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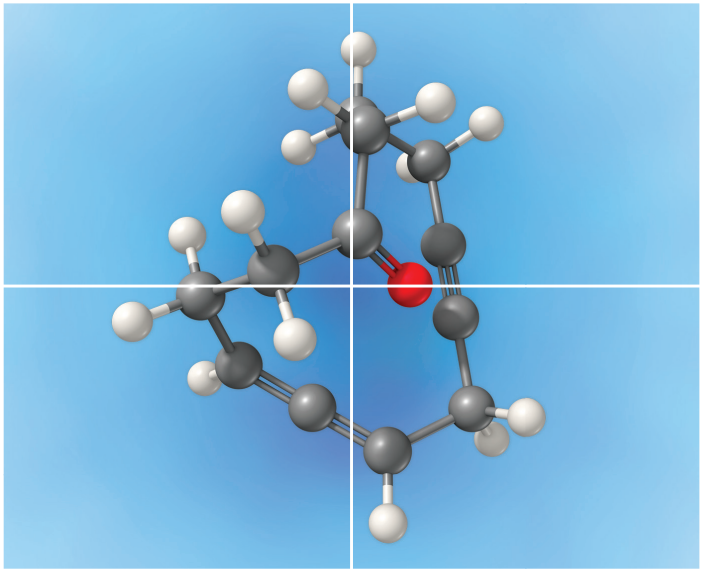

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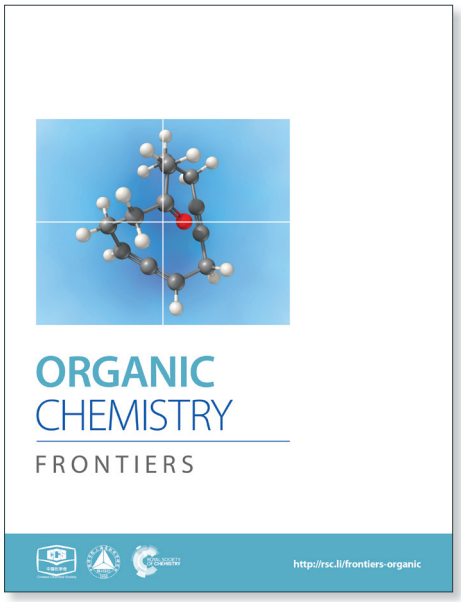


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ARTICLE TYPE

# Asymmetric Synthesis of (*S*)-Tylophorine and (*S*)-Cryptopleurine via one-pot Curtius Rearrangement and Friedel-Crafts Reaction Tandem Sequence

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A general and practical enantioselective synthetic approach to both phenanthroindolizidine and phenanthroquinolizidine alkaloids (*S*)-tylophorine and (*S*)-cryptopleurine was developed, which features a stereoselective alkylation and a one-pot Curtius reaction rearrangement/intramolecular cyclization cascade sequence.

Phenanthroindolizidine and phenanthroquinolizidine alkaloids are a group of pentacyclic natural products (Figure 1), which mainly isolate from *Tylophoraindica*, *Pergularia*, and *Cynanchum* species.[1] They exhibit a variety of biological activities, including antitumor, antiamoebic, and antifungal activities,[2, 3] among which antitumor activity is well studied. Because of their remarkable bioactivities coupled with their low natural abundance and interesting structures, numerous synthetic strategies have been developed.[1, 4, 5]

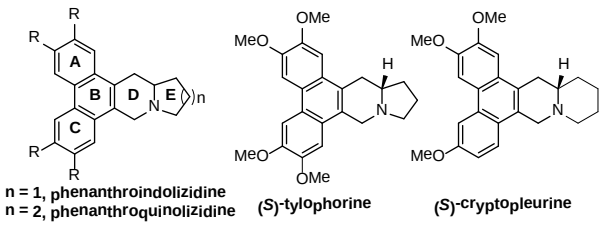
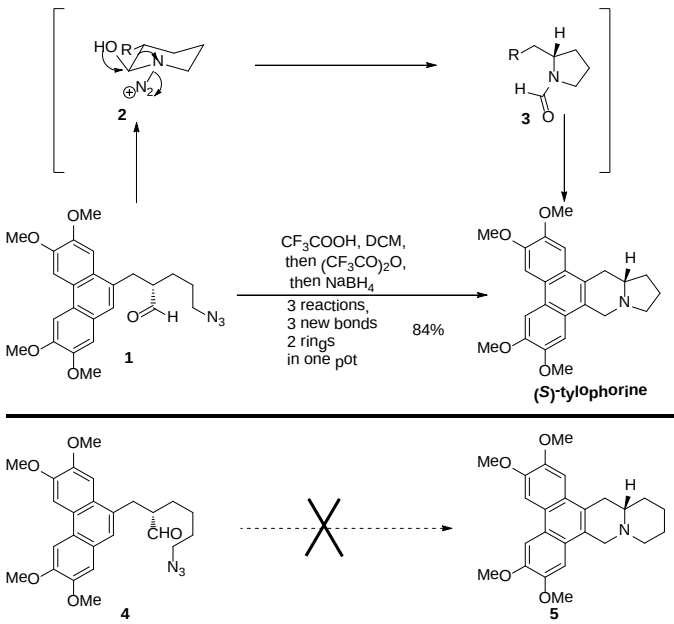


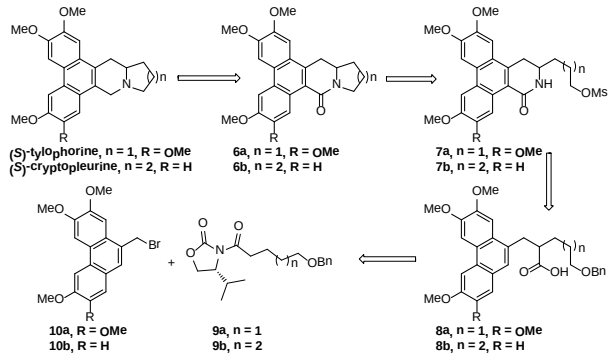

**Fig1.** Representatives of phenanthroindo/quinolizidine alkaloids.

Although great synthetic effort has been paid on the total synthesis of these alkaloids, highly efficient and practical strategies are still desirable. We have great interest in cascade and rearrangement reactions, which can usually construct skeletons of organic molecules in an amazing way with high efficiency. Recently, we developed a novel strategy to phenanthroindolizidine alkaloid (*S*)-tylophorine from azidoaldehyde **1**, featuring a one-pot intramolecular Schmidt/Bischler−Napieralski/imine-reduction cascade sequence, in which three new chemical bonds and two rings formed in good yield (Scheme 1).[6] The key step of the cascade sequence was the initial transformation from azidoaldehyde **1** to six-membered ring imtermediate azidohydrin **2**, which was followed by alkyl migration to furnish formamide **3** (Scheme 1). However, when the strategy was applied to the synthesis of phenanthroquinolizidine alkaloid **5**, it was found that the initial Schmidt rearrangement step did not occur under similar reaction conditions. Attempting to execute this transformation, various Lewis acids and Brønsted acids were screened, none of which proved to be effective for this rearrangement, giving no reaction or very complex result. Main reason for the failure of the transformation is believed to be that formation of a seven-membered ring is unfavorable due to its relatively large energy of transition state. Therefore, to explore a general and expedient synthetic strategy for the rapid preparation of both types of alkaloids, an alternative design was taken into consideration (Scheme 2).



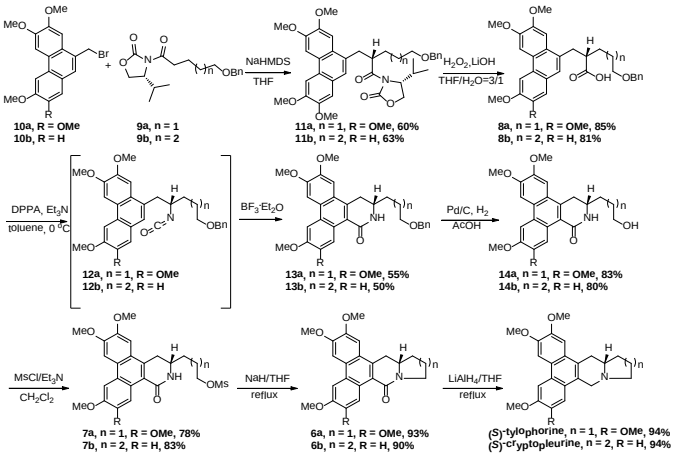

**Scheme 1.** Intramolecular Schmidt/Bischler−Napieralski/imine-reduction cascade sequence of aldehyde.

Retrosynthetically, (*S*)-tylophorine was used as an example to showcase our synthetic strategy. The target molecule could be accessible via reduction from lactam **6a**, which could be easily derived from lactam **7a** via an intramolecular nucleophilic substitution. The D ring of compound **7a** was planned to construct through a Curtius rearrangement/intramolecular cyclization sequence from acid **8a**, which could be prepared from oxazolinone **9a** and phenanthryl bromide **10a** using Evans` stereoselective alkylation protocol.




**Scheme 2**. Retrosynthetic analysis of phenanthroindo/quinolizidine alkaloids.

Based on the design above, the synthesis of (*S*)-tylophorine started with Evans` stereoselective alkylation from readily available phenanthryl bromide **10a**[7] and oxazolinone **9a**[8] under standard conditions, [9, 10] giving compound **11a** as a single diastereoisomer after chromatographic purification (Scheme 3). After hydrolysis, the precursor of the desired Curtius rearrangement acid **8a** was obtained. Since the discovery of Curtius rearrangement 100 years ago, this classic reaction has been investigated extensively and applied frequently in the total synthesis of natural products.[11] The precursor of the Curtius rearrangement is acyl azides, which can usually produce an important synthetic intermediate isocyanate under thermal conditions. The process can also be induced by photolysis, but this pathway always gives rise to several side-products in addition to the desired isocyanate.[12] Common nucleophiles added to the isocyanate include water, alcohols, and amines, resulting the corresponding amines, carbamates, and ureas. However, internal electron-rich arenes as nucleophiles were rarely reported, which may probably due to their relatively poor nucleophilicity, and usually harsh conditions are needed.[4, 13] Unexpected, when the acid **8a** was treated with diphenylphosphorylazide (DPPA) and triethylamine in toluene at 0 $^{o}$C, isocyanate **12a** formed, crude sample of which was verified by $^{1}$H NMR and HRMS after flash chromatography. The formation of isocyanate under such a mild reaction condition is really uncommon, and detailed reasons are unclear by now, which deserves further investigations. After extensive screening of Lewis acids and Brønsted acids, $BF_3{\cdot}Et_2O$ was found to be the optimal catalyst for this transformation, giving lactam **13a** in 55% yield over 2 steps. Pentacyclic lactam **6a**, obtained from compound **13a** through sequential hydrogenation, methansulfonation, and intramolecular nucleophilic substitution, was reduced by lithium aluminium hydride, giving (*S*)-tylophorine in good yield with 94% ee. (*S*)-Cryptopleurine could be also prepared in comparable yield with 98% ee, using similar procedures from phenanthryl bromide **10b** and oxazolinone **9b**. Melting points, NMR spectra, and optical rotations were in accordance with literatures (details see experimental section).




**Scheme 3.** Synthesis of (S)-tylophorine and (S)-crytopleurine.

## Conclusions

In summary, we have developed an efficient and practical enantioselective strategy for the synthesis of (*S*)-tylophorineand (*S*)-cryptopleurine. Advantages of this new approach include: 1) a stereoselective alkylation to introduce the stereogeniccenter, which also enables the synthesis of the antipode via converting the Evans auxiliary, and 2) an unprecedented one-pot Curtius rearrangement/intramolecular cyclization cascade sequence to construct the D ring.

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