Synthetic Methods

DOI: 10.1002/anie.201300571

Intramolecular Larock Indole Synthesis: Preparation of 3,4-Fused Tricyclic Indoles and Total Synthesis of Fargesine**

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The indole nucleus is arguably one of the most significant heterocycles since they are found in numerous natural products and bioactive molecules.[1] Among the naturally occurring indole alkaloids, 3,4-fused indoles (those in which the 3-position of the indole is bridged to the 4-position) have been considered attractive synthetic targets because of their biological activities and synthetic challenges. Examples include the well-known dehydrobufotenine,[2] lysergic acid,[3] welwistatin,[4] communesin F,[5] dragmacidin E,[6] decursivine,[7] penitrem D,[8] indolactam V,[9] and diazonamide A,[10] where the indole is bridged with different ring sizes (6-, 7-, 8-, 9-, and 12-membered rings) and various tethers linked by carbon, nitrogen, and oxygen atoms at different positions (Figure 1).

Accordingly, various strategies have been developed for the construction of 3,4-fused tricyclic indoles,[2–10] including Witkop photocyclizations,[11] 6π-electrocyclizations,[12] intramolecular Fischer indole syntheses,[13] transition metal catalyzed reactions,[14] Diels–Alder reactions,[15] Friedel–Crafts reactions,[16] and Pictet–Spengler reactions.[17] However, most of these methods are based on the introduction of functional groups to the 3- or 4-positions of existing indoles with subsequent cyclization. As a further complication, the direct functionalization of the indole 4-position is extremely difficult since most electrophiles prefer reaction at either the 5- or 7-position. The preparation of 4-substituted indole derivatives, the precursor of 3,4-fused tricyclic indoles, normally requires multistep synthesis.[9c,10c,14f,15b] The development of general synthetic methods for the rapid synthesis of these skeletons in a single operation remains an important challenge facing organic chemists.

In connection with some of our work on the total synthesis of indole alkaloids,[3a,7b,c,9a,18] we have endeavored to identify a general approach for the rapid access to 3,4-fused tricyclic indoles. It was envisaged that this approach would not only expedite the total synthesis of 3,4-fused indole alkaloids but also enable the modular construction of a library of their analogues for additional medicinal chemistry studies. Palladium-catalyzed transformations generally require only a catalytic amount of a metal complex and tolerate a large number of functional groups, and have thus made a major impact on the synthesis of indoles. We were curious whether a palladium-catalyzed intramolecular Larock indolization process (Scheme 1a) could be applied for the preparation of such polycyclic indoles.[19] To the best of our knowledge, although

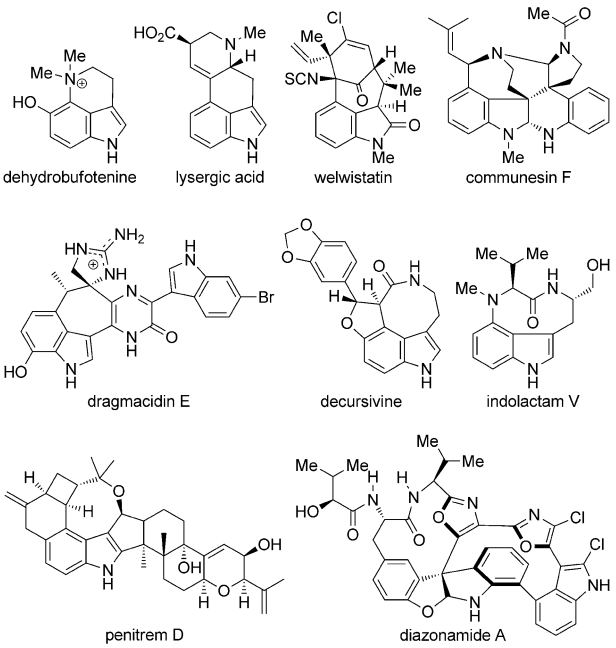
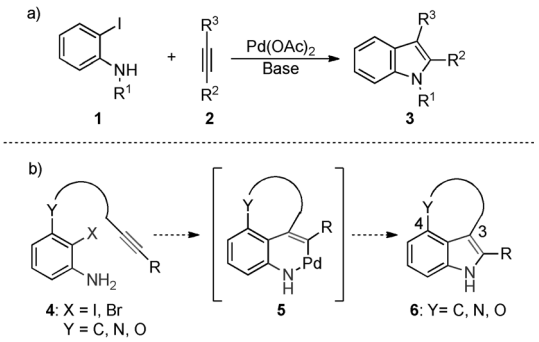


Figure 1. Selected examples of 3,4-fused indole alkaloids.



Scheme 1. Synthesis of 3,4-fused tricyclic indoles by intramolecular Larock indolization.

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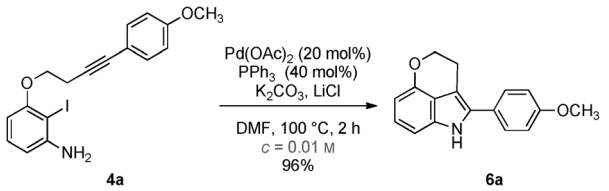
[**] We are grateful to the National Natural Science Foundation of China (Nos. 21290180, 20972007), the National Basic Research Program of China (973 Program, NO. 2010CB833200), and the Ph.D. Programs Foundation of the Ministry of Education of China (No. 20120001110100) for their financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300571.

an intramolecular Larock indolization has been reported in the literature,[20] the synthesis of 3,4-fused tricyclic indole moieties by an intramolecular Larock indole synthesis has never been reported.[21] Herein, we present our first results (Scheme 1b).

To test the feasibility of this concept, the compound **4a** was initially prepared and subjected to the typical Larock indolization conditions. Gratifyingly, the desired 3,4-fused tricyclic indole product **6a** was obtained cleanly in 96% yield as the only product (Scheme 2). It is worth mentioning that although the use of $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%) at the same substrate concentration gave **6a** in 87% yield, the use of a lower amount of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%), or higher substrate concentration (0.05 M) resulted in decreased reaction efficiency.



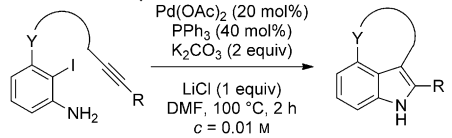
Scheme 2. Realization of the intramolecular Larock indolization. DMF = *N*,*N*-dimethylformamide.

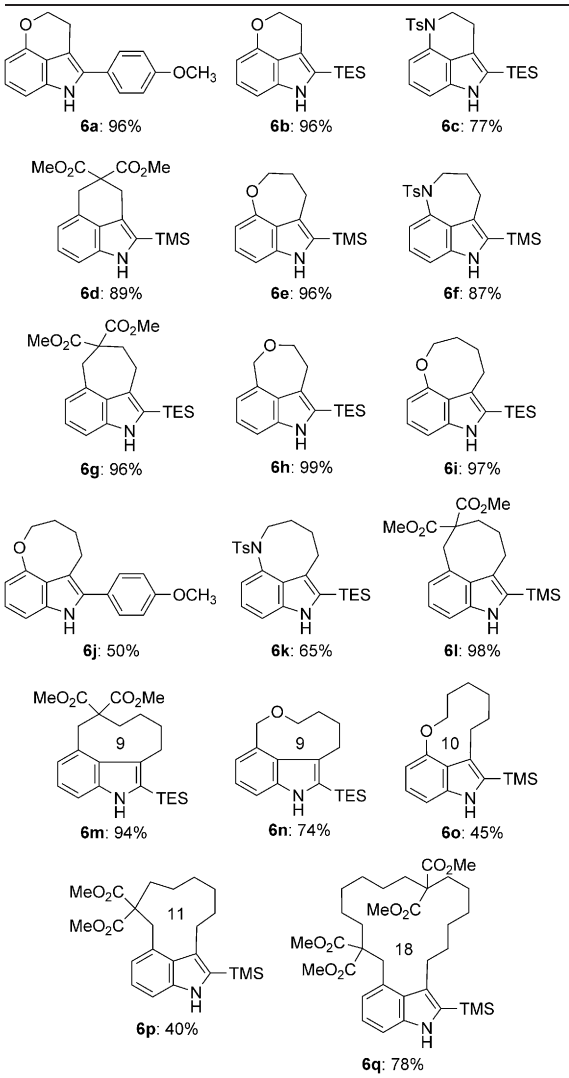
Encouraged by these initial results, the substrate scope of this reaction was next examined using different sets of 2-iodoanilines containing carbon, oxygen, or nitrogen tethers (Table 1). The transformation was found to be very general, and the desired tricyclic indoles (**6a**–**6q**) were obtained in reasonable yields. The substrates leading to six- and seven-membered-ring fused indoles were first examined and gave the desired cyclization products in good to excellent yield (**6a**–**6h**). The intramolecular reaction was next extended to generate 3,4-medium-ring (8- to 11-membered rings) fused indoles, which are especially difficult to prepare.[22,23,14i] Surprisingly, the desired 3,4-fused tricyclic indole products could be still obtained in good to excellent yield (**6i**–**6n**), although the 10- and 11-membered tricyclic products were obtained in relatively low yields (**6o** and **6p**). The efficiency of our method was further demonstrated by the observation that the 18-membered tricyclic product **6q** could be obtained in 78% yield.

After studying the reaction of 2-iodoaniline derivatives, we explored the reaction of the inert 2-bromoaniline derivatives, which are more stable and more readily available. Treatment of **7** under the optimal reaction conditions gave the desired product in only 27% yield and the starting material was largely recovered (Table 2). Considering the lower reactivity of aryl bromide, a variety of ligands were screened.[24] Although all tested ligands could furnish the desired product, Me-phos and dppp gave the best results and the desired product could be obtained in 95% yield.

To probe the utility of our method, we applied it to the rapid total synthesis of the natural product fargesine, which was isolated from the root and stem of *Evodia fargesii* Dode.[25] Thus, reductive coupling of the known aldehyde **8**[26]

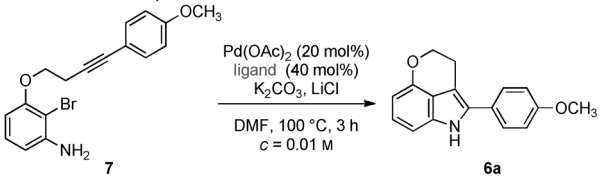
Table 1: Synthesis of 3,4-fused tricyclic indole systems by an intramolecular Larock indole synthesis.





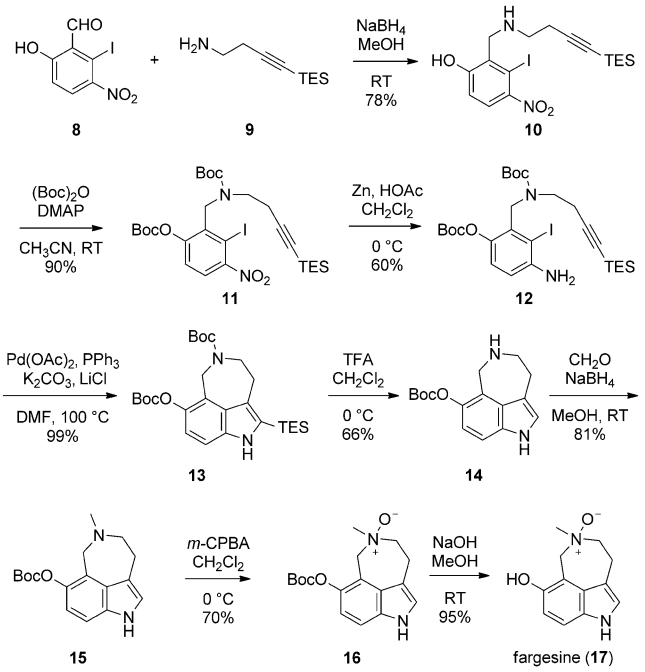
TES = triethylsilyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

Table 2: Reaction optimization of 2-bromoaniline derivative **7**.



PPh_3	PCy_3	Cy_2P	tBu_2P	dppp
27%	47%	95%	37%	95%

and the primary amine **9** afforded the secondary amine **10** in 78% yield. Boc protection of both the oxygen and nitrogen atoms gave **11** in 90% yield. Reduction of the nitro group with Zn in HOAc provided the key precursor 2-iodoaniline **12** in 60% yield. Treatment of **12** under our optimized reaction conditions successfully afforded the desired tricyclic product **13** in nearly quantitative yield. Selective removal of the Boc group on N, and TES with TFA gave **14** in 66% yield. Reductive amination of **14** (81%) and subsequent oxidation of **15** with *m*-CPBA yielded the desired N-oxide **16** in 70% yield.[27] Finally, removal the Boc group on O of **16** under basic conditions afforded fargesine (**17**) in 95% yield, and the characterization data (NMR spectra, MS) were essentially identical to those reported for the natural material.[25] Therefore, the first total synthesis of fargesine was accomplished in eight steps and in 15% overall yield (Scheme 3).



Scheme 3. Total synthesis of fargesine. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, *m*-CPBA = *meta*-chloroperoxybenzoic acid.

In summary, we have developed a new and general strategy for the construction of 3,4-fused tricyclic indoles, the core structure of numerous natural products and bioactive molecules, by an intramolecular Larock indolization reaction. The common, medium- and large-ring fused tricyclic indoles can be prepared by using this method. The utility of this method is demonstrated through the first total synthesis of fargesine. The application of this methodology in the total synthesis of other natural products and related systems for bioactivity studies is in progress in our laboratory and will be reported in due course.

Received: January 22, 2013
Published online: March 20, 2013

Keywords: natural products · nitrogen heterocycles · palladium · synthetic methods · total synthesis

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