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.

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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-bromoanilide7 and benzyl isocyanide (combination A), the 7-oxanorbornene 1 was obtained in 73% yield, whereas the combination of fumaric acid monobenzylamide and p-bromo-phenyl isocyanide10 gave the 7-oxanorbornene 2 in 45% yield (combination B). The diastereoselectivity was >10:1 for both cases as judged from the 1H NMR spectra, and the structures were determined by analogy with the products in the previous studies by us8 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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product 3 in 66% yield (run 2). Neither K$_2$CO$_3$ nor Cs$_2$CO$_3$ in THF/CH$_3$CN (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). 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) 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 produced was chemically pure (>98%) as judged from 1H NMR spectrum to indicate the allylation proceeded not only regioselectively but also stereoselectively. 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 worked well at rt on 3 (2.6 mM in CH$_2$Cl$_2$) 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.

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).

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). Those structures were also unambiguously clarified on the basis of NMR and mass spectroscopic analysis. The skeletal diversity has been thus generated by the same reaction sequences starting from the same 7-oxanorbornene skeleton.
In summary, we have demonstrated the simultaneous generation of both skeletal and appendage-based diversities controlled by \( \sigma \)-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 hetertetracycle \( L \) 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 \( \sigma \)-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.

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

References and notes


10. Prepared from p-bromoaniline by two-step reactions including formylation (HCOOH, Ac2O, pyridine, THF, 0 °C→rt) and dehydration (POCl3, Et3N, CH2Cl2, 0 °C in 81% yield; Obrecht, R.; Herrmann, R.; Ugi, I. Synthesis 1985, 400–402.


12. Selected spectroscopic data for (E)-isomer of 4: 1H NMR (300 MHz, CDCl3) 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); 13C NMR (150 MHz, CDCl3) 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, 127.6, 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 C39H35O4N3Br (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 1H NMR spectra: 4 (10:1), 5 (6:4), 6 (6:4), 8 (9:7), and 10 (6:4).

14. We have found that the double bond can be selectively hydrogenated quantitatively (H2, Pd/C, MeOH, rt).

15. The isolated yields in these reactions are supposed to be due to the crowding 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.

16. Selected spectroscopic data for (E)-isomer of 8: 1H NMR (300 MHz, CDCl3) 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), 3.52 (d, 1H, J = 6.9 Hz); 13C NMR (125 MHz, CDCl3) 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, 122.9, 119.0, 87.8, 83.3, 66.9, 55.9, 53.6, 52.9, 45.6, 43.7; ESI-MS calcd for C39H35O4N3Br (M+H+) m/z 688.1733, found 688.1805.