or ring-closing/opening reactions are frequently used,⁵ and a combination of these techniques is sometimes used for higher degree diversity-oriented synthesis (DOS).⁶ In this paper, we report our attempts⁷ to construct a diverse molecular library starting from a Ugi four-component coupling reaction (4CR),^{3,8} which is a well-known MCR that gives rise to α -acylaminoamides via the reaction of aldehyde, amine, carboxylic acid, and isocyanide.⁹ Syntheses of skeletally diverse 12- to 16-membered macrocycles with defined stereochemistry were successfully achieved in the present DOS approach.

RESULTS AND DISCUSSION

The present DOS study features chemoselective introduction of allyl groups to the Ugi 4CR products followed by cyclization of the macrocyclic ring by ring-closing metathesis (RCM). When cyclized, the α -acylaminoamides are known to function as mimetics for loop or β -turn motifs of peptides, and therefore a diverse library of cyclized Ugi 4CR products is expected to be a promising source for chemotherapeutic drugs for various diseases caused by undesirable protein/receptor or protein/protein interactions.¹⁰ The introduction of the allyl groups is carried out by either *N*-allylation or amidation of ester functional groups as follows.

First, we attempted to determine the most efficient conditions for the Ugi 4CR. The results for the synthesis of **5** are shown in Table 1. Here, equimolar amounts of benzaldehyde (**1**), 4-bromophenyl isocyanide (**2**), succinic acid mono-4-bromoanilide (**3**), and 4-bromophenylethylamine (**4**) were used for the reactions. Under standard conditions at 50 °C in MeOH, the Ugi 4CR product **5** was obtained in a disappointing yield of only 27% (run 1). Perchloric acid as an additive¹¹ improved the yield to 60% (run 2). The use of 2,2,2-trifluoroethanol (TFE) alone as a solvent¹² was found to be the most efficient, giving **5** in 82% yield even at rt (run 3).

Table 1. Optimization of reaction conditions for the Ugi 4CR for **5**.



Run	Conditions	Yield (%)
1	MeOH, 50 °C, 45 h	27
2	HClO ₄ (0.05 equiv), MeOH/TFE (4:1), rt → 50 °C, 18 h	60
3	TFE, rt, 40 h	82

Using the optimized procedure, five Ugi 4CR products (**6-10**) were synthesized using other building blocks for isocyanide (ethyl isocyanoacetate) and carboxylic acid (acrylic acid, glutaric acid monoamide, adipic acid monoamide) as shown in Figure 1. In all cases, the reaction proceeded quite smoothly in 86-95% yield.

Allylation conditions were next explored on **5** (Table 2). In all runs, the allylating agent (6 equiv) and base (6 equiv) were applied to **5** at rt. At first, allyl bromide and NaH were used (run 1). After 12 h, the desired bisallyl amide **11** was obtained in 44% isolated yield. Changing the base to Cs₂CO₃ caused the reaction to be sluggish, but the yield was much improved to 70% (run 2). CsOH in THF, used in our previous study,^{13,14} was found to drive the reaction smoothly, though some decomposition was observed to yield **11** in 50% after 3 h (run 3). As the allylation agent, allyl iodide was much more effective than

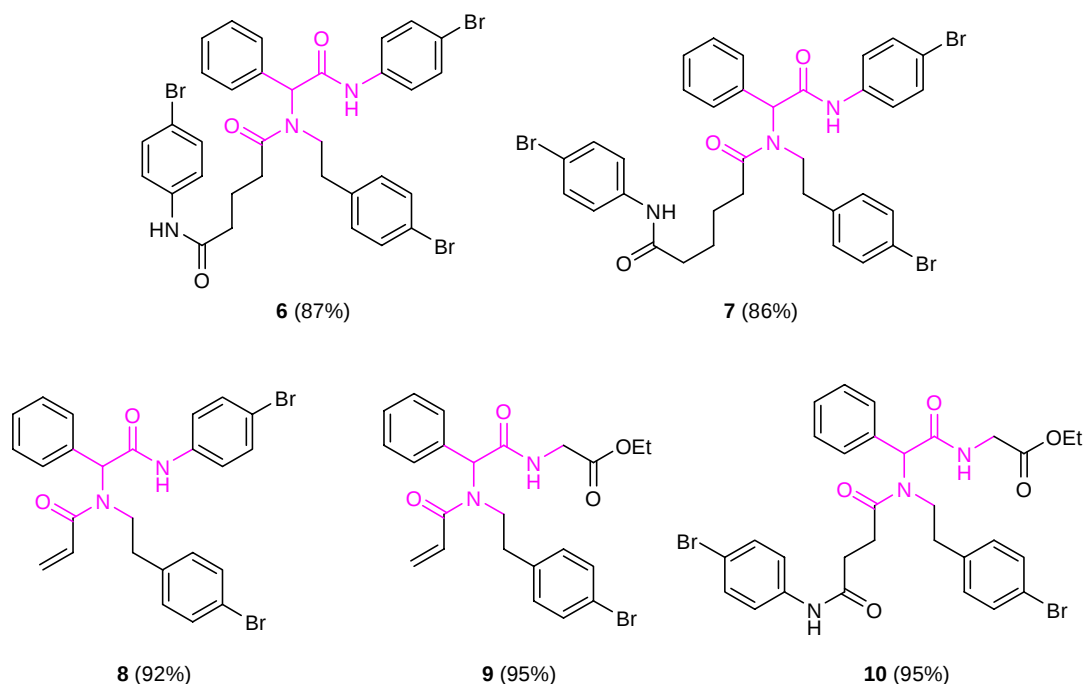


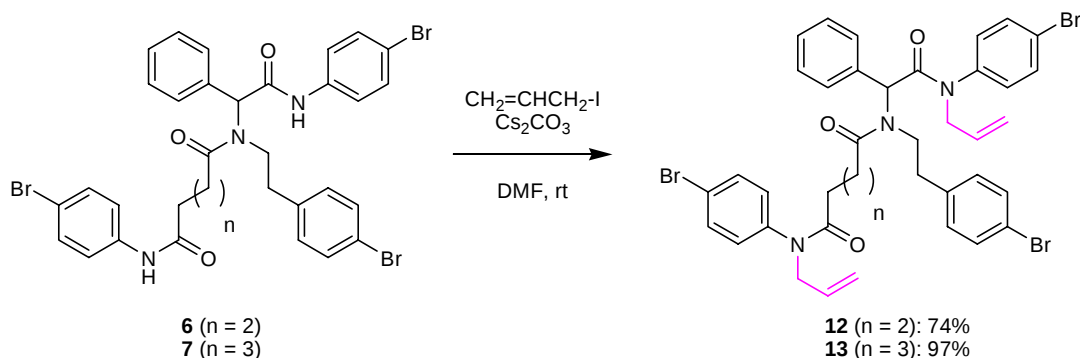
Figure 1. Five Ugi 4CR products synthesized by the procedure optimized in Table 1. In parentheses are shown isolated yields.

Table 2. Optimization of the conditions for allylation of the bisanilide **5**.

Run	Allylation agent (6 equiv)	Base (6 equiv)	Solvent	Time (h)	Yield (%)
1	CH ₂ =CHCH ₂ Br	NaH	DMF	12	44
2	CH ₂ =CHCH ₂ Br	Cs ₂ CO ₃	DMF	46	70
3	CH ₂ =CHCH ₂ Br	CsOH	THF	3	50
4	CH ₂ =CHCH ₂ I	Cs ₂ CO ₃	DMF	1.5	86

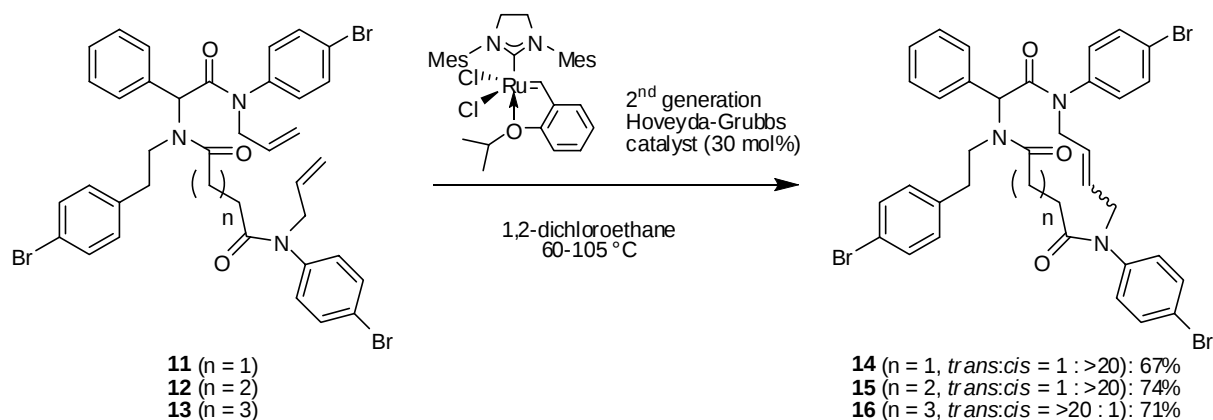
allyl bromide. Thus, the combination of allyl iodide and Cs_2CO_3 in DMF afforded **11** in 86% yield after 1.5 h (run 4).

By the procedure thus established, the other bis-*N*-allyl amides **12** and **13** were also successfully prepared in 74% and 97% yields, respectively, as shown in Scheme 1.



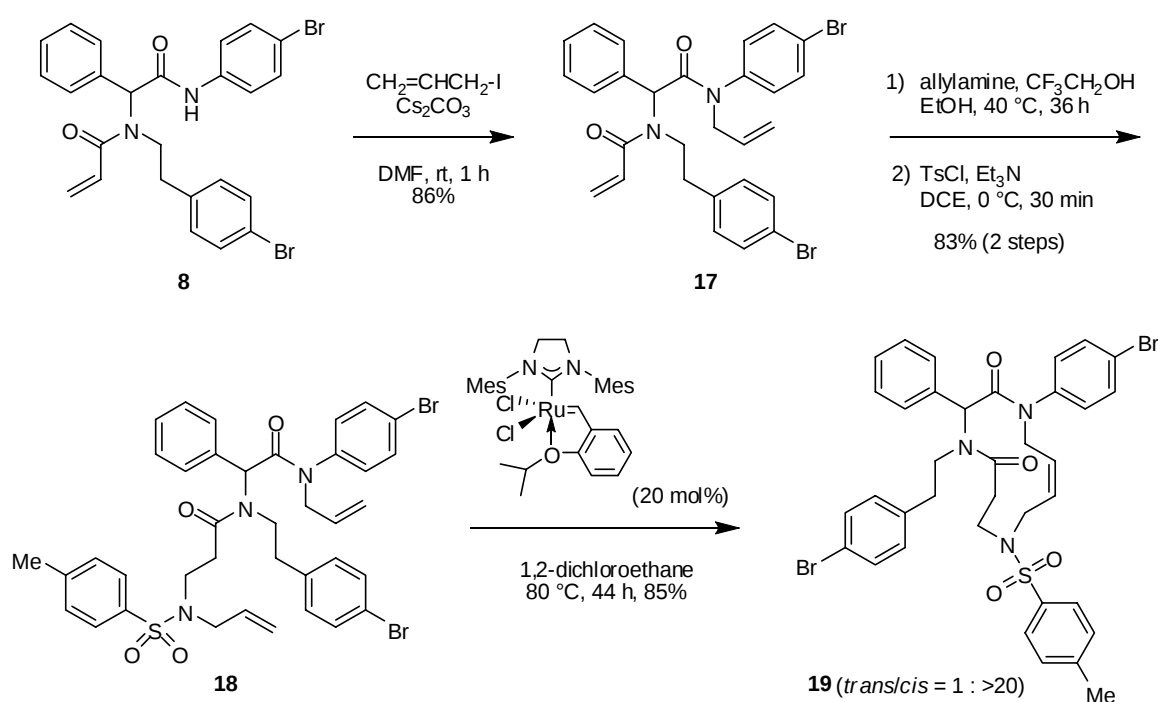
Scheme 1. Preparation of bis-*N*-allyl amides **12** and **13**.

Formation of the 13-, 14-, and 15-membered macrocycles from bis-*N*-allyl amides **11-13** was next attempted by RCM. The results are summarized in Scheme 2. The concentration was 1.2 mM for the substrates **11-13**, which were treated with 30 mol% of 2nd generation Hoveyda-Grubbs catalyst¹⁵ in 1,2-dichloroethane (DCE) at 60-105 °C. From **11** and **12**, 13- and 14-membered macrocycles **14** and **15** were provided in 67% and 74% yields, respectively. The geometry of the double bond formed was determined from ^1H NMR spectra to be *cis* with >95% purity in both cases. On the other hand, the diallyl substrate **13** gave the 15-membered macrocycle **16** in 71% yield with exclusive *trans* selectivity (>95%). Interestingly, the selectivities for **14** and **15** did not correspond with the calculated thermodynamic stabilities, and thus were further investigated as discussed below.



Scheme 2. Ring-closing metathesis for the formation of geometry-defined macrocycles **14-16**.

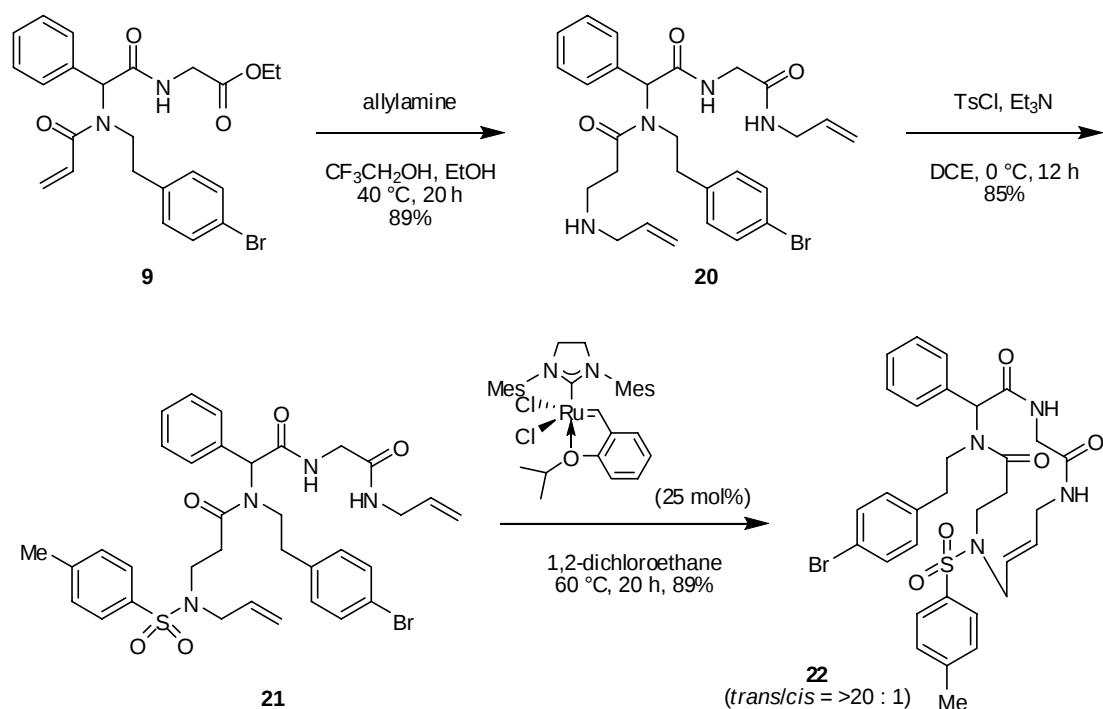
The monoanilide **8** was transformed into the 12-membered macrocycle **19** (Scheme 3). At first, *N*-allylation was achieved by the same procedure (allyl iodide, Cs₂CO₃, DMF, rt, 1 h) as used above for the syntheses of **12** and **13**, which was optimized as shown in Table 2. The reaction also readily proceeded in this case, giving the *N*-allyl anilide **17** in 86% yield. 1,4-Conjugate addition of allylamine to **17** smoothly proceeded at 40 °C in 83%. The secondary amine thus generated was tosylated to afford **18** quantitatively. With these two allyl groups introduced, **18** was finally cyclized by RCM (20 mol% of 2nd generation Hoveyda-Grubbs catalyst, DCE, 80 °C, 44 h) to provide the *cis* macrocycle **19** in 85% yield predominantly. No *trans* isomer was detected in the ¹H NMR spectrum.¹⁶ It should be noted that the acylation step (**17**→**18**) is a diversification process, so that appendage-based diversity can be introduced on this 12-membered macrocyclic skeleton.



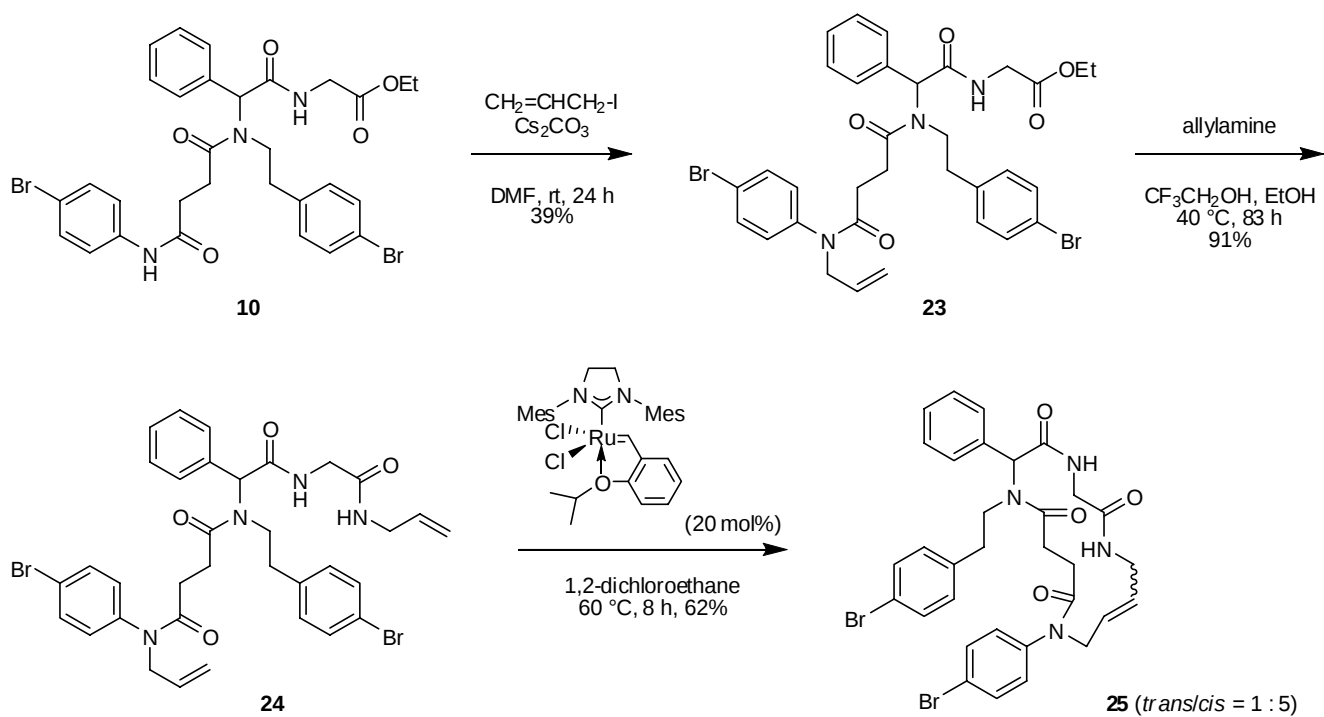
Scheme 3. Synthesis of 12-membered macrocycle **19** from the Ugi 4CR product **8**.

Another type of 15-membered macrocycle, **22**, can be synthesized from **9** bearing acrylamide and ethyl ester functionalities (Scheme 4). Amidation and 1,4-conjugate addition simultaneously took place with allylamine on **9** at 40 °C to afford **20** in 89% yield. The secondary amine was tosylated to give **21** (85%), which was further subjected to cyclization by RCM at 60 °C over 20 h to form the 15-membered macrocycle **22** in good yield (89%). From ¹H NMR analysis, the olefin geometry was found to be *trans*; the selectivity is identical to **16**, which is also a 15-membered macrocycle synthesized by the other

pathway.¹⁶ Since the process includes acylation (**20**→**21**), diverse appendages can be installed on the macrocyclic skeleton to achieve structural diversity.



Scheme 4. Synthesis of 15-membered macrocycle **22** from the Ugi 4CR product **9**.



Scheme 5. Synthesis of 16-membered macrocycle **25** from the Ugi 4CR product **10**.

The largest macrocycle constructed in the present work is 16-membered cyclic **25** (Scheme 5). To construct this macrocycle, we first attempted mono-*N*-allylation of **10**. With the procedure optimized in the present study, the desired *N*-allyl amide **23** was obtained in 39% yield. Attempts to improve the yield under various conditions were unsuccessful; overalkylation and decomposition were observed in all reactions. Amidation of **23** with allylamine gave **24** in good yield (91%), and final cyclization with the metathesis catalyst provided the 16-membered macrocycle **25** in 62% yield with *trans/cis* = 1:5 selectivity.¹⁶

An inversion of the process from **10** to **24** was also attempted to improve the overall yield. Amidation of **10** with allylamine in EtOH at 40 °C gave an *N*-allyl amide in 99% yield (data not shown), followed by anilide-selective *N*-allylation (allyl iodide, Cs₂CO₃, DMF, rt, 24 h) to furnish the RCM substrate **24** in 42% yield. It should be noted that the desired *N*-allylation took place selectively to give **24**, though the intermediary substrate carries three amide protons. Here, anilide groups in the Ugi 4CR products thus act as σ -elements,^{13,17} different appendages that pre-encode skeletal information, to convert the common Ugi 4CR product skeleton to various macrocyclic skeletons, as also demonstrated in our previous study.¹⁴ The two-step yield (42%) is somewhat higher than that shown in Scheme 5 (35%). For a construction of a library of skeletally diverse small molecules, however, the process shown in Scheme 5 is desirable (see below).

The thermodynamic stabilities of the macrocycles obtained in the present study were evaluated by molecular modeling. Here, geometrical optimization was carried out by molecular mechanics calculations with a MMFF94S force field for both *cis* and *trans* isomers on a BARISTA software (version 1.2.2; CONFLEX Co., Tokyo, Japan). The results are summarized in Table 3. It is seen that the calculations for 15- and 16-membered macrocycles are in agreement with the experimental results (runs 4-6), whereas the experiments for smaller 12-, 13-, and 14-membered macrocycles do not correspond with the calculated

Table 3. Comparison of experimental and calculated data for olefin geometrical selectivity in the RCM reactions.

Run	Macrocyclic product	Ring size	Experimental selectivity (<i>trans/cis</i>)	Thermodynamic stability (MMFF94S) <i>trans/cis</i> (kcal/mol)
1	19	12	1 : >20	+62.8 / +70.4
2	14	13	1 : >20	+106.6 / +112.5
3	15	14	1 : >20	+115.4 / +120.8
4	16	15	>20 : 1	+118.4 / +125.0
5	22	15	>20 : 1	+14.1 / +15.0
6	25	16	1 : 5	+58.4 / +56.8

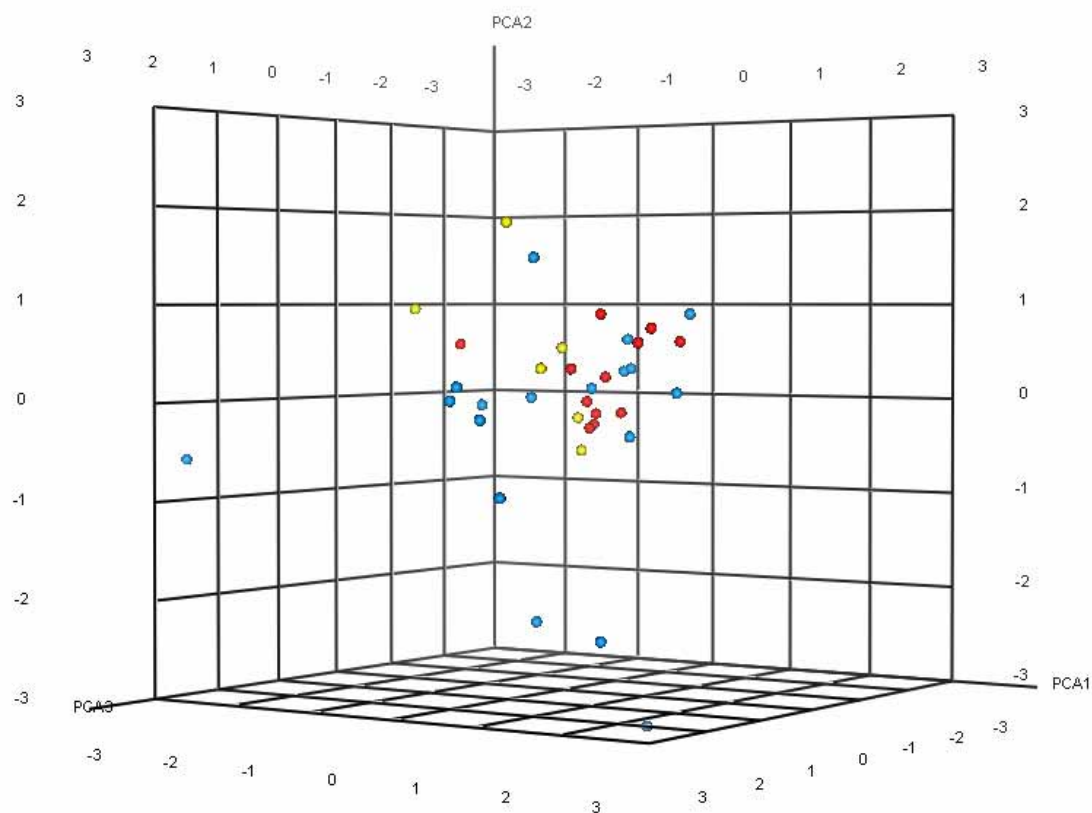


Figure 2. Principal component analysis for the molecules synthesized in the present study. Compounds are divided into three categories; yellow (the Ugi 4CR products **5-10**), red (the (*E*)- and (*Z*)-isomer of macrocycles **14-16**, **19**, **22**, and **25**), and blue (the other synthetic intermediates and reagents used for the Ugi 4CR).

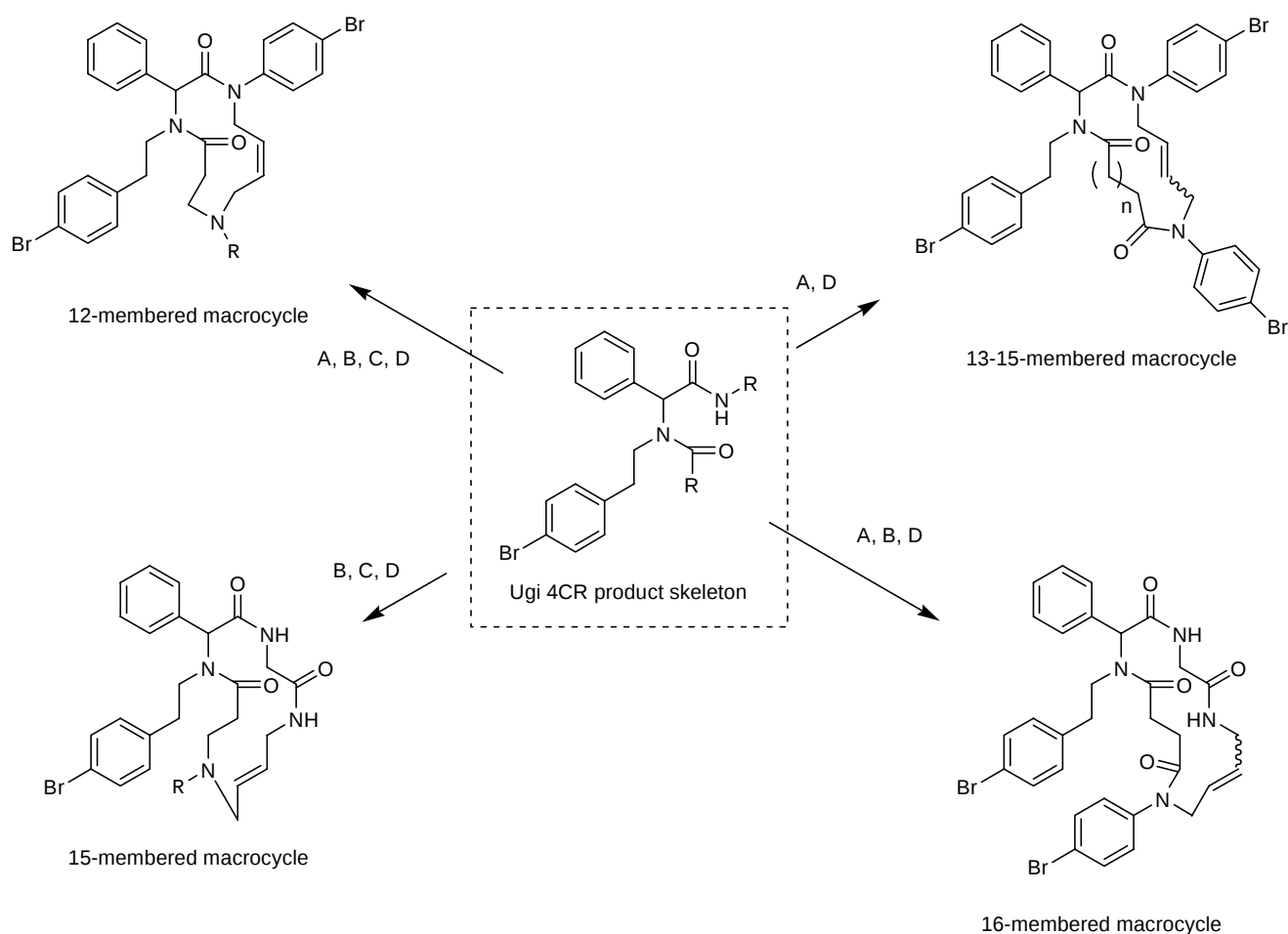
data despite the thermodynamic conditions employed (80-105 °C, runs 1-3). It is generally accepted that RCM for macrocycles preferably gives a *trans* isomer via isomerization by a secondary metathesis reaction.¹⁸ In the present study, therefore, steric interactions or by other factors were thought to interfere with the selectivities of **14**, **15**, and **19**.

For visualization and evaluation of the macrocycles library produced by the above-described strategy, we performed principal component analysis using a MOE (Molecular Operating Environment) software (Chemical Computing Group Inc., Montreal, Quebec, Canada). Fifty-seven descriptors were calculated for the three-dimensional structure of each product shown in this paper, and all descriptors were subjected to principal component analysis. Five principal components were generated to represent 83.4% of the total number of descriptors. Three principal components, that represent 83.4% of the total descriptors, were used to visualize the molecular diversity of the Ugi 4CR products and macrocycles in Figure 2. It is seen in this chemical space that macrocycles (red) are distributed differently from the Ugi 4CR products (yellow) and the synthetic intermediates (blue). Unexpectedly, however, these groups stay close to each

other in this three-dimensional space. Because of this, the compound library would be useful to study the structure-activity relationships of known biologically functional compounds, rather than to discover new small molecules for use in chemical genetics studies.

In conclusion, we have shown in the present study that the combination of the Ugi 4CR and the post-Ugi reactions (*N*-allylation, amidation, *N*-acylation, RCM) generates skeletally diverse 12- to 16-membered macrocycles. To enable selective incorporation of allyl groups, an anilide group is employed as a σ -element in these DOS processes. As summarized in Scheme 6, these reactions are performed in the same order: A (*N*-allylation), B (amidation), C (*N*-acylation), and D (RCM). As a result, a large number of macrocycles with diverse skeletons and appendages are now accessible by the present DOS strategy. In addition, we examined the chemical space of small molecules in the present study and showed that this process for acquiring skeletal diversity also results in a clear expansion of the chemical space.

We have already demonstrated the liquid-phase synthesis of the 15-membered macrocycle related to **22** on our MPEG platform.⁷ Works are in progress toward a solid-phase demonstration of this process and realization of a macrocycles library comprised of thousands of compounds.



Scheme 6. Organic synthesis for skeletal diversity shown in the present study. A: *N*-allylation, B: amidation with allylamine, C: *N*-acylation, D: RCM.

EXPERIMENTAL

General: The experimental techniques and the characterizing apparatuses used are summarized in our previous paper.¹⁹ The Hoveyda-Grubbs catalyst (2nd Generation, [301224-40-8])¹⁵ was purchased from Aldrich Co.

Triamide 5. To a stirred solution of 4-bromophenyl isocyanide (**2**, 25.7 mg, 0.141 mmol) and succinic acid mono-4-bromoanilide (**3**, 36.0 mg, 0.141 mmol) in TFE (0.5 mL) at rt were added benzaldehyde (**1**, 10.0 mg, 0.0942 mmol) and 4-bromophenylethylamine (**4**, 0.0219 mL, 0.141 mmol). The resultant solution was stirred for 40 h, and then concentrated under reduced pressure. Purification by column chromatography on silica gel (10 g, EtOAc/hexane = 3:7) afforded the triamide **5** (57.0 mg, 82%) as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 8.06 (brs, 1 H), 7.72 (brs, 1 H), 7.48-7.26 (m, 15 H), 6.74 (d, *J* = 8.5 Hz, 2 H), 6.09 (s, 1 H), 3.69 (m, 1 H), 3.44 (m, 1 H), 2.96-2.85 (m, 2 H), 2.70 (m, 1 H), 2.65-2.52 (m, 2 H), 2.20 (m, 1 H); HRMS (ESI) *m/z* 739.9760 ([M+H]⁺), calcd for C₃₂H₂₉⁷⁹Br₃N₃O₃ 739.9759.

Triamide 6. By the same procedure for the synthesis of **5**, the triamide **6** was synthesized in 87% yield as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 8.41 (brs, 1 H), 7.53 (brs, 3 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 7.45 (s, 5 H), 7.40 (d, *J* = 8.5 Hz, 3 H), 7.38-7.31 (m, 5 H), 6.58 (d, *J* = 8.5 Hz, 2 H), 5.89 (brs, 1 H), 3.49 (m, 1 H), 3.32 (m, 1 H), 2.58-2.44 (m, 2 H), 2.44-2.30 (m, 2 H), 2.22-2.04 (m, 2 H); HRMS (ESI) *m/z* 753.9919 ([M+H]⁺), calcd for C₃₃H₃₁⁷⁹Br₃N₃O₃ 753.9916.

Triamide 7. By the same procedure for the synthesis of **5**, the triamide **7** was synthesized in 86% yield as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 8.17 (brs, 1 H), 7.68 (brs, 1 H), 7.50-7.25 (m, 15 H), 6.77 (d, *J* = 8.0 Hz, 2 H), 5.82 (brs, 1 H), 3.57-3.42 (m, 2 H), 2.66 (m, 1 H), 2.46 (m, 1 H), 2.38-2.27 (m, 4 H), 1.84-1.62 (m, 4 H); HRMS (ESI) *m/z* 768.0070 ([M+H]⁺), calcd for C₃₄H₃₃⁷⁹Br₃N₃O₃ 768.0072.

Triamide 8. By the same procedure for the synthesis of **5**, the triamide **8** was synthesized in 92% yield as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 8.32 (brs, 1 H), 7.50 (brs, 3 H), 7.42 (brs, 3 H), 7.38-7.33 (m, 3 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 6.75 (d, *J* = 7.5 Hz, 2 H), 6.56 (dd, *J* = 15.0, 10.0 Hz, 1 H), 6.40 (dd, *J* = 15.0, 1.5 Hz, 1 H), 6.20 (s, 1 H), 5.77 (dd, *J* = 10.0, 2.0 Hz, 1 H), 3.61-3.54 (m, 2 H), 2.70 (m, 1 H), 2.25 (m, 1 H); HRMS (ESI) *m/z* 541.0124 ([M+H]⁺), calcd for C₂₅H₂₃⁷⁹Br₂N₂O₂ 541.0126.

Triamide 9. By the same procedure for the synthesis of **5**, the triamide **9** was synthesized in 95% yield as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.48 (brs, 2 H), 7.45-7.38 (m, 4 H), 7.30 (d, *J* = 7.5 Hz, 2 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 6.55 (dd, *J* = 16.5, 10.0 Hz, 1 H), 6.46 (dd, *J* = 16.0, 2.0 Hz, 1 H), 6.37 (brs, 1 H), 6.18 (brs, 1 H), 5.77 (dd, *J* = 10.5, 2.0 Hz, 1 H), 4.17 (q, *J* = 7.5 Hz, 2 H), 4.09 (dd, *J* = 18.0, 5.5 Hz, 1 H), 4.00 (dd, *J* = 18.0, 4.5 Hz, 1 H), 3.60-3.42 (m, 2 H), 2.63 (m, 1 H), 2.12 (m, 1 H), 1.25 (t, *J* = 7.5 Hz, 3 H); HRMS (ESI) *m/z* 473.1077 ([M+H]⁺), calcd for C₂₃H₂₆⁷⁹BrN₂O₄ 473.1076.

Triamide 10. By the same procedure for the synthesis of **5**, the triamide **10** was synthesized in 95% yield as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 8.07 (s, 1 H), 7.46-7.25 (m, 9 H), 7.24 (d, *J* = 8.5 Hz, 2

H), 6.65 (d, $J = 8.0$ Hz, 2 H), 6.58 (brs, 1 H), 6.01 (brs, 1 H), 4.07 (q, $J = 7.5$ Hz, 2 H), 4.03 (m, 1 H), 3.95 (m, 1 H), 3.57 (m, 1 H), 3.42 (m, 1 H), 2.89-2.76 (m, 2 H), 2.76-2.65 (m, 2 H), 2.65-2.55 (m, 2 H), 2.14 (m, 1 H), 1.24 (t, $J = 7.5$ Hz, 3 H); HRMS (ESI) m/z 672.0709 ($[M+H]^+$), calcd for $C_{30}H_{32}^{79}Br_2N_3O_5$ 672.0709.

Bis-*N*-allyl Amide 11. To a stirred suspension of the triamide **5** (9.20 mg, 0.0124 mmol) and Cs_2CO_3 (24.2 mg, 0.0744 mmol) in DMF (0.2 mL) at rt were added allyl iodide (0.0068 mL, 0.0744 mmol). The resultant mixture was stirred for 1 h, and then quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (2 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Purification by column chromatography on silica gel (5 g, EtOAc/hexane = 1:4) afforded the bis-*N*-allyl amide **26** (8.80 mg, 86%) as a pale yellow oil: 1H NMR (500 MHz, $CDCl_3$) δ 7.56-7.25 (m, 9 H), 7.23 (d, $J = 8.0$ Hz, 2 H), 7.11 (d, $J = 9.0$ Hz, 4 H), 6.56 (d, $J = 8.5$ Hz, 2 H), 5.87 (s, 1 H), 5.85-5.70 (m, 2 H), 5.16-5.00 (m, 4 H), 4.30-4.20 (m, 3 H), 4.14 (dd, $J = 10.0, 6.5$ Hz, 1 H), 3.48-3.31 (m, 2 H), 2.77 (m, 1 H), 2.70-2.54 (m, 2 H), 2.50 (m, 1 H), 2.31 (m, 1 H), 1.88 (m, 1 H); HRMS (ESI) m/z 820.0384 ($[M+H]^+$), calcd for $C_{38}H_{37}^{79}Br_3N_3O_3$ 820.0385.

Bis-*N*-allyl Amide 12. By the same procedure for the synthesis of **11**, the bis-*N*-allyl amide **12** was synthesized from **6** in 74% yield as a pale yellow oil: 1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, $J = 8.0$ Hz, 2 H), 7.41-7.22 (m, 7 H), 7.23 (d, $J = 8.5$ Hz, 2 H), 7.10 (d, $J = 7.5$ Hz, 2 H), 7.04 (d, $J = 8.5$ Hz, 2 H), 6.57 (d, $J = 8.5$ Hz, 2 H), 5.85 (s, 1 H), 5.83-5.72 (m, 2 H), 5.16-4.97 (m, 4 H), 4.30-4.12 (m, 4 H), 3.39 (m, 1 H), 3.29 (m, 1 H), 2.52-2.42 (m, 2 H), 2.34 (m, 1 H), 2.34-2.04 (m, 2 H), 2.00-1.80 (m, 3 H); HRMS (ESI) m/z 834.0542 ($[M+H]^+$), calcd for $C_{39}H_{39}^{79}Br_3N_3O_3$ 834.0542.

Bis-*N*-allyl Amide 13. By the same procedure for the synthesis of **11**, the bis-*N*-allyl amide **13** was synthesized from **7** in 97% yield as a pale yellow oil: 1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, $J = 8.0$ Hz, 2 H), 7.40-7.22 (m, 7 H), 7.25 (d, $J = 7.0$ Hz, 2 H), 7.11 (d, $J = 7.5$ Hz, 2 H), 7.01 (d, $J = 8.0$ Hz, 2 H), 6.51 (d, $J = 8.5$ Hz, 2 H), 5.86 (s, 1 H), 5.84-5.72 (m, 2 H), 5.14-4.98 (m, 4 H), 4.30-4.20 (m, 3 H), 4.14 (dd, $J = 15.0, 6.5$ Hz, 1 H), 3.38 (m, 1 H), 3.28 (m, 1 H), 2.46-2.32 (m, 2 H), 2.23 (m, 1 H), 2.10-2.00 (m, 2 H), 1.85 (m, 1 H), 1.66-1.50 (m, 4 H); HRMS (ESI) m/z 848.0697 ($[M+H]^+$), calcd for $C_{40}H_{41}^{79}Br_3N_3O_3$ 848.0698.

13-Membered Macrocycle 14. To a stirred solution of the bis-*N*-allyl amide **11** (4.9 mg, 0.0060 mmol) in DCE (5.0 mL) at 60 °C was added a solution of the 2nd generation Hoveyda-Grubbs catalyst (0.38 mg, 0.0060 mmol)¹⁵ in DCE (1.0 mL) three times. The temperature was raised up to 105 °C over 64 h, when the mixture was cooled to rt and concentrated under reduced pressure. Purification by column chromatography on silica gel (5 g, EtOAc/hexane = 3:7) afforded the 13-membered macrocycle **14** (3.20 mg, 67%) as a colorless oil. 1H NMR spectrum shows the double bond newly formed is *cis* ($J < 10$ Hz). Data for **14**: 1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.26 (m, 15 H), 6.59-6.51 (m, 2 H), 5.94 (brs, 2 H), 5.78

(brs, 1 H), 5.36-4.82 (m, 2 H), 3.74-3.48 (m, 3 H), 3.14 (m, 1 H), 2.76 (m, 1 H), 2.47 (m, 1 H), 2.37-2.10 (m, 2 H), 2.10-1.84 (m, 2 H); HRMS (ESI) m/z 792.0042 ($[M+H]^+$), calcd for $C_{36}H_{33}^{79}Br_3N_3O_3$ 792.0072.

14-Membered Macrocycle 15. By the same procedure for the synthesis of **14** (rt→60 °C over 58 h), the 14-membered macrocycle **15** was synthesized from **12** in 74% yield as a colorless oil. 1H NMR spectrum shows the double bond newly formed is *cis* ($J = <10$ Hz). Data for **15**: 1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, $J = 9.0$ Hz, 3 H), 7.50-7.31 (m, 7 H), 7.26-7.18 (m, 5 H), 6.60 (d, $J = 7.5$ Hz, 2 H), 6.17-6.12 (m, 2 H), 5.18 (s, 1 H), 5.02-4.93 (m, 2 H), 3.66 (m, 1 H), 3.35-3.21 (m, 2 H), 3.16 (m, 1 H), 2.66 (m, 1 H), 2.41-2.22 (m, 4 H), 2.15-2.07 (m, 2 H), 1.77 (m, 1 H); HRMS (ESI) m/z 806.0221 ($[M+H]^+$), calcd for $C_{37}H_{35}^{79}Br_3N_3O_3$ 806.0229.

15-Membered Macrocycle 16. By the same procedure for the synthesis of **14** (40→60 °C over 39 h), the 15-membered macrocycle **16** was synthesized from **13** in 71% yield as a colorless oil. 1H NMR spectrum shows the double bond newly formed is *trans* ($J = 15.0$ Hz). Data for **16**: 1H NMR (500 MHz, $CDCl_3$) δ 7.53 (brs, 2 H), 7.44-7.18 (m, 9 H), 7.08 (brs, 2 H), 6.59 (d, $J = 8.5$ Hz, 2 H), 6.51 (d, $J = 8.5$ Hz, 2 H), 5.89 (m, 1 H), 5.78 (m, 1 H), 5.36 (s, 1 H), 5.15 (m, 1 H), 4.80 (m, 1 H), 3.83 (m, 1 H), 3.41-3.30 (m, 2 H), 3.19-3.12 (m, 2 H), 3.12-3.02 (m, 2 H), 2.63 (m, 1 H), 2.52 (m, 1 H), 2.38 (m, 1 H), 2.26-2.10 (m, 2 h), 2.05 (m, 1 H), 1.57 (m, 1 H); HRMS (ESI) m/z 820.0375 ($[M+H]^+$), calcd for $C_{38}H_{37}^{79}Br_3N_3O_3$ 820.0385.

N-Allyl Amide 17. By the same procedure for the synthesis of **11**, the *N*-allyl amide **17** was synthesized from **8** in 86% yield as a pale yellow oil: 1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.28 (m, 7 H), 7.25 (d, $J = 8.5$ Hz, 2 H), 7.16 (d, $J = 7.0$ Hz, 2 H), 6.55 (d, $J = 8.5$ Hz, 2 H), 6.53 (dd, $J = 17.0, 10.0$ Hz, 1 H), 6.42 (dd, $J = 17.0, 2.0$ Hz, 1 H), 5.80 (s, 1 H), 5.86-5.70 (m, 2 H), 5.09 (d, $J = 10.5$ Hz, 1 H), 5.05 (dd, $J = 17.0, 1.5$ Hz, 1 H), 4.30 (dd, $J = 14.5, 6.5$ Hz, 1 H), 4.18 (dd, $J = 14.5, 6.5$ Hz, 1 H), 3.56-3.40 (m, 2 H), 2.52 (m, 1 H), 1.93 (m, 1 H); HRMS (ESI) m/z 581.0440 ($[M+H]^+$), calcd for $C_{28}H_{27}^{79}Br_2N_2O_2$ 581.0439.

Tosylate 18. To a stirred solution of the acrylamide **17** (20.5 mg, 0.0352 mmol) in EtOH (0.4 mL) at 40 °C were added allylamine (0.0528 mL, 0.704 mmol) and TFE (0.008 mL). The resultant mixture was stirred for 42 h, cooled to rt, and concentrated under reduced pressure. Purification by column chromatography on silica gel (5 g, MeOH/ $CHCl_3$ = 1:19) afforded the intermediary secondary amine (18.7 mg, 83%) as an yellow pale oil: 1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.27 (m, 5 H), 7.27-7.20 (m, 4 H), 7.12 (d, $J = 7.0$ Hz, 2 H), 6.78 (brs, 1 H), 6.55 (d, $J = 8.5$ Hz, 2 H), 5.95-5.84 (m, 2 H), 5.79 (m, 1 H), 5.19 (dd, $J = 17.0, 1.5$ Hz, 1 H), 5.09 (d, $J = 10.0$ Hz, 2 H), 5.05 (d, $J = 17.0$ Hz, 1 H), 4.26 (dd, $J = 15.0, 6.5$ Hz, 1 H), 4.17 (dd, $J = 17.0, 6.5$ Hz, 1 H), 3.47-3.31 (m, 2 H), 3.31-3.22 (m, 2 H), 2.94-2.86 (m, 2 H), 2.68 (m, 1 H), 2.56-2.44 (m, 2 H), 1.88 (m, 1 H); HRMS (ESI) m/z 638.1024 ($[M+H]^+$), calcd for $C_{31}H_{34}^{79}Br_2N_3O_2$ 638.1018.

To a stirred solution of the secondary amine thus obtained (18.7 mg, 0.0292 mmol) in CH_2Cl_2 (0.30 mL) at 0 °C were added triethylamine (0.0061 mL, 0.044 mmol) and TsCl (6.10 mg, 0.0321 mmol). The resultant mixture was stirred for 30 min, warmed to rt, and concentrated under reduced pressure. Purification by column chromatography on silica gel (5 g, $\text{MeOH}/\text{CHCl}_3 = 1:19$) afforded the tosylate **18** (23.4 mg, 100%) as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 7.69 (d, $J = 8.0$ Hz, 2 H), 7.42-7.24 (m, 9 H), 7.12 (d, $J = 8.0$ Hz, 2 H), 6.57 (d, $J = 8.5$ Hz, 2 H), 5.83 (s, 1 H), 5.77 (m, 1 H), 5.65 (m, 1 H), 5.21-5.00 (m, 4 H), 4.25 (dd, $J = 14.5, 6.5$ Hz, 1 H), 4.16 (dd, $J = 15.0, 6.5$ Hz, 1 H), 3.85-3.74 (m, 2 H), 3.50-3.26 (m, 4 H), 2.82 (m, 1 H), 2.72 (m, 1 H), 2.51 (m, 1 H), 2.39 (s, 3 H), 1.87 (m, 1 H); HRMS (ESI) m/z 792.1101 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{38}\text{H}_{40}^{79}\text{Br}_2\text{N}_3\text{O}_4\text{S}$ 792.1106.

12-Membered Macrocycle 19. By the same procedure for the synthesis of **14** (80 °C over 44 h), the 12-membered macrocycle **19** was synthesized from **18** in 85% yield as a colorless oil. ^1H NMR spectrum shows the double bond newly formed is *cis* ($J = 9.4$ Hz). Data for **19**: ^1H NMR (500 MHz, CDCl_3) δ 7.76-7.28 (m, 15 H), 7.08 (brs, 2 H), 5.84-5.68 (m, 3 H), 4.92 (brs, 1 H), 4.41 (brs, 1 H), 4.09 (m, 1 H), 3.83 (m, 1 H), 3.73 (m, 2 H), 3.34-3.24 (m, 2 H), 3.02 (m, 1 H), 2.96-2.80 (m, 2 H), 2.43 (s, 3 H), 2.33 (m, 1 H); HRMS (ESI) m/z 764.0786 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{36}\text{H}_{36}^{79}\text{Br}_2\text{N}_3\text{O}_4\text{S}$ 764.0793.

Secondary Amine 20. By the same procedure for the synthesis of **18**, the secondary amine **20** was synthesized from **9** in 89% yield as a pale yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 7.44-7.36 (m, 5 H), 7.32 (d, $J = 8.5$ Hz, 2 H), 6.79 (d, $J = 8.0$ Hz, 2 H), 5.93-5.77 (m, 2 H), 5.93-5.77 (m, 2 H), 5.31 (brs, 1 H), 5.26-5.12 (m, 3 H), 5.10 (d, $J = 10.5$ Hz, 1 H), 4.08 (dd, $J = 16.5, 6.5$ Hz, 1 H), 3.90-3.80 (m, 2 H), 3.76 (dd, $J = 16.5, 5.5$ Hz, 1 H), 3.52 (m, 1 H), 3.37 (m, 1 H), 2.93 (m, 1 H), 2.87 (m, 1 H), 2.77-2.65 (m, 3 H), 2.52-2.42 (m, 2 H); HRMS (ESI) m/z 541.1815 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{27}\text{H}_{34}^{79}\text{BrN}_4\text{O}_3$ 541.1814.

Tosylate 21. By the same procedure for the synthesis of **18**, the tosylate **21** was synthesized from **20** in 85% yield as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.67 (d, $J = 8.1$ Hz, 2 H), 7.47-7.25 (m, 9 H), 6.90 (d, $J = 8.1$ Hz, 2 H), 6.03 (brs, 1 H), 5.75 (m, 1 H), 5.58 (m, 1 H), 5.18-5.02 (m, 4 H), 4.96 (d, $J = 9.9$ Hz, 1 H), 4.07 (dd, $J = 16.8, 7.2$ Hz, 1 H), 3.85-3.70 (m, 5 H), 3.59-3.44 (m, 1 H), 3.44-3.32 (m, 2 H), 3.23 (m, 1 H), 2.84-2.64 (m, 2 H), 2.62-2.46 (m, 2 H), 2.41 (s, 3 H); HRMS (ESI) m/z 695.1900 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{34}\text{H}_{40}^{79}\text{BrN}_4\text{O}_5\text{S}$ 695.1903.

15-Membered Macrocycle 22. By the same procedure for the synthesis of **14** (60→80 °C over 18 h), the 15-membered macrocycle **22** was synthesized from **21** in 89% yield as a colorless oil. ^1H NMR spectrum shows the double bond newly formed is *trans* ($J = 15.8$ Hz). Data for **22**: ^1H NMR (500 MHz, CDCl_3) δ 7.72 (d, $J = 8.0$ Hz, 2 H), 7.54 (brs, 1 H), 7.46-7.39 (m, 5 H), 7.35 (d, $J = 7.5$ Hz, 2 H), 7.31 (d, $J = 8.0$ Hz, 2 H), 6.89 (d, $J = 8.5$ Hz, 2 H), 6.00 (brs, 1 H), 5.58-5.44 (m, 2 H), 5.05 (s, 1 H), 4.06-3.91 (m, 2 H), 3.91-3.80 (m, 2 H), 3.67 (m, 1 H), 3.56-3.38 (m, 3 H), 3.28-3.14 (m, 2 H), 3.00-2.90 (m, 2 H), 2.88-2.73 (m, 2 H), 2.44 (s, 3 H); HRMS (ESI) m/z 667.1607 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{32}\text{H}_{36}^{79}\text{BrN}_4\text{O}_5\text{S}$ 667.1590.

N-Allyl Amide 23. By the same procedure for the synthesis of **11**, the *N*-allyl amide **23** was synthesized from **10** in 39% yield as a pale yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, J = 8.5 Hz, 2 H), 7.47 (brs, 2 H), 7.43-7.34 (m, 3 H), 7.28 (brs, 2 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.67 (d, J = 8.0 Hz, 2 H), 6.26 (s, 1 H), 5.75 (m, 1 H), 5.15 (d, J = 9.5 Hz, 1 H), 5.04 (d, J = 17.5 Hz, 1 H), 4.30-4.10 (m, 5 H), 3.81 (dd, J = 18.0, 4.5 Hz, 1 H), 3.74 (m, 1 H), 3.41 (m, 1 H), 2.80-2.64 (m, 2 H), 2.47 (m, 1 H), 2.33 (m, 1 H), 2.24 (m, 1 H), 1.98 (m, 1 H), 1.24 (t, J = 7.0 Hz, 3 H); HRMS (ESI) m/z 712.1015 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{33}\text{H}_{36}^{79}\text{Br}_2\text{N}_3\text{O}_5$ 712.1022.

Bis-N-allyl Amide 24. By the same procedure for the synthesis of **18**, the bis-*N*-allyl amide **24** was synthesized from **23** in 91% yield as a pale yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, J = 8.5 Hz, 2 H), 7.44-7.34 (m, 5 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.18-7.08 (m, 2 H), 7.04 (d, J = 8.5 Hz, 2 H), 6.74 (d, J = 8.0 Hz, 2 H), 5.90-5.66 (m, 2 H), 5.63 (s, 1 H), 5.15 (d, J = 16.5 Hz, 1 H), 5.12 (d, J = 10.0 Hz, 1 H), 5.05 (d, J = 10.0 Hz, 1 H), 5.03 (d, J = 17.5 Hz, 1 H), 4.21-4.17 (m, 2 H), 4.12 (dd, J = 16.5, 7.5 Hz, 1 H), 3.87 (m, 1 H), 3.82-3.68 (m, 3 H), 3.37 (m, 1 H), 2.71-2.55 (m, 3 H), 2.38 (m, 1 H), 2.30 (m, 1 H), 2.20 (m, 1 H); HRMS (ESI) m/z 723.1185 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{34}\text{H}_{37}^{79}\text{Br}_2\text{N}_4\text{O}_4$ 723.1182.

16-Membered Macrocycle 25. By the same procedure for the synthesis of **14** (60 °C over 18 h), the 16-membered macrocycle **25** was synthesized from **24** in 62% yield as a colorless oil. ^1H NMR spectrum shows the double bond newly formed is *cis* predominantly (5:1) (J = <10 Hz and 17.2 Hz for major and minor isomers, respectively). Data for **25**: ^1H NMR (500 MHz, CDCl_3) δ 7.60-7.26 (m, 11 H), 6.93 (brs, 1 H), 6.78-6.68 (m, 2 H), 6.00 (brs, 1 H), 5.90-5.66 (m, 2 H), 4.28-3.94 (m, 2 H), 3.86 (brs, 2 H), 3.57 (m, 1 H), 3.37 (m, 1 H), 2.99 (m, 1 H), 2.90-2.70 (m, 2 H), 2.70-2.40 (m, 3 H), 2.34 (m, 1 H), 2.17 (m, 1 H); HRMS (ESI) m/z 695.0873 ($[\text{M}+\text{H}]^+$), calcd for $\text{C}_{32}\text{H}_{33}^{79}\text{Br}_2\text{N}_4\text{O}_4$ 695.0869.

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16. In our preliminary publication on this work,⁷ the stereochemistry of the macrocycles **19**, **22**, and **25** was erroneously reported. By extensive NMR spectroscopic analyses (COSY and ¹H-¹H homonuclear decoupling NMR measurements), the correct stereochemistries have been determined to be *cis*, *trans*, and *cis* for **19**, **22**, and **25**, respectively. See the EXPERIMENTAL section for details.
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