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Asymmetric formal total synthesis of the stemofoline alkaloids: the evolution, development, and application of a catalytic dipolar cycloaddition cascade

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ABSTRACT

A formal synthesis of didehydrostemofoline and isodidehydrostemofoline has been accomplished by preparing an intermediate in the Overman synthesis of these alkaloids from commercially available 2-deoxy-D-ribose. The work presented in this account chronicles the evolution of our explorations to identify the optimal steric and electronic control elements necessary to generate the tricyclic core structure of these alkaloids in a single operation from an acyclic precursor. The key step in the synthesis is a novel dipolar cycloaddition cascade sequence that is initiated by cyclization of a rhodium-derived carbene onto the nitrogen atom of a proximal imine group to generate an azomethine ylide that then undergoes spontaneous cyclization via dipolar cycloaddition. The synthesis features several other interesting reactions, including a Boord elimination to prepare a chiral allylic alcohol, a highly diastereoselective Hirama–Itô cyclization, and a useful modification of the Barton decarboxylation protocol.

1. Introduction

1.1. Isolation and biological activity

The *Stemonacea* family is a small group of flowering plants native to various regions of Southeast Asia.[1] Herbal extracts from a variety of these plants have been used for centuries as pesticidal agents and to treat respiratory diseases. These plant extracts have yielded a number of biologically active alkaloids that have been the focus of extensive biological and medical research.[2] Arguably the most complex members of the *Stemona* family of alkaloids are those of the stemofoline family, which are characterized by a caged hexacyclic architecture and differ in the geometry of the C(11)–C(12) double bond and the oxidation state of the four-carbon side chain R (Fig. 1). Three species of the *Stemona* genus (*Stemona tuberosa*, *Stemona japonica*, and *Stemona sessilifolia*) are officially listed in the modern edition of the Pharmacopoeia of the People's Republic of China as herbal antitussive agents, and the ground up roots of these plants are still sold in local markets and herb shops for medicinal and agricultural purposes.[1] Owing to the similar appearance of many of the *Stemona* species and their visual similarities to plants belonging to other genera, the incorrect common

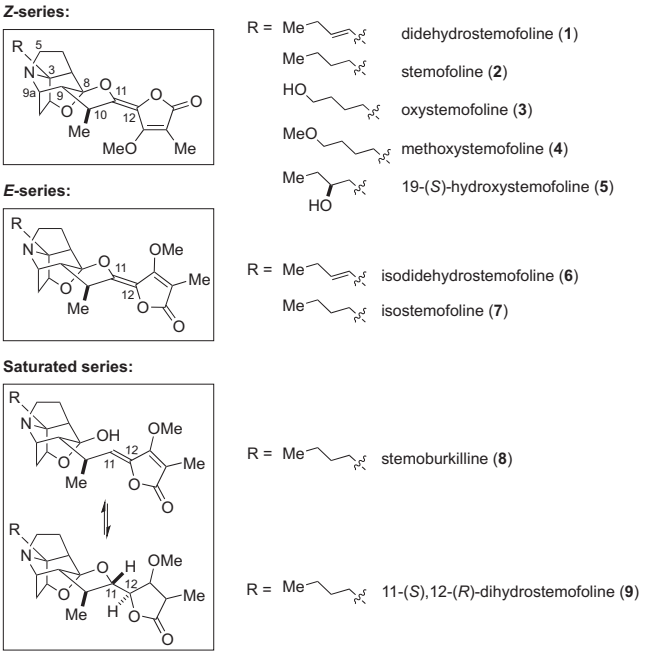

Fig. 1. The stemofoline alkaloids.

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names are often used at these markets to sell plants that do not contain the active principles found in the *Stemona* species. Accordingly, one must be vigilant when studying or using the plant materials for medical or research applications. In fact, didehydrostemofoline (**1**) was first erroneously reported to be isolated from *Asparagus racemosus* and originally named asparagamine A.[3] The roots of *A. racemosus*, which are also sold as an herbal antitussive remedy, bear a striking resemblance to the roots of the *Stemona* plants, thereby giving rise to an early suspicion that **1** actually originated from a *Stemona* plant. Corroborating this hypothesis, **1** was later isolated from *Stemona collinsae*,[4] and a recent report confirmed that **1** is not present in *A. racemosus* altogether.[5]

The stemofoline alkaloids were first isolated by Irie and coworkers from *S. japonica*,[6] and they were later isolated from other *Stemona* species.[7] Many of these alkaloids exhibit strong insecticidal activity because of their activity as insect acetylcholine (AChE) receptor antagonists.[8] In a recent screen for AChE inhibitory activity, didehydrostemofoline (**1**) was found to be among the most potent of the stemofoline alkaloids.[9] Didehydrostemofoline also exhibits in vivo anti-oxytocin activity and antitumor activity against gastric carcinoma,[4,10] whereas stemofoline (**2**) has been shown to be effective at increasing the sensitivity of clinically used anticancer drugs such as paclitaxel, vinblastine, and doxorubicin by reversing P-glycoprotein mediated multi-drug resistance.[11] Continued interest in these alkaloids is reflected in more recent work in which a number of semisynthetic analogs were prepared and found to possess potent AChE inhibitory activity.[9,12]

The complex molecular architecture coupled with the diverse biological activities of these alkaloids has inspired considerable interest from the synthetic community.[1,13,14] However, despite considerable effort, the only two accounts of the total syntheses of these alkaloids are Kende's synthesis of (±)-isostemofoline (**7**)[15] and Overman's syntheses of (±)-**1** and (±)-**6**.[16] Other interesting approaches toward these alkaloids have also been reported.[13] For example, Thomas applied an intramolecular Mannich reaction to construct the skeleton of stemofoline (**2**),[13d,e] and Gin prepared the core structure of stemofoline by a novel process that featured an intramolecular dipolar cycloaddition.[13a,e]

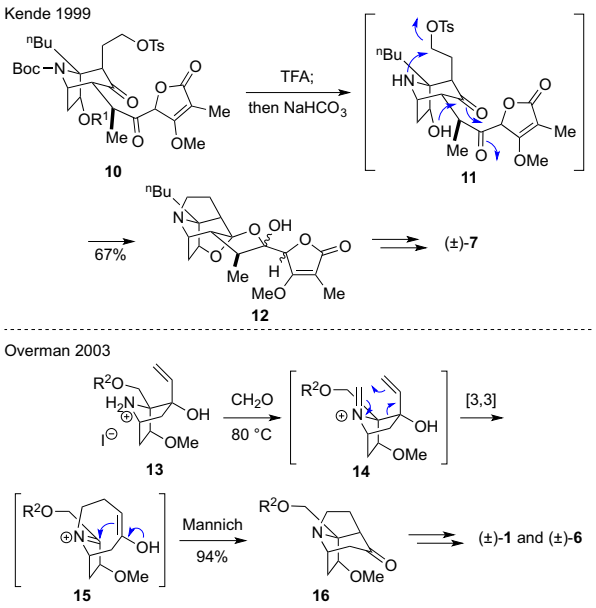
1.2. Total syntheses of the stemofoline alkaloids

Both the Overman and Kende approaches to the stemofoline alkaloids relied upon the use of impressive cascade processes to construct the bridged polycyclic core (Scheme 1). In Kende's synthesis of (±)-isostemofoline (**7**),[15] the core structure was constructed at an advanced stage by a sequence that was initiated by treating the azabicycle **10** with TFA to effect MOM and BOC-deprotection and liberate the intermediate aminoalcohol **11**, which spontaneously collapsed to the pentacyclic amine **12**. The Overman approach[16] to racemic **1** and **6** relied on the use of their prototypal aza-Cope–Mannich methodology in which **13** was heated with paraformaldehyde to generate the iminium ion **14**, which underwent an aza-Cope reaction to give **15** that cyclized via an intramolecular Mannich reaction to deliver the tricycle **16**.

Although the Kende and Overman syntheses set a high bar for the construction of the stemofoline core, the completed total syntheses were long requiring >30 steps. Furthermore, neither of these total syntheses was enantioselective. We thus believed that there was considerable opportunity to develop new chemistry that would lead to the first enantioselective syntheses of the *Stemofoline* alkaloids by a shorter sequence of reactions.

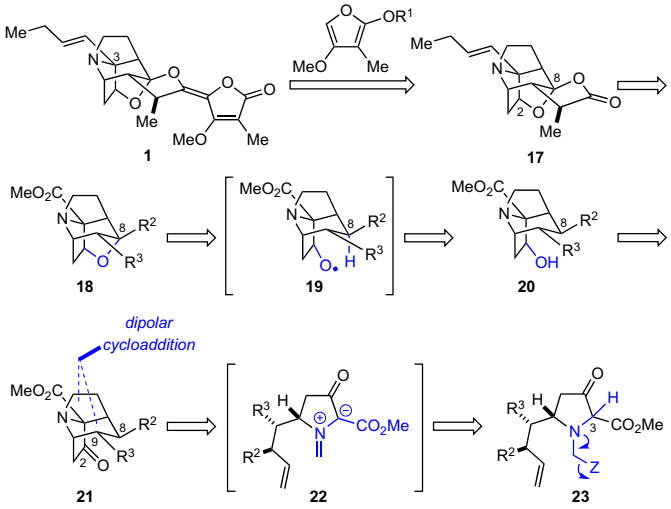
1.3. Initial planning

Members of the *Stemona* alkaloids have long been a focus of attention in our group because of the many challenges associated



Scheme 1. Prior approaches to the stemofoline core as applied to total synthesis (R^1=MOM, R^2=TIPS).

with fabricating the polycyclic cores of these naturally occurring bases. Our first introduction to these alkaloids resulted in an extraordinarily concise synthesis of croomine[17] using sequential vinylogous Mannich reactions.[18] We were similarly intrigued by the obvious challenges associated with developing short, enantioselective syntheses of representative members of the even more complex stemofoline group. Although the details of our plans to access these alkaloids have progressed through a number of iterations, the critical elements of our approach have remained the same (Scheme 2). In our original plan, we envisioned that the lactone **17** would serve as a key intermediate, and a number of tactics were envisioned for its conversion into didehydrostemofoline (**1**). A key step in producing **17** would involve the remote functionalization of the C(8)-position by a hydroxy radical **19** at C(2)[19] that would be derived from the *endo*-alcohol **20** by reaction with hypervalent iodine as prescribed by seminal work from Suárez.[20] Alcohol **20** would be derived from the stereoselective reduction of ketone **21** by attack of a hydride reagent from the least hindered face of the ketone. The critical disconnection in the overall strategy, however, involved forming the tricyclic core of the stemofoline alkaloids by the intramolecular 1,3-dipolar cycloaddition of an olefinic



Scheme 2. Novel 1,3-dipolar cycloaddition approach to stemofoline core.