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Total Synthesis of Phenanthroindolizidine Alkaloids through an Amidyl Radical Cascade/Rearrangement Reaction

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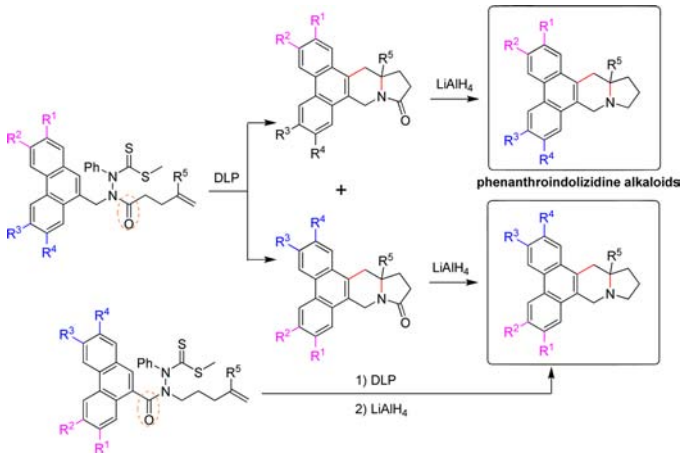
ABSTRACT



A short and general synthesis of the phenanthroindolizidine alkaloids is reported, featuring an unusual amidyl radical 5-*exo*/5-*exo*/rearrangement cascade of a xanthate precursor. Second, using an amidyl radical 5-*exo*/6-*endo* cascade to synthesize a phenanthroindolizidine alkaloid exclusively has been developed through a small structural modification.

Phenanthroindolizidine alkaloids are a group of pentacyclic alkaloids isolated mainly from *Cynanchum*, *Pergularia*, *Tylophora*, and some other genera of the Asclepiadaceae family.[1] Since the first isolation of tylophorine (**1a**) in 1935 from *Tylophora indica*,[2] to date more than 60 alkaloids of this class have been isolated, as representatively exemplified by antofine (**1b**) and deoxypergularinine (**1c**). In 1984, a novel phenanthroindolizidine alkaloid hypoestestatin 1 (**1d**), which bears a methyl group at the 13a-position (Figure 1), was reported by Pettit *et al.*[3] These alkaloids have potent biological activities, such as anti-arthritis,[4] antilupus,[5] antiamoebic,[6] anti-inflammatory

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effects,[7] antitumor activity,[8−15] and antiviral activity against the tobacco mosaic virus (TMV).[16] Because of their potent biological and pharmacological activities, numerous synthetic approaches to the natural phenanthroindolizidines and their analogues have been reported.[17]

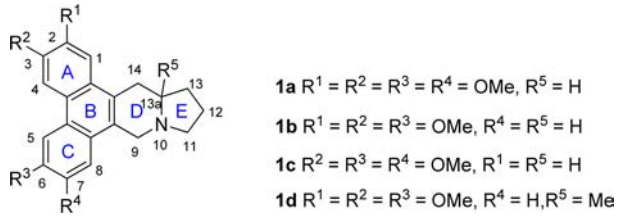
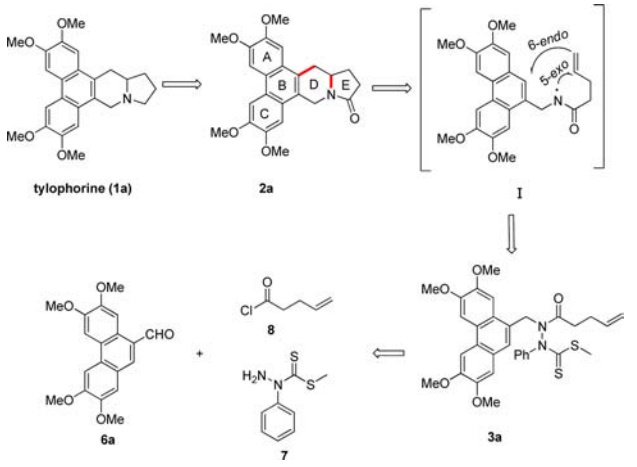


Figure 1. Examples of the phenanthroindolizidine alkaloids.

Radical reactions are important components of the organic synthesis repertoire, but most of the radical reactions involve carbon-centered radicals, whereas heteroatom-centered radicals remain relatively unappreciated. Amidyl-centered radicals are especially reactive and useful synthetic intermediates for the construction of complex structures. In the past decades, various precursors for the amidyl-centered radicals were reported, such as *N*-iodoamides,[18] *N*-acyltriazenes,[19] *N*-hydroxypyridine-2-thioneimidate esters,[20] and *N*-(phenylthio)amides.[21,22] However, these precursors are either unstable or difficult to prepare. Thiosemicarbazides and thiosemicarbazones have proven to be very practical progenitors of nitrogen radicals.[23] They have the following advantages: easy to prepare, can be used in standard stannane chemistry or under tin-free conditions, and the reactivity of the precursor may be modulated by modifying the substituents on the nitrogen. Amidyl radical cascade reactions to build nitrogen heterocyclic alkaloids are well precedented,

Scheme 1. Retrosynthetic Analysis of Tylophorine



including the elegant synthesis of 13-deoxyserratine[24] and a fortucine alkaloid[25] by Zard.

We have been engaged in the total synthesis of phenanthroindolizidine alkaloids, and we intend to gain a general, facile, concise access to synthesizing this class of alkaloids through a nitrogen-centered (amidyl) radical cascade process. Using (±)-tylophorine as an example, retrosynthetic analysis is shown in Scheme 1. The target molecule **1a** could be accessible via reduction from acylamide **2a**, which was envisioned to be constructed from the intermediate **I** through a 5-*exo* cyclization onto the alkene followed by a 6-*endo* cyclization onto the phenanthrene. If this radical cascade process could be realized, it would simultaneously form D and E rings in one step and be convenient to synthesize D and E ring modified analogues. The radical precursor **3a** could be easily prepared from pent-4-enoic acid and compound **6a**.

The readily prepared phenanthrene carbaldehyde **6a** served as the starting material in the total synthesis of **1a** (Scheme 2). In the step where **6a** reacted with **7**, owing to the poor solubility of the compound **6**, different solvents were screened, among which DMSO, ethanol, dichloromethane (DCM), and toluene gave a low yield or no reaction. But fortunately when **6a** and **7** were refluxed in 1,2-dichloroethane (DCE) for 30 h, hydrazone **5a** was obtained in 97% yield after recrystallization in ethanol, which was subsequently conducted by a BF_3-promoted hydrostannation in DCM for 15 min and converted into hydrazide **4a** in 95% yield.[26] The radical precursor **3a** was readily obtained in 86% yield by acylation of **4a** with pent-4-enoyl chloride in the presence of 4-DMAP. Pleasingly, when we treated precursor **3a** in refluxing DCE with dilauroyl peroxide (DLP) the expected radical cascade did occur and afforded the desired acylamide **2a** in 66% yield after flash-column chromatography. Then, the tylophorine was obtained through reduction by $LiAlH_4$ in refluxing THF in 95% yield.

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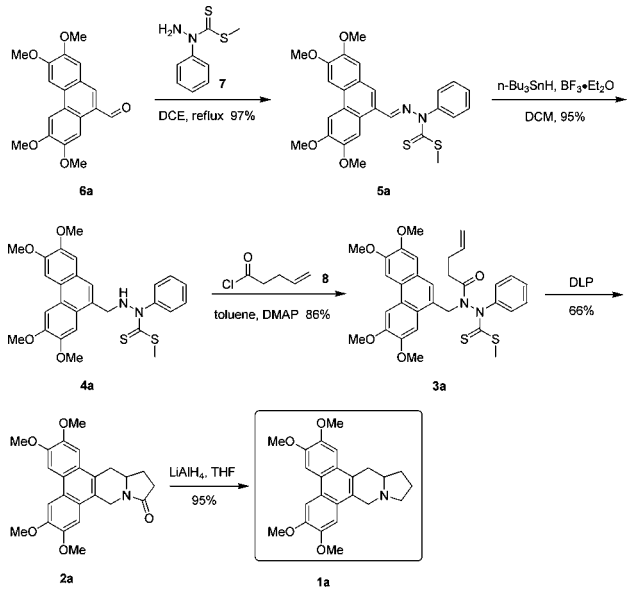
Scheme 2. Approach to the Tylophorine



Encouraged by the above success, we applied this method to the synthesis of antofine (**1b**) and hypoestestatin 1 (**1d**). However, this time we achieved an amazing result (Scheme 3). When precursor **3b** was refluxed in DCE with DLP, two products in a 1:1 ratio were obtained simultaneously, which were separated from each other by column chromatography and finally determined to be **2b** and **2c**. The spectroscopic data of the synthetic **2b** and **2c** match the literature.[27,28] Similarly, when R^5 was methyl, we obtained the acylamide **2d** and **2e**, whose ^1H and ^{13}C NMR spectra were identical with those reported by Ishibashi.[29] Antofine (**1b**) and deoxypergularinine (**1c**) were then achieved through reduction of **2b** and **2c** by $LiAlH_4$ in refluxing THF respectively, while acylamide **2d**, **2e** were reduced to give hypoestestatin 1 (**1d**) and alkaloid **1e** respectively.

Due to the fact that two products could be generated from the radical precursor **3b** or **3c**, the mechanism of the cascade reaction was not through a 5-*exo*/6-*endo* process as we initially thought. The mechanism is not clear in every detail, but we can elucidate the main step in the process. As shown in Scheme 4, precursor **3b** is initiated by DLP to obtain nitrogen-centered (amidyl) radical **II**, followed by a 5-*exo* addition to the internal olefin almost exclusively[30] to give the desired carbon-centered radical **III**, for which there are two pathways in subsequent steps. In one pathway, the carbon-centered radical undergoes 6-*endo* direct cyclization onto the phenanthrene as we initially expected to give **IV**. In another pathway, the carbon-centered radical undergoes another 5-*exo* cyclization

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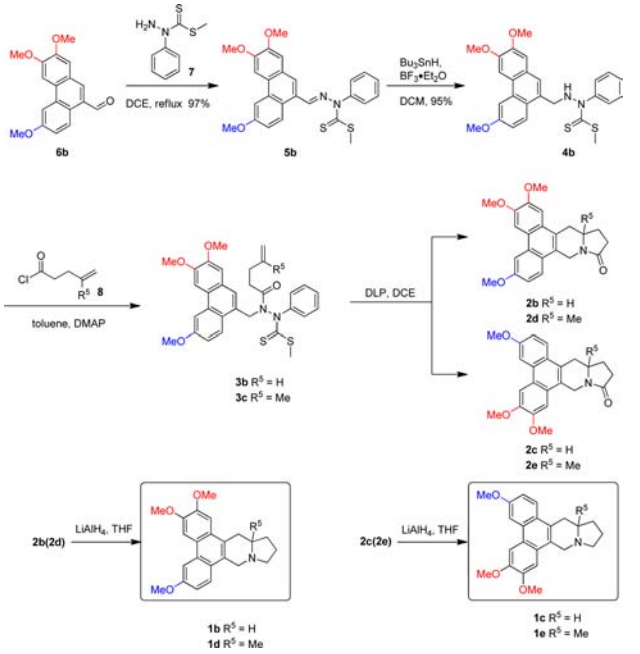
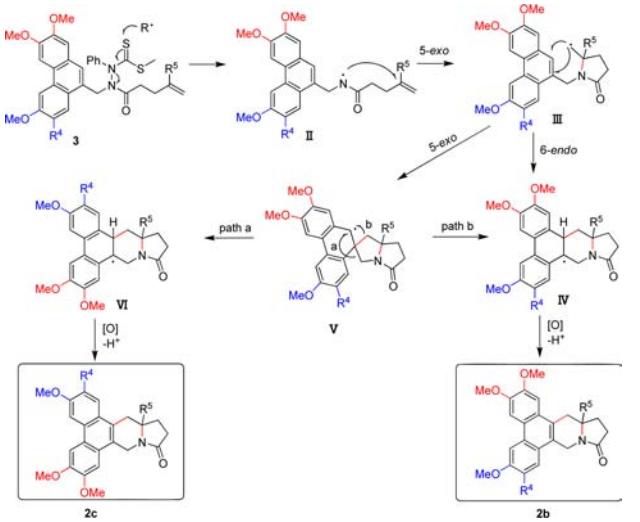
Scheme 3. Approach to the Antofine (**1b**), Deoxypergularinine (**1c**), Hypoestestatin 1 (**1d**), and **1e**



Scheme 4. Proposed Mechanism for the Amidyl Radical Cascade/Rearrangement



under thermodynamic control[31] onto the phenanthrene[32] to give the spiro intermediate **V**, which rearranges through path a to **VI** or path b to **IV**. Radical **IV** and **VI** then undergo oxidization and deprotonation to give the amides **2b** and **2c**, respectively. Although the 5-*exo*/6-*endo* mechanism cannot be ruled out, direct evidence convinced us

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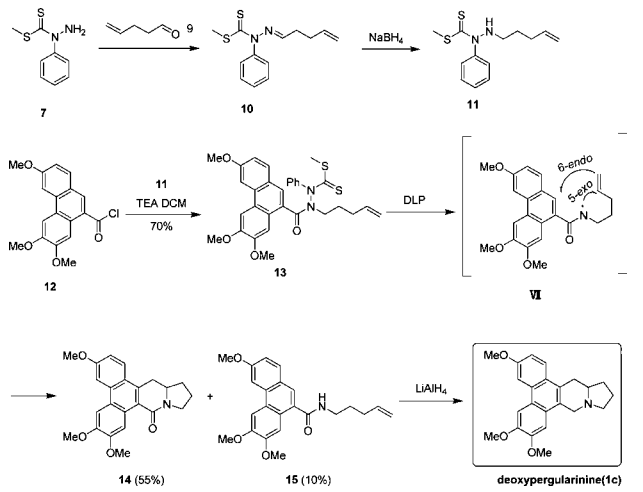
Scheme 5. Approach to the Deoxypergularinine (**1c**)



that the 5-*exo*/5-*exo*/rearrangement process must have occurred.

We were intrigued by the possibility of the exclusive 5-*exo*/6-*endo* cascade cyclization of the carbon-centered radical. To avoid the formation of a 5-*exo* spiro ring, a small structural modification was performed.[24] Compound **13** was synthesized through acylation of **12** and **11**, which was obtained from **7**. Then the radical precursor **13** was subjected to the above reaction conditions, and the formed amidyl radical **VII** sequentially underwent 5-*exo* cyclization and 6-*endo* cyclization, which was controlled in a kinetic manner,[33] to give the amide **14** exclusively. The rate for the ring closures of nitrogen-centered radicals **VII** was significantly slower than that of **II**; thus, the amidyl radical **VII** can be quenched by allylic hydrogen atom abstraction,[22] and the byproduct **15** was separated by flash-column chromatography in 10% yield (Scheme 5).

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In conclusion, we have achieved a general and concise amidyl radical cascade/rearrangement route to the synthesis of phenanthroindolizidine alkaloids. This strategy featured an internal amidyl 5-*exo*/5-*exo*/rearrangement radical cascade process as the key step to give alkaloids in five steps. This route can be applied not only to the synthesis of 13a-H phenanthroindolizidine alkaloids but also to the synthesis of 13a-methyl phenanthroindolizidine alkaloids. There were two paths in the rearrangement step, so this route can achieve two alkaloids from one single starting phenanthrene carbaldehyde. If the two paths gave the same product, the efficiency of this step was satisfying; for example, tylophorine (**1a**) can be obtained in 50% overall yield. Meanwhile the second strategy was focused on an exclusive 5-*exo*/6-*endo* radical cascade cyclization, by which compound deoxypergularinine (**1c**) was synthesized in 5 steps and 35% overall yield. The mechanisms of the cascade reactions were explored and may enlighten other organic chemists. The total syntheses of other complex, bioactive alkaloids through the two radical cascade processes are in progress and will be reported in due course.

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Supporting Information Available. Detailed experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for compounds **1a**–**e**, **2a**–**e**, **4a**–**b**, **5a**–**b**, **10**, **11**, **14**, **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.