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Simultaneous accumulation of both skeletal and appendage-based diversities on tandem Ugi/Diels–Alder products

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Abstract—Diversity-oriented organic synthesis (DOS) is a key concept for construction of skeletally diverse small molecule libraries to discover drug-like small molecules. Here, we describe a DOS class to transform a complex 7-oxanorbornene skeleton, which is readily accessible by a tandem Ugi/Diels–Alder reaction, into two heterotricycle skeletons selectively by using tandem ROM/CM/RCM reaction. In the present study, the mode of cyclization is pre-encoded by building blocks used in the complexity-generating tandem Ugi/Diels–Alder reaction. Since variable alkenes can be used in the CM reaction, our approach can be extended to construct both skeleton- and appendage-diverse small molecule libraries.

Recently, small molecules have been paid much attention in biological studies such as chemical biology and chemical genetics.[1,2] Such biologically important small molecules are usually supplied from natural resources or synthetic chemical libraries, which are composed of skeletally diverse small molecules. Diversity-oriented organic synthesis (DOS) is defined by Schreiber et al. as an efficient synthetic strategy toward such libraries by effective accumulation of appendage, stereochemical, and skeletal diversities.[2,3] Two approaches have been proposed for skeletal diversity: (1) reagent-based approach and (2) substrate-based approach. Though the latter approach is especially suitable for construction of a skeletally diverse small molecule libraries by a split-pool solid-phase organic synthesis, there had been no successful example for the simultaneous accumulation of both skeletal and appendage-based diversities. Here, we report a demonstration in this DOS class. We installed a 'σ-element',[3–5] different appendages that pre-encode skeletal information, into the 7-oxanorbornene skeleton for chemical control in the subsequent reaction, and successfully led the skeleton to two different heterotricycle skeletons by the tandem ring-opening metathesis/cross metathesis/ring-closing metathesis (ROM/CM/RCM) reactions, where the mode of cyclization is controlled by the σ-element. It is also found that various alkenes can be used for the CM reaction so that appendage-based diversity is installed simultaneously in the tandem reactions.[6,7]

The 7-oxanorbornenes **1** and **2** used in the present study were synthesized in solution phase by mixing furfural, benzylamine, fumaric acid monoamide and isocyanide in a ratio of 1:1:1:1 in MeOH at rt for 48 h (Scheme 1).[8,9] From fumaric acid mono-*p*-bromoanilide[7] and benzyl isocyanide (combination A), the 7-oxanorbornene **1** was obtained in 73% yield, whereas the combination of fumaric acid monobenzylamide and *p*-bromophenyl isocyanide[10] gave the 7-oxanorbornene **2** in 45% yield (combination B). The diastereoselectivity was >10:1 for both cases as judged from the ^{1}H NMR spectra, and the structures were determined by analogy with the products in the previous studies by us[7] or others.[8,9]

A selective allylation method of the *p*-bromoanilide functionality was next explored by using the 7-oxanorbornene **1** thus prepared, since no general method for this purpose was available (Table 1). At first, we treated LiOH (8 equiv) and allyl bromide (2 equiv) with **1** at 0 °C, but the allylated product was not obtained at all, only recovering **1** quantitatively after 3 days (run 1). The use of ether and water (1:2) as solvents at rt was found to be effective to give the desired monoallylated

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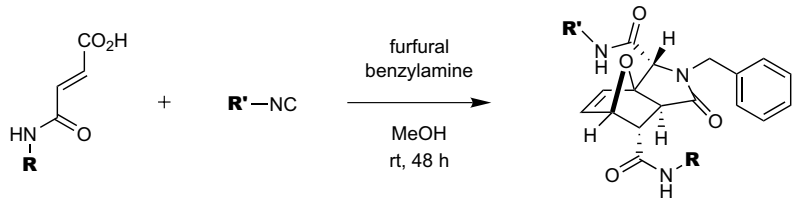
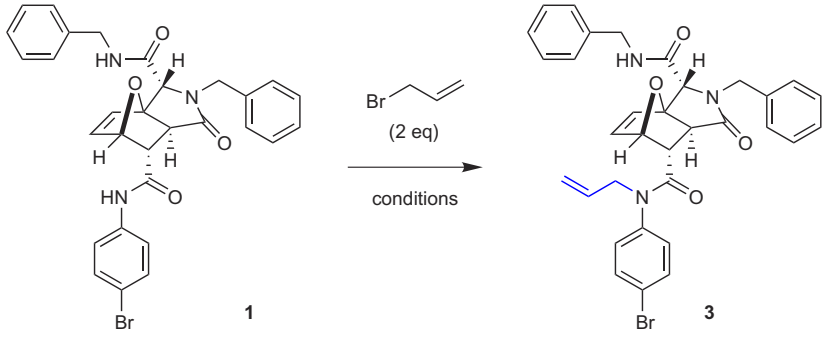


combination A: **R** = *p*-bromophenyl, **R'** = Bn
combination B: **R** = Bn, **R'** = *p*-bromophenyl

1 (**R** = *p*-bromophenyl, **R'** = Bn): 73%
2 (**R** = Bn, **R'** = *p*-bromophenyl): 45%

Scheme 1.

Table 1. Model study for selective allylation



Run	Base	Solvent	Temperature	Time (h)	Yield[a] (%)
1	$LiOH·H_2O$ (8 equiv)	THF	0 °C	72	0
2	$LiOH·H_2O$ (8 equiv)	Et_2O/H_2O (1:2)	rt	72	66
3	K_2CO_3 (8 equiv)	THF/CH_3CN (1:1)	rt	72	0
4	Cs_2CO_3 (8 equiv)	THF/CH_3CN (1:1)	rt	72	0
5	CsOH (8 equiv)	THF	0 °C	16	79
6	KHMDS (2 equiv)	THF	−10 °C → rt	16	0

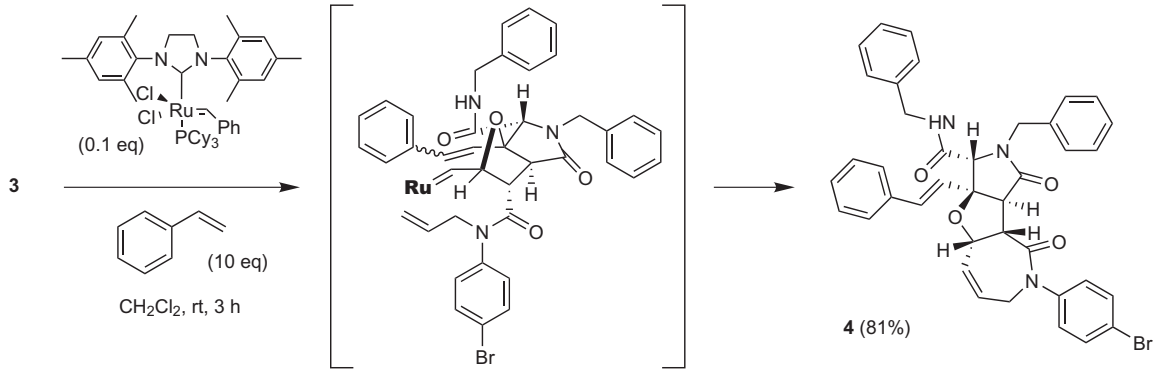
[a] Yields for chromatographically pure compound.

product **3** in 66% yield (run 2). Neither K_2CO_3 nor Cs_2CO_3 in THF/CH_3CN (1:1) induced the allylation (runs 3 and 4). The best result was attained by the use of CsOH in THF at 0 °C for 16 h (run 5).[4] Under these reaction conditions, the desired product **3** was produced in 79% yield, and only a trace amount of the diallylated product was detected. Interestingly, the effect of using anhydrous KHMDS (2 equiv)[9] was found to be too severe for **1** even at −10 °C, giving a complex, messy reaction mixture after 16 h (run 6). In all runs, the *N*-allyl anilide **3** produced was chemically pure (>98%) as judged from ^1H NMR spectrum to indicate the allylation proceeded not only regioselectively but also stereo- selectively. We suppose the geometry is *trans* as illustrated in Table 1 due to the conjugation with the *p*-bromophenyl group.

With the selective allylation method in hand, we next explored selective transformations of the 7-oxanorbornene skeletons into heterotricycles by olefin metathesis. After several preliminary experiments, we found that 0.1 equiv of the second-generation Grubbs catalyst[11] worked well at rt on **3** (2.6 mM in CH_2Cl_2) and styrene (10 equiv) to give the heterotricycle **4** in 81% yield after 3 h (Scheme 2 and Fig. 1). It should be noted that the reaction did not take place even by using 0.2 equiv of the Grubbs catalyst at higher temperature (35 °C) when the concentration for **3** was lower (0.3 mM). The structure of the heterotricycle **4** was determined by extensive NMR measurements and LC-MS.[12,13]

Under the optimized conditions, the metathesis reaction of **3** with allyl bromide and 3-butenyl bromide proceeded also quite smoothly to provide the heterotricycles **5** and **6** in comparable yields, respectively (Fig. 1).[13]

On the other hand, allylation of the *p*-bromoanilide moiety of the 7-oxanorbornene **2** was also realized by the same procedures shown in Table 1 (run 5) to give **7** regio- and stereoselectively in 77% yield. Under the optimized conditions using the second-generation Grubbs catalyst, the subsequent tandem metathesis reaction successfully transformed **7** into the heterotricycles **8**, **9**, and **10** of the expected skeleton different to that of **4**, **5**, or **7** in lower but acceptable yields (72% for **8**, 98% for **9**, and 93% for **10** after correction based on recovered **7**).[13,14] Those structures were also unambiguously clarified on the basis of NMR and mass spectroscopic analysis.[15] *The skeletal diversity has been thus generated by the same reaction sequences starting from the same 7-oxanorbornene skeleton.*



Scheme 2.

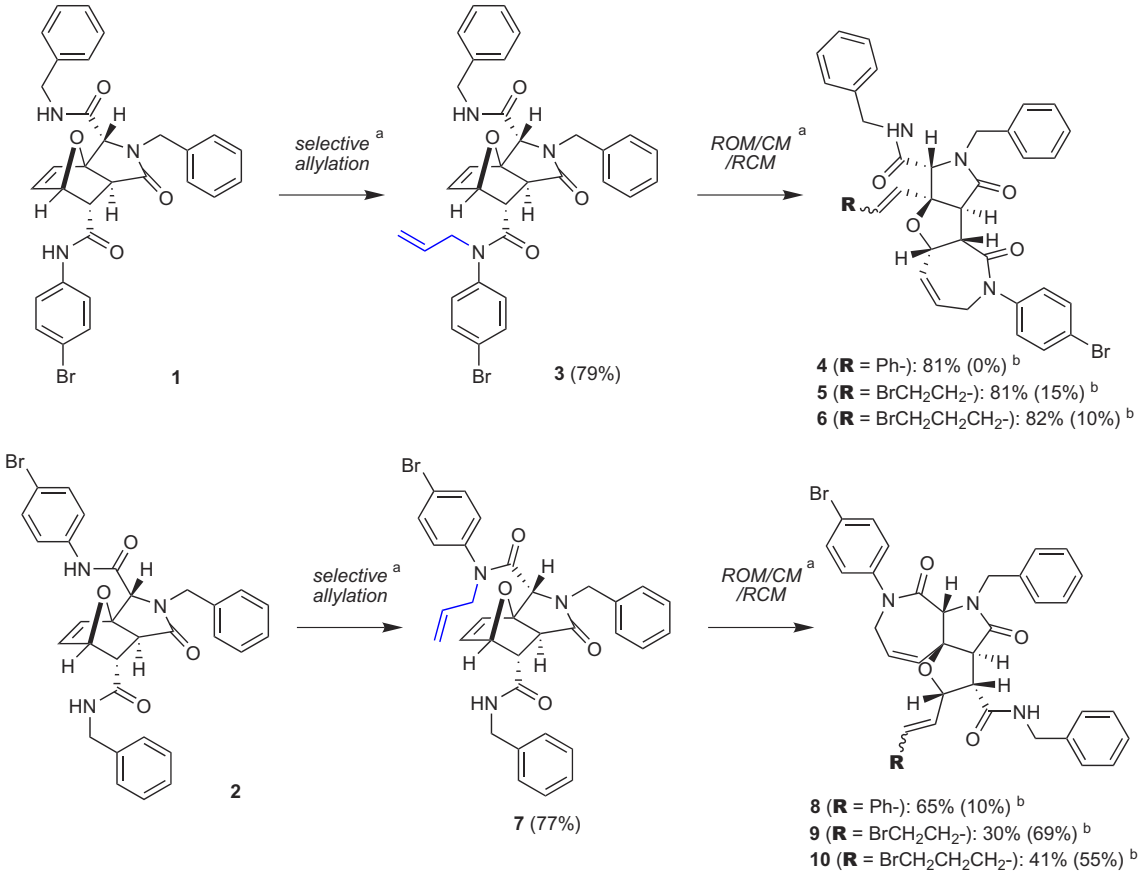
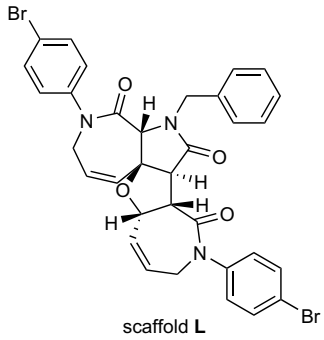
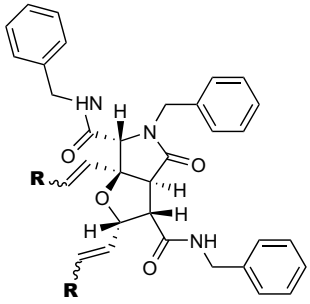


Figure 1. Allylation followed by ROM/CM/RCM to generate skeletal diversity starting from 7-oxanorbornenes **1** and **2**. [a]For reaction conditions, see Table 1 (run 5) and Scheme 2. [b]Yield for recovered 7-oxanorbornene **3** or **7**.

In summary, we have demonstrated the simultaneous generation of both skeletal and appendage-based diversities controlled by σ-elements starting from structurally complex tandem Ugi/Diels–Alder products. We have at first developed a selective allylation method of the anilide functionality in the presence of monoalkylamide of the tandem Ugi/Diels–Alder reaction products. The procedure for transforming the monoallylated products into two heterotricycle skeletons was established by ROM/CM/RCM reactions. The appendage-based accumulation of molecular diversity was simultaneously achieved by the addition of three alkenes to the reaction mixture. We are currently studying the syntheses of heterotetracycle **L**[9] and heterodicycle **M** (Fig. 2) by ROM/RCM and ROM/CM, respectively, starting from the tandem Ugi/Diels–Alder reaction products which carry various patterns of σ-elements. The strategy shown here is apparently effective for split-pool realization of skeletally diverse small molecule libraries for the discovery of biologically interesting drug-like small molecules.



scaffold **L**



scaffold **M**

Figure 2. Other skeletons potentially included in our DOS approach.

References and notes

1. Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127–1152; Crews, C. M.; Splittgerber, U. *Trends Biochem. Sci.* **1999**, *24*, 317–320; Stockwell, B. R. *Nat. Rev. Genet.* **2000**, *1*, 116–125; Mootz, H. D.; Muir, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 9044–9045; Chen, J. *Chem. Biol.* **2002**, *9*, 543–544; Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51–61.
2. Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
3. Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.
4. Sello, J. K.; Andreana, P. R.; Lee, D. S.; Schreiber, S. L. *Org. Lett.* **2003**, *5*, 4125–4127.
5. Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613–618; Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095–14104.
6. For our recent efforts in this field, see; Oikawa, M.; Tanaka, T.; Kusumoto, S.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 787–790; Oikawa, M.; Ikoma, M.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 2371–2375; Oikawa, M.; Takeda, Y.; Sasaki, M. *Tetrahedron Lett.* **2005**, *46*, 4667–4670.
7. Oikawa, M.; Ikoma, M.; Sasaki, M. *Tetrahedron Lett.* **2005**, *46*, 415–418.
8. Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851–1854; Paulvannan, K. *J. Org. Chem.* **2004**, *69*, 1207–1214.
9. Lee, D. S.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709–712.
10. Prepared from *p*-bromoaniline by two-step reactions including formylation (HCOOH, Ac_2O, pyridine, THF, 0 °C→rt) and dehydration ($POCl_3$, Et_3N, CH_2Cl_2, 0 °C) in 81% yield; Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400–402.
11. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
12. Selected spectroscopic data for (*E*)-isomer of **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–6.97 (m, 12H), 6.91 (d, 2H, $J = 6.9$ Hz), 6.60 (d, 1H, $J = 15.6$ Hz), 6.22 (d, 1H, $J = 15.6$ Hz), 6.18 (m, 1H), 6.08 (d, 1H, $J = 11.1$ Hz), 5.67 (br t, 1H, $J = 5.4$ Hz), 5.25 (d, 1H, $J = 15.0$ Hz), 4.76 (dd, 1H, $J = 2.4$, 4.5 Hz), 4.46 (dd, 1H, $J = 5.4$, 10.5 Hz), 4.36 (dd, 1H, $J = 6.0$, 8.4 Hz), 4.26 (dd, 1H, $J = 6.0$, 8.4 Hz), 4.02 (d, 1H, $J = 6.6$ Hz), 3.75 (s, 1H), 3.63 (q, 1H, $J = 8.4$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 167.6, 167.3, 142.1, 136.8, 136.4, 135.3, 132.3, 132.0, 130.8, 128.9, 128.7, 128.5, 128.4, 128.0, 127.9, 127.7, 127.7, 127.6, 127.4, 127.4, 126.8, 119.9, 85.1, 77.1, 71.8, 54.9, 50.5, 46.4, 45.8, 44.0; FAB-HR-MS calcd for $C_{39}H_{35}O_4N_3Br$ ($M+H^+$) *m*/*z* 688.1733, found 688.1818.
13. The *E*/*Z* selectivity at the newly formed double bond of the acyclic moiety was determined from ^{1}H NMR spectra; **4** (>10:1), **5** (6:4), **6** (6:4), **8** (>10:1), **9** (7:3), and **10** (6:4). We have found that the double bond can be selectively hydrogenated quantitatively (H_2, Pd/C, MeOH, rt).
14. The low isolated yields in these reactions are supposed to be due to the crowdness of the skeleton. Though nearly quantitative amount of the unreacted **7** can be recovered intact, we are currently studying the reaction conditions to improve the yields.
15. Selected spectroscopic data for (*E*)-isomer of **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–6.98 (m, 19H), 6.11 (m, 1H), 5.82 (br t, 1H, $J = 5.8$ Hz), 5.79 (m, 1H), 5.46 (d, 1H, $J = 15.0$ Hz), 5.27 (d, 1H, $J = 14.1$ Hz), 5.17 (d, 2H, $J = 10.5$ Hz), 4.47 (t, 1H, $J = 7.5$ Hz), 4.34 (d, 2H, $J = 5.1$ Hz), 4.10 (s, 1H), 3.89 (d, 1H, $J = 14.1$ Hz), 3.60 (s, 1H), 3.32 (d, 1H, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 171.1, 167.0, 139.8, 137.7, 136.8, 135.3, 134.2, 132.9, 132.4, 131.7, 128.9, 128.7, 128.6, 128.5, 128.0, 127.8, 127.6, 127.5, 126.8, 122.2, 119.2, 119.0, 87.8, 83.3, 66.9, 55.9, 53.6, 52.9, 45.6, 43.7; ESI-MS calcd for $C_{39}H_{35}O_4N_3Br$ ($M+H^+$) *m*/*z* 688.1733, found 688.1805.