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Skeletal Diversity via a Folding Pathway: Synthesis of Indole Alkaloid-Like Skeletons

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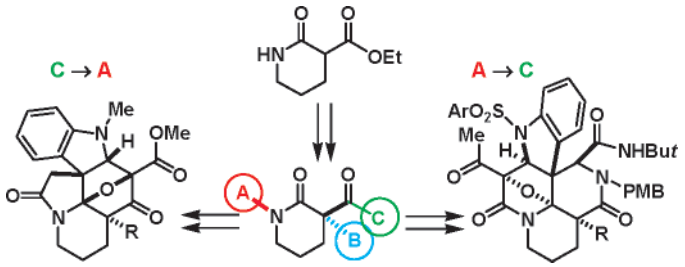
ABSTRACT



Inspired by the skeletal diversity of naturally occurring indole alkaloids and the rich potential of chemistry developed by Padwa and co-workers, we conceived a pathway entailing six modes of intramolecular reactions leading to indole alkaloid-like skeletons. In this context, an efficient folding pathway via a rhodium-catalyzed tandem cyclization–cycloaddition involving three of the modes has been developed (two of which are shown above) that affords densely functionalized compounds with three distinct skeletons in a stereocontrolled manner.

Diversity-oriented synthesis (DOS), which aims to yield skeletally and stereochemically diverse products having high appending potential, may prove to be an effective means of exploring biology and medicine with chemistry.[1−3] Two approaches have been used to generate skeletal diversity in a small number of steps: reagent-based differentiation and substrate-based folding.[4] The folding strategy involves the conversion of a collection of substrates with pre-encoded skeletal information into products having distinct skeletons using a common set of reaction conditions. This report presents new illustrations of the folding strategy in DOS.

To achieve the synthesis of skeletally diverse compounds inspired by naturally occurring and biologically active indole alkaloids (Figure 1a), we considered the rhodium(II)-catalyzed consecutive cyclization−cycloaddition reactions shown in Figure 1b developed by Padwa and co-workers.[5,6] Upon treatment of a Rh(II) catalyst with an α-diazo ketocarbonyl such as **1**, cyclization of the resulting rhodium carbenoid and neighboring carbonyl oxygen produces a carbonyl ylide, which can be a participant in a 1,3-dipolar cycloaddition with an indole 2,3-double bond leading to fused skeletons **2** in a single step.[7] This powerful bond-forming reaction could lead to multicyclic skeletons with both differing topologies and the ability to display dense functionality.

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(6) For reviews, see: (a) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123−140. (b) Padwa, A.; Weingarten, D. M. *Chem. Rev.* **1996**, *96*, 223−269. (c) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477−9504.
(7) Regio- and stereoselectivities of the cycloaddition may be governed by a complex interplay of factors such as the nature of the 2,3-dipole, alkene polarity, ring strain, and nonbonded interactions in the transition state: See refs 5, 6, and 9.

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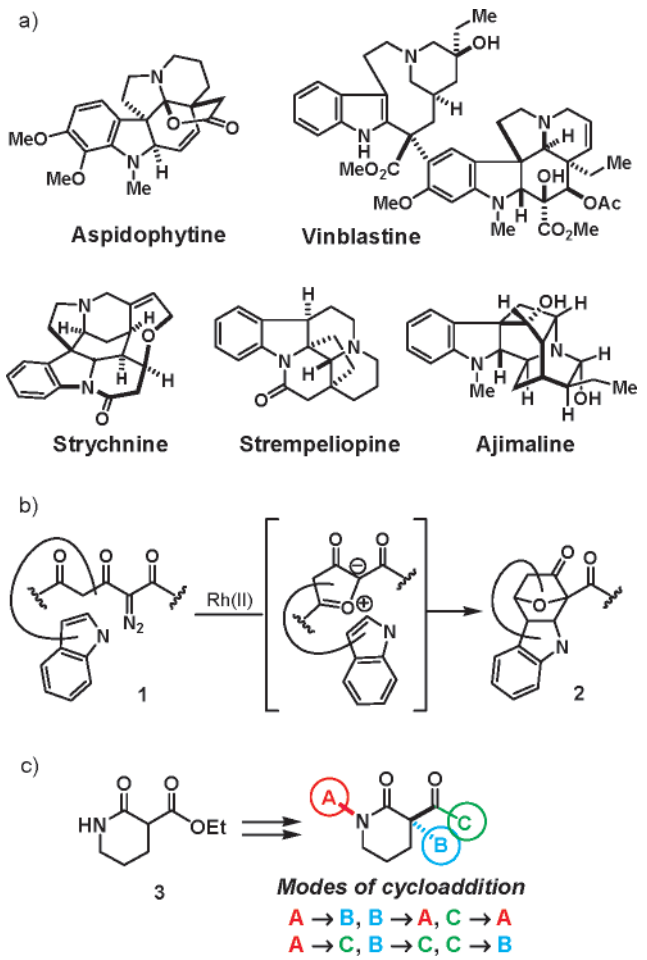
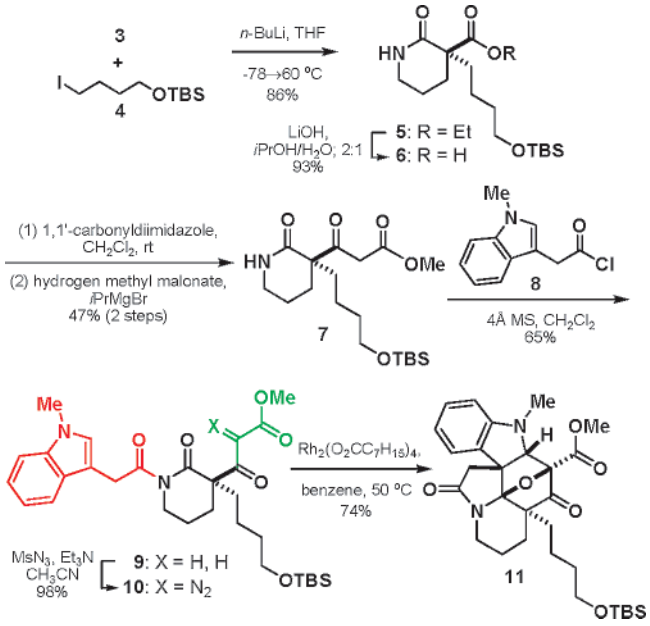


Figure 1. (a) Naturally occurring indole alkaloids; (b) Rh(II)-catalyzed consecutive cyclization-cycloaddition reactions to produce fused skeletons; (c) Multiple modes of cycloaddition using versatile scaffold **3**. (Notation, e.g. A → B, is short for: carbonyl ylide on site A reacts with dipolarophile on site B.)

Different combinations of α-diazo ketocarbonyls and indole groups on different sites of a common scaffold **3** enable various modes of intramolecular reactions under the same conditions (Figure 1c). We therefore envisioned scaffold **3** having three sites (**A**−**C**), each site being capable of installing either α-diazo ketocarbonyl or indole groups through the use of lactam, ester, or *β*-ketocarbonyl functionality. For example, α-diazo ketocarbonyl and indole groups could be installed at sites A and B, respectively (a mode of cyclization designated as A → B, where the carbonyl ylide on site A reacts with dipolarophile on site B). In addition, an alkyl linker with a terminal silyl ether group, selected to allow primary protein-binding assays using small molecule microarray technology, can be installed at site C.[8] Overall, by applying a similar logic to each of the reactive combinations indicated in Figure 1c, six

Scheme 1. Execution of the C → A Folding Pathway



distinct modes of rhodium-catalyzed intramolecular cycloadditions can in principle be realized. Here we describe our progress toward diversity-oriented syntheses that exploit this strategy.

We first developed a mode C → A reaction sequence using Padwa's general protocol (Scheme 1).[5b,9] Synthesis of **10** possessing α-diazoketocarbonyl and indole groups at sites C and A, respectively, commenced with the installation of the alkyl linker **4** on site B of **3** via *C*-alkylation producing **5**. After conversion of **5** into an activated ester, the *β*-ketoester was installed on site C by a coupling reaction with a magnesium enolate.[10]

The indole functionality was attached to site A by *N*-acylation of **7** with **8** using 4 Å molecular sieves as a neutral acid scavenger. The resulting compound **9** was then converted to the α-diazo ketoester **10** in 98% yield. Treatment of **10** with a catalytic amount of rhodium(II) octanoate dimer in benzene at 80 °C resulted in the formation of a presumed carbonyl ylide intermediate that underwent cycloaddition to produce hexacyclic **11** in 74% yield as a single isomer.[9]

Next, we investigated a pathway for the mode A → B (Scheme 2). *C*-Alkylation of **3** with **12**[11] produced **13** having an indole group at site B. Site C was manipulated to afford **14** by installing a linker having a terminal silyl ether. The lactam **14** was exposed to **15** in toluene at 120 °C to yield the *N*-acetoacetylated product **16**, which was converted to the α-diazoimide **17**. Treatment of **17** with rhodium(II) catalyst in benzene at 50 °C gave hexacyclic **18** in good

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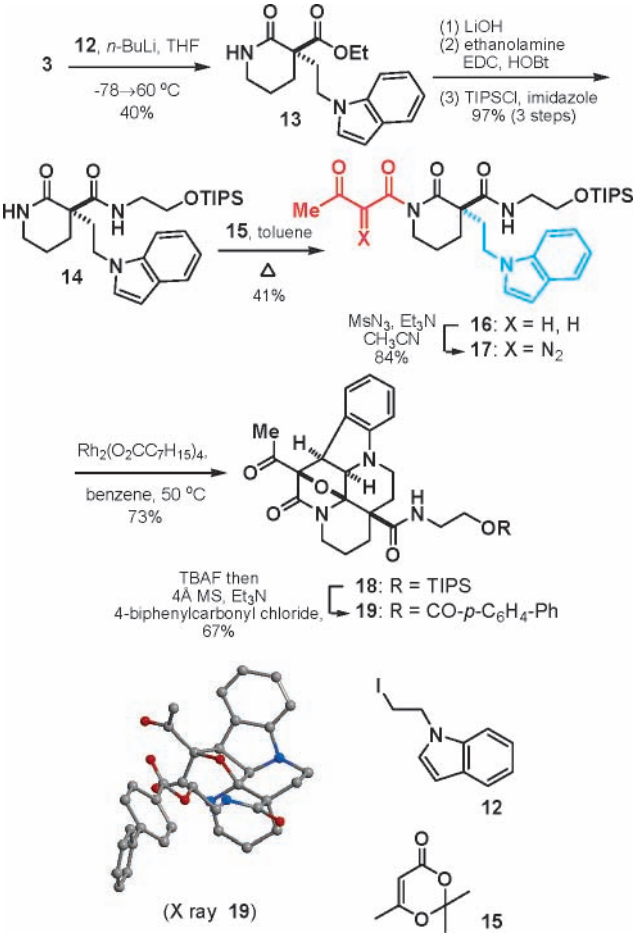
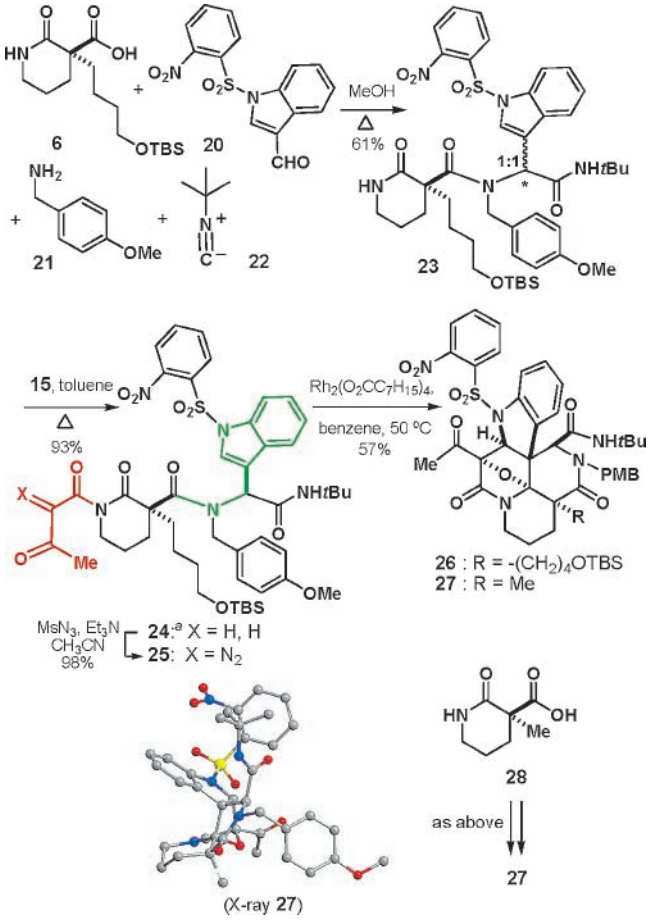
Scheme 2. Execution of the A → B Folding Pathway



Scheme 3. Execution of the A → C Folding Pathway



[a] Separable 1:1 diastereomeric mixture of **24** and *epi*-**24**.

yield (74%) with complete diastereoselectivity.[5a] The stereochemistry was unambiguously determined by X-ray crystallographic analysis of crystalline *p*-phenylbenzoate ester **19**.[12,13]

To synthesize a substrate for the mode A → C reaction, we used the Ugi four-component condensation reaction (Ugi 4CC)[14] as shown in Scheme 3. Carboxylic acid **6**, indole-3-carboxaldehyde **20**,[15] *p*-methoxy benzylamine **21**, and *tert*-butyl isocyanide **22** were joined in a single step to afford **23** in 67% yield as a 1:1 diastereomeric mixture. After conversion into the β-ketoimide, the diastereomers **24** and ***epi*-24** were separated and transformed into their diazoimides. The Rh(II)-catalyzed consecutive reaction of the densely functionalized **25** proceeded smoothly to produce hexacyclic **26** in 57% yield (two steps) in a highly stereocontrolled manner. X-ray analysis of crystalline **27**[13,16] revealed the structure and stereochemistry of the product **26** with its vicinal quaternary carbon centers.

In conclusion, we have developed a folding pathway for the synthesis of indole alkaloid-like skeletons using (1) a stereocontrolled tandem reaction that can be used with elaborate substrates and (2) a versatile scaffold that allows for multiple modes of intramolecular reactions in a systematic fashion (Scheme 4). The pathway A → C is expected to provide an approach to diverse indole alkaloid-like compounds in only four steps, involving a pair of complexity-generating processes,[17] a Ugi 4CC and a Rh-catalyzed tandem reaction. A goal for the future is to achieve stereochemical diversification in the overall pathway. It is hoped that the pathways shown here will provide effective probes for chemical genetic studies aimed at dissecting biology.[1,18]

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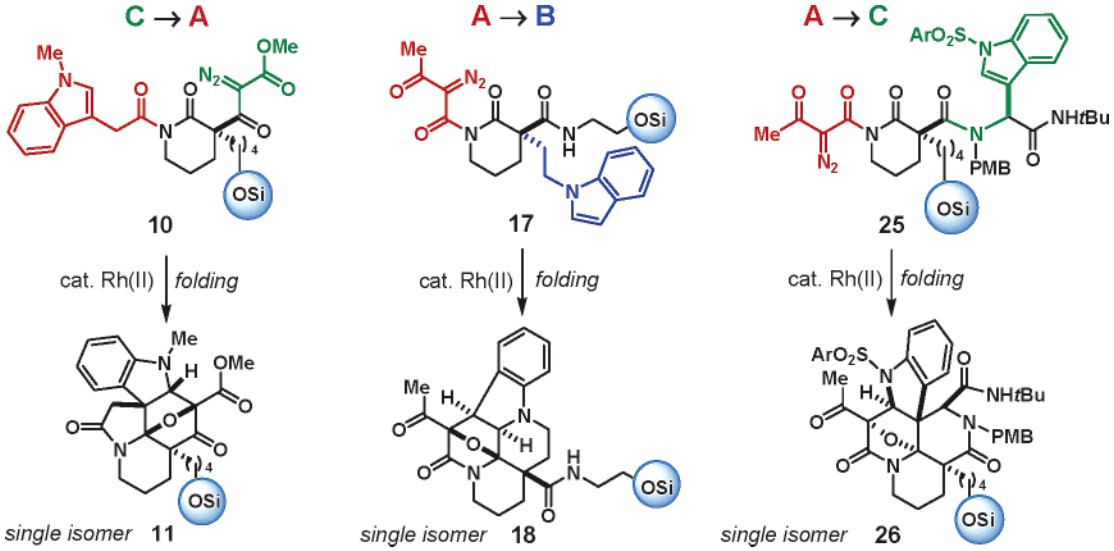
Scheme 4. Folding Strategy Yielding a Collection of Products Having Diverse Indole Alkaloid-Like Skeletons



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Supporting Information Available: Characterization data for **9**, **11**, **16**, **18**, **24**, ***epi*-24**, and **26** and X-ray crystallographic files (CIF) for **19** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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