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Divergent and Expeditious Access to Fused Skeletons Inspired by Indole Alkaloids and Transtaganolides

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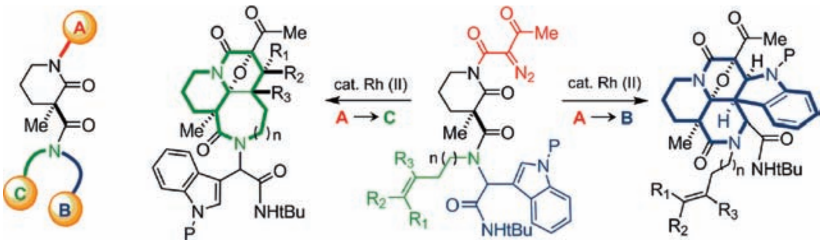
ABSTRACT



We report the development of a divergent synthetic process entailing four-step access to the elaborate fused skeletons reminiscent of aspidophytines and transtaganolides. A variety of branched precursors were synthesized on the basis of Ugi condensations and installation of diazoimide and subjected to rhodium-catalyzed tandem reactions. Switching of cyclization modes was demonstrated by the choice of the amine building blocks installed at site C.

A family of indole alkaloids is one of the most valuable resources for discovering biologically intriguing natural products.[1] In addition to the densely functionalized multicyclic molecular architectures, we took notice of the characteristic structural features of these alkaloids: *the fused skeleton composed of indole and piperidine as the common substructures* as shown in Figure 1a. Inspired by the structural features, we began to develop an expeditious synthetic process that allows coupling of the substructures followed by pairing of the functional groups to construct fused skeletons reminiscent of the indole alkaloids. Previously, we developed a synthetic process to access indole alkaloid-like fused skeletons utilizing a piperidine-based scaffold.[2] Although this approach is capable of generating skeletal diversity based on variations of the cyclization modes, laborious manipulations required preparation of a series of cyclization precursors, a major drawback in the development of pilot libraries.

In this work, we devised a second-generation strategy based on a unified four-step synthetic process that provides access to natural product analogues.[3−5] As shown in Scheme 1a, Ugi four-component condensation[6] of the piperidine scaffold **1**

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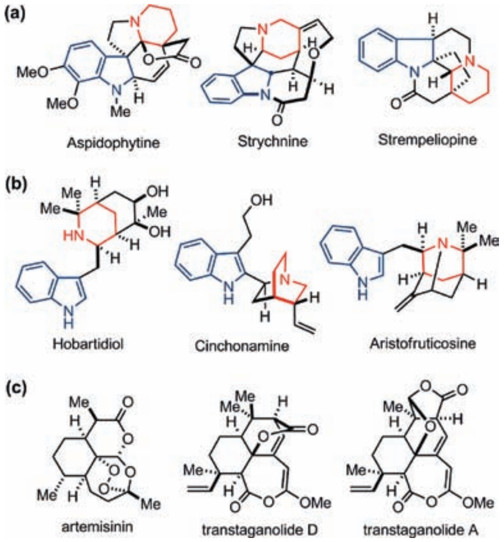
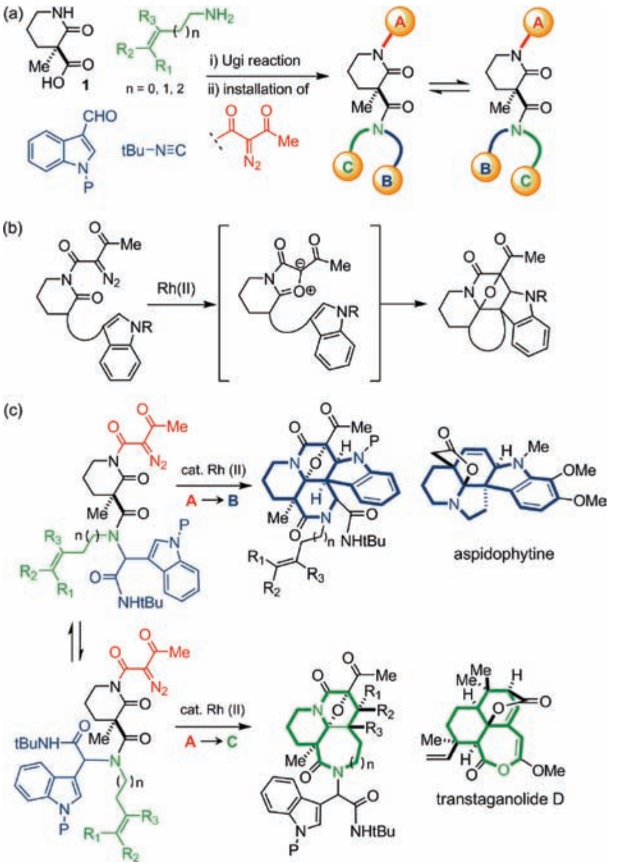


Figure 1. Structures of natural products: (a) fused alkaloids composed of indole (blue) and piperidine (red) groups; (b) alkaloids with a piperidine-based core linked with an indole; (c) Ca^{2+}-ATPase inhibitors, artemisinin, and transtaganolides (basiliolides).

Scheme 1. (a) Synthesis of Branched Precursors with Three Sites A−C for the Pairing of Functional Groups; (b) Rh(II)-Catalyzed Tandem Cyclization−Cycloadditions; (c) Divergent Synthesis of Fused Skeletons Reminiscent of Naturally Occurring Aspidophytines and Transtaganolides



followed by stepwise installation of α-diazocarbonyl group[7] affords cyclization precursors in three steps. To perform annulations between piperidine and indole substructures, we adopted Padwa's protocol, a rhodium-catalyzed tandem cyclization−cycloaddition (Scheme 1b).[8,9] As shown in Scheme 1c, the cycloaddition between the ylide generated at site A with the indole group at site B would construct a hexacyclic skeleton analogous to the framework of the indole alkaloid, aspidophytine.[10] Conversely, given the dynamic conformational equilibrium of the tertiary amide bond, the cycloaddition exploiting the olefin group at site C is also capable of yielding a distinct tetracyclic product. The cycloadduct with an intact indole moiety also has a certain degree of structural resemblance to a series of naturally occurring alkaloids as shown in Figure 1b. Meanwhile, an alternative synthetic strategy was pursued for the cyclic frameworks of the Ca^{2+}-ATPase inhibitors, artemisinins, and transtaganolides (Figure 1c).[11] It was envisaged that the tetracyclic core formed by the A → C mode cycloaddition would imitate the fused skeleton of transtaganolides[12,13] as shown in Scheme 1c.

In an effort to access a large group of natural product analogues, we first synthesized a precursor **6** with an indole ring and a *p*-methoxybenzyl group installed at sites B and C, respectively (Scheme 2). Ugi condensation of racemic scaffold **1**, indole-3-carboxaldehyde derivative **2**, *tert*-butylisonitrile **3**,

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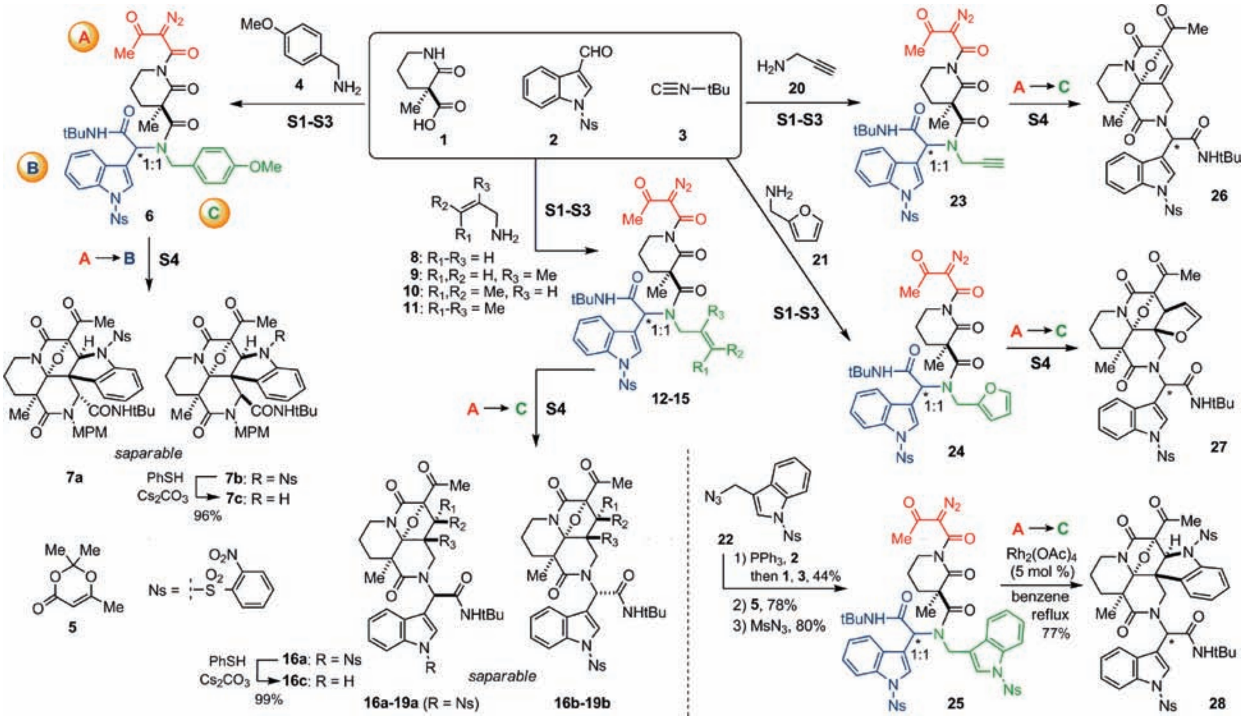
Scheme 2. Four-Step Synthesis of Hexacyclic **7** and Tetracyclic (**16**−**19** and **26**−**28**) Based on Ugi Reaction and Rhodium-Catalyzed Divergent Cyclizations of Branched Precursors **6**, **12**−**15**, and **23**−**25**[a]



[a] Reagents and conditions: **S1**: amine (**4**, **8**−**11**, **20**−**21**), MeOH, reflux; **S2**: **5**, toluene, reflux; **S3**: MsN_3, Et_3N, CH_3CN; **S4**: $Rh_2(OAc)_4$ (5 mol %); benzene, reflux. Yields for each step are shown in Table 1.

and *p*-methoxybenzylamine **4** afforded a dipeptidyl product as a 1:1 diastereomeric mixture in 78% yield (Table 1, entry 1). This intermediate was subsequently converted into cyclization precursor **6** with a diazoimide group in two steps: *N*-acetoacetylation upon heating with **5** and subsequent diazo transfer.[2] By performing three-step manipulations with allyl amine **8** in place of **4**, we then synthesized a branched precursor **12** with an indole group and a terminal olefin at sites B and C, respectively (entry 2). Upon treatment of **6** with 5 mol % of $Rh_2(OAc)_4$ catalyst in refluxing benzene, the tandem reaction proceeded via a cyclization mode A → B to yield cycloadduct **7** with a hexacyclic skeleton in 78% yield. The 1:1 diastereomeric mixture of indole alkaloid analogues **7a** and **7b** was easily separated by conventional silica gel chromatography. Rhodium-catalyzed reaction of **12** effected an 1,3-dipolar cycloaddition of the ylide intermediate with the terminal olefin at site C to form **16** as a separable 1:1 diastereomeric mixture in 94% yield. The nosyl groups in **7b** and **16a** were efficiently removed with PhSH and Cs_2CO_3 to liberate aniline and indole groups, respectively.[14] X-ray analyses of the crystalline **7b** and **16b** clearly showed the multicyclic core structures with consecutive quaternary centers.[15] The stereochemistry of each diastereomer is also determined as depicted in Scheme 2. X-ray analysis also showed that both cycloadditions via distinct cyclization modes exhibit identical and exquisite stereoselectivities. By this means, complete switching of the cyclization modes was accomplished by installation of a dipolarophile at site C. The divergence of the synthetic process with high levels of stereoselectivity is promising for the development of small molecule libraries with structural diversity.

Table 1. Attempts toward the Four-Step Synthesis Employing a Variety of Amine Building Blocks As Shown in Scheme 2

entry	amine	S1[a] (%)	S2[a] (%)	S3[a] (%)	S4[a] (%)	overall yield[b] (%)
1	**4**	78	80	**6**, 91	**7**, 78	44
2	**8**	76	72	**12**, 96	**16**, 94	49
3	**9**	59	69	**13**, 88	**17**, 83	30
4	**10**	59	87	**14**, 84	**18**, 93	40
5	**11**	56	93	**15**, 94	**19**, 80	39
6	**20**	62	85	**23**, 84	**26**, 83	37
7	**21**	64	74	**24**, 93	**27**, 87	38

[a] Yields for each step were reported for the 1:1 mixtures of diastereomers. [b] Overall yields for the four-step manipulations.

To explore the scope of the divergent reactions, we attempted to control the cyclization modes by altering the

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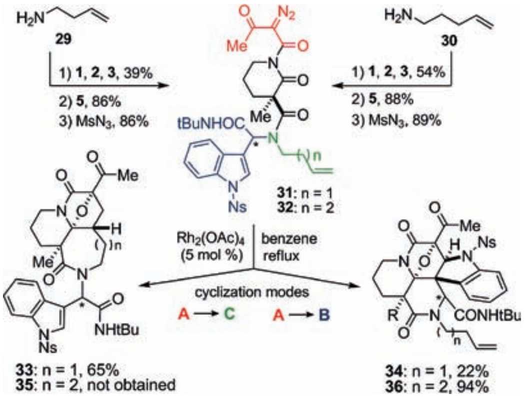
group installed at site C. Initially, we intended to shift cyclization modes from A → C into A → B by increasing the steric hindrance of the dipolarophiles at site C and designed a series of cyclization precursors **13**−**15** bearing di-, tri-, and tetrasubstituted olefinic groups (Table 1, entries 3−5). Precursors **13**−**15** were systematically synthesized in good yields by adapting the three-step transformation with amine building blocks **9**−**11**. In spite of our intention to shift cyclization modes, all of the branched precursors **13**−**15** were uniformly converted by cyclization mode A → C to afford cyclized products **17**−**19** in good to excellent yields. The indole groups at site B remained intact for all of these reactions. Notably, the sterically demanding tri- and tetra-substituted olefins at site C efficiently act as dipolarophiles to furnish **18** and **19** with multiple (up to five) quaternary centers on the cyclic core (entries 4 and 5). Similarly, precursors **23** and **24**, bearing acetylene and furan groups at site C, were then synthesized as above employing **20** and **21** (entries 6 and 7). Both cycloadditions occurred exclusively at site C to produce cycloadducts **26** and **27** in good to excellent yields as a 1:1 mixture of separable diastereomers. In all attempts, both of the diastereomers generated by the Ugi condensations were equally converted. Thus, this synthetic process allows simultaneous access to a diastereomeric pair of separable cycloadducts and thereby provokes stereochemical variations in the collections.

With an aim to identify a crucial element for the site selectivities, we next designed branched precursor **25** and installed a pair of identically functionalized indole rings in a branched fashion (Scheme 2). In this attempt, we employed azide **22** as a precursor to the corresponding amine building block due to its instability. This azide was then utilized to conduct a tandem Staudinger/aza-Wittig/Ugi condensation[16] to form the tetrapeptidyl product. The rhodium-catalyzed reaction of **25** again proceeded via the A → C mode to form **28** in 77% yield. Estimating the equivalent reactivities of each of the indole rings as dipolarophiles, it is likely that the peptidyl substituent at site B plays a pivotal role in the control of the cyclization modes.

The reactions described above demonstrate the preference of the cycloadditions via the A → C mode; however, switching the cyclization modes was attempted by increasing the ring sizes formed via the cycloadditions exploiting an olefin group at site C (Scheme 3). To this end, precursors **31** and **32** were synthesized in the three steps using amines **29** and **30**, respectively. The rhodium-catalyzed cyclization of **31** afforded a seven-membered ring as a major product, which resulted in the formation of tetracyclic **33** in 65% yield and along with hexacyclic **34** in 22% yield via the A → B mode. In contrast, cycloaddition of **32** proceeded with the indole group at site B to produce **36**[15] in 94% yield without formation of the eight-membered ring to give **35**. The cycloaddition via the A → C mode leading to **35** was impeded by the entropic barrier for medium-sized ring formation, and eventually, complete switching of the cyclization mode was achieved. Thus, the synthetic process allows divergent access to hexacyclic and tetracyclic skeletons that are analogous to the frameworks of aspidophytines and transtaganolides, respectively.

Scheme 3. Synthesis of Branched Precursors **31** and **32** Using Amines **29** and **30** with Different Methylene Lengths and Attempts To Switch the Cyclization Modes



In conclusion, a variety of branched precursors were synthesized in three steps employing the Ugi condensation and a stepwise installation of a diazoimide group. Making use of the dynamic conformational equibria of the tertiary amides, we developed an expeditious and flexible synthetic process featuring divergent cyclizations leading to fused skeletons reminiscent of indole alkaloids or oxygenated terpenes. Furthermore, site-controlled cyclizations have been achieved using an appropriate choice for the amine building block. This four-step procedure not only generates stereochemical variation in the libraries but also enables practical access to a collection of highly elaborate cyclic molecules with sufficient quantities (>100 mg) in excellent yields (>30% overall yields). Various sorts of the functional groups incorporated into the core skeletons involving amino acetal, β-ketoimide, and indole/olefin groups could be readily utilized for further manipulations in the development of small molecule libraries. Further synthetic investigations and preliminary screenings of biological activities are currently underway.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds **7**, **16**−**19**, **26**−**28**, **33**, **34**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) CIF files were deposited with the Cambridge Crystallographic Data Centre (CCDC): CCDC-247775 (**7b**), CCDC-727471 (**16b**), and CCDC-727472 (**36b**).

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