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Synthesis of the Common Core Structure of the Stemofoline Alkaloids

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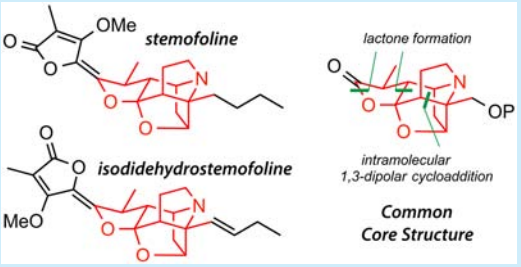
Supporting Information

ABSTRACT: A novel synthetic route to the common core structural motif of the stemofoline alkaloids has been developed. The key transformations include (1) an intramolecular 1,3-dipolar cycloaddition reaction of a highly functionalized nitrone, (2) the subsequent formation of a caged structure via lithiated allylic sulfoxide, and (3) the concomitant sila-Pummerer reaction of α-silylalkenyl sulfoxide to prepare a thioester precursor. A series of stereochemistries on the highly caged core structure characteristic of the stemofoline alkaloids was successfully assembled.



The stemona alkaloids constitute an intriguing family of natural products characterized by a highly saturated polycyclic skeleton around a common pyrrolo[1,2-*a*]azepine core (Figure 1).[1] Within this family, the stemofoline alkaloid

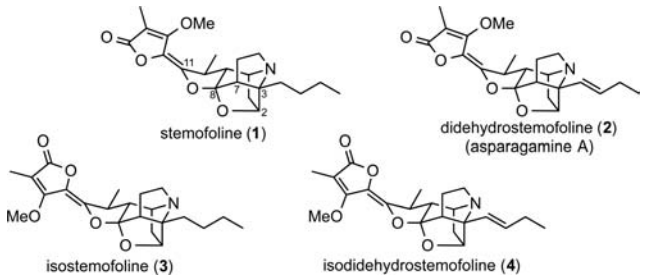
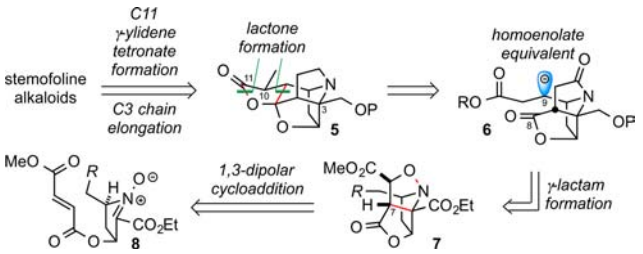


Figure 1. Structures of the stemofoline alkaloids.

group contains the highest level of complexity. A representative member of these alkaloids is stemofoline (**1**), isolated by Uyeo and co-workers in 1970.[2,3] Recently, **1** and structurally similar stemofoline alkaloids with a common C3−C7 bond and a C2−C8 oxygen bridge on the parent stemona alkaloid structure have been examined for their potential antiacetylcholine esterase (AChE) activities.[4] The strongest inhibitor in this group, didehydrostemofoline (**2**), also known as asparagamine A,[5] rivals galanthamine in the AChE activity, which was recently approved by the FDA for treatment of Alzheimer's disease. The insect antifeedant activity of **2** is comparable to that of the prominent natural product, azadirachtin.[4a,b] In addition, **2** is reported to exhibit in vivo antioxytocin activity, in vitro antitumor activity,[6] and potent in vitro antimultidrug resistance activity through the inhibition of P-glycoprotein.[7] These interesting bioactivities as well as the complex structures of these stemofoline alkaloids have raised considerable interest in the synthesis and derivatization of these alkaloids.[8]

The first total synthesis of (±)-isostemofoline (**3**), an 11*E* isomer of stemofoline, was reported by Kende in 1999.[9] Overman's group then applied their aza-Cope-Mannich reaction cascade to the total synthesis of didehydrostemofoline (**2**) and isodidehydrostemofoline (**4**).[10] Recently, an enantioselective formal synthesis of **2** and **4** was finally accomplished by Martin by way of Overman's late stage intermediate.[11] Several stemofoline derivatives were semisynthetically prepared by Pyne from natural didehydrostemofoline (**2**).[12] Their biological assays suggested that the variations on the C-3 side chain moiety and the presence of the γ-ylidene tetronate moiety on C-11 substantially affected the anti-AchE activity[12] and anti-P-glycoprotein activity[13] of these compounds. We have since launched a synthetic campaign toward the stemofoline alkaloids, bearing in mind that the strategy would also allow extensive derivatization.[14] Our retrosynthetic analysis along these lines is shown in Scheme 1. Since reliable methods for introducing γ-ylidene tetronate into a lactone[15] and C-3 side chain moiety from the C-3 formyl intermediate[12] were previously reported, we targeted the common intermediate lactone **5** with the C10 methyl group to secure the option to

Scheme 1. Retrosynthetic Analysis



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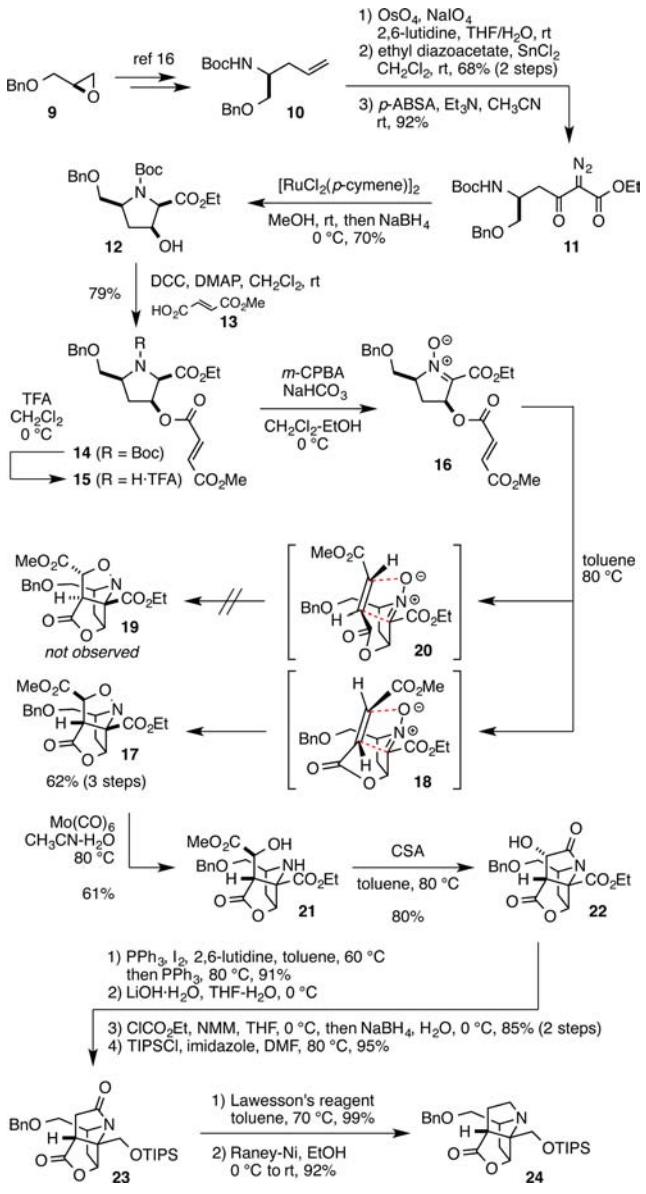
synthesize a series of stemofoline alkaloids and their derivatives. Retrosynthesis of the lactone moiety would lead to homoenolate **6** that could mediate an intramolecular attack from C9 to the C8 carbonyl moiety and the ensuing cyclization and methylation. The lactam moiety in **6** was deemed equivalent to the oxazolidine in **7** via N−O cleavage and lactamization. The intramolecular 1,3-dipolar cycloaddition reaction of nitrone **8** was thus envisaged as an ideal cyclization strategy for introducing the C-7 stereochemistry.

The route to the pivotal intermediate **5** commenced with the transformation of commercially available (*S*)-benzyl glycidyl ether (**9**) to prepare the known terminal olefin **10** (Scheme 2).[16] This olefin was subjected to the Lemieux−Johnson oxidation and Roskamp's reaction,[17] followed by diazotization to give the corresponding diazoketoester **11**. Among the known procedures for implementing the N−H insertion reaction, Che's methodology[18] employing $[RuCl_2(p\text{-cymene})]_2$ as the catalyst followed by the in situ $NaBH_4$ reduction of ketone

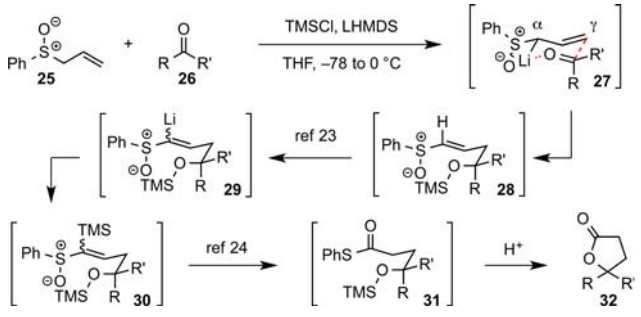
Scheme 2. Construction of the Core Structure via an Intramolecular 1,3-Dipolar Cycloaddition Reaction



proved to give **12** in 70% isolated yield. The secondary alcohol of **12** was then acylated with fumaric acid monomethyl ester **13** to furnish **14**. An attempt to remove the Boc group and to transform **14** to a nitrone was initially hampered by the *β*-elimination of the fumarate moiety. This seemingly unavoidable elimination was suppressed by first isolating the secondary amine as the trifluoroacetate salt **15**. The salt was then subjected to *m*-CPBA oxidation by means of a slow neutralization with solid $NaHCO_3$, thereby affording the desired nitrone **16** regioselectively in good conversion yield. While the 1,3-dipolar cycloaddition reaction proceeded to some extent during oxidation, it was driven to completion by heating in toluene to give only the desired diastereomer **17** in a 62% overall yield via the arrangement **18**. Formation of the undesired isomer **19** via the arrangement **20** was not observed because of the molecular strain which hampered the overlap between the nitrone moiety and the double bond in **20**. The high selectivity of this cycloaddition allowed the successful construction of the C7 stereochemistry in the target molecule. The next task was to transform the methoxycarbonyl oxazolidine moiety. Cleavage of the N−O bond in **17** with $Mo(CO)_6$[19] gave **21**, which was then subjected to cyclization under acidic conditions to afford the *α*-hydroxy lactam **22**. The hydroxy group in **22** was removed by means of the Appel reaction followed by one-pot deiodination of the *α*-iodo lactam with additional PPh_3. Further transformations were facilitated by reduction of the C3 ethoxycarbonyl group via the mixed anhydride and protection of the resultant alcohol with a TIPS group to afford **23**. Preliminary studies focused on the formation of the bond between C8 and C9 suggested that the additional ring strain caused by the amide or a potential enolization of the amide would be a major obstacle. Accordingly, we decided to eliminate these factors by reducing the amide before cyclization. Reduction of the amide in **23** was performed by treatment with Lawesson's reagent followed by desulfurization of the resultant thiolactam with Raney nickel to give the tertiary amine **24**, which was ready for C8−C9 bond formation.

The intended formation of the caged structure concomitant with the *γ*-lactone formation necessitated the transformation of **24** into a homoenolate equivalent.[20] Among the various candidates, we envisioned utilizing an allylic sulfoxide as a three-carbon homologation substructure. Scheme 3 represents our proposed route to this goal. Inspired by the pioneering work of Evans,[21] the allylic sulfoxide **25** would be treated with LHMDS in the presence of the carbonyl compound **26**, followed by addition of TMSCl. If the lithiated allylic sulfoxide were to attack the carbonyl group[22] in **26** from the *γ*-position

Scheme 3. Allylic Sulfoxide as a Potential Equivalent to the Homoenolate Unit



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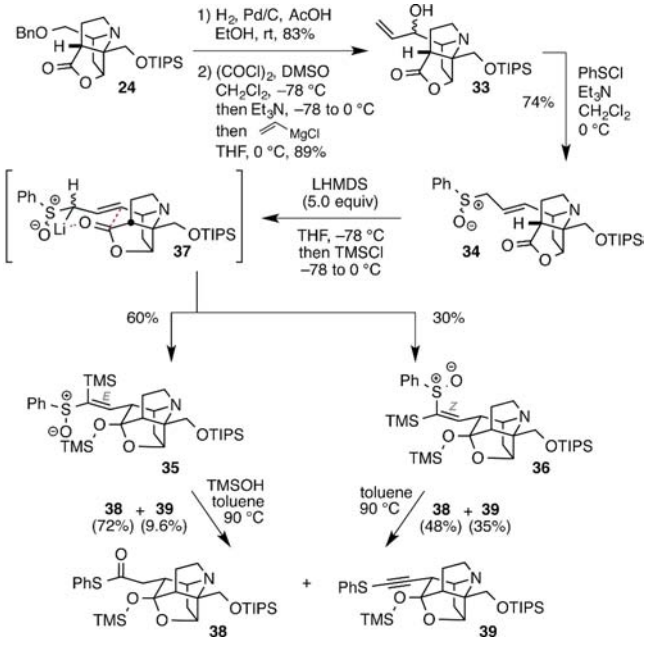
via **27**, silylation of the resulting alkoxide and the second deprotonation of alkenylsulfoxide **28** would afford an α-lithiated intermediate[23] **29** that would again be silylated to give the α-silylalkenyl sulfoxide adduct **30**. This species is known to undergo a sila-Pummerer rearrangement to give a thioester **31**.[24] Cyclization under acidic conditions would eventually give the γ-lactone **32**. The transformation described in Scheme 3 would require an allylic sulfoxide moiety to serve as a potential homoenolate equivalent. Therefore, we pursued the synthesis of the allylic sulfoxide intermediate from **24** as described in Scheme 4. Removal of the benzyl group and Swern oxidation,

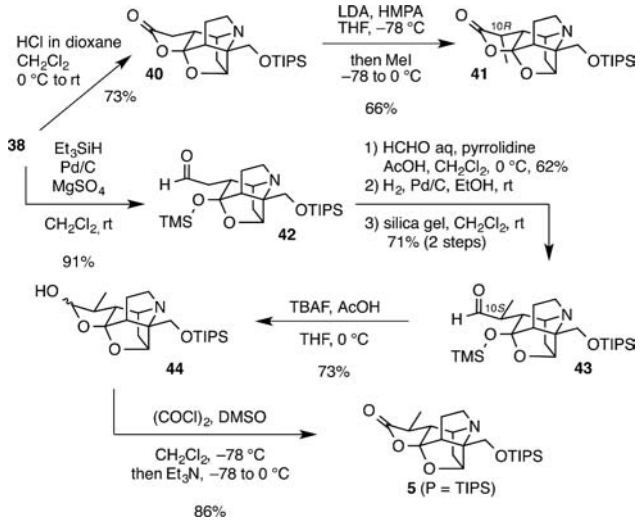
Scheme 4. Toward the Enclosure of the Polycyclic Core Structure



followed by the one-pot introduction of the vinyl group, gave the allylic alcohol **33**. Mislow–Evans rearrangement from **33** gave the desired allylic sulfoxide **34** solely as the *E* isomer. To our delight, the planned cage formation reaction of the lithiated **34** directly provided a separable 2:1 mixture of the *E* (**35**) and *Z* (**36**) isomers equipped with a vinyl TMS group and a C8–C9 bond, possibly via the intermediate **37**. Transformation of **35** and **36** into the thioester **38** was then effected by heating in toluene. During the course of optimization of the transformation of **35** into **38**, it was revealed that the addition of excess trimethylsilanol to help recombine with the thionium ion increased the yield of the thioester **38** (47% to 72%) and lowered the yield of the thioalkyne **39** (44% to 9.6%). Combined with the transformation from **36**, the desired thioester **38** was obtained in 58% yield over two steps from **34**.

With the thioester **38** in hand, the remaining tasks include the formation of the lactone moiety and the stereoselective introduction of the C10 methyl group (Scheme 5). While acidic treatment of the thioester **38** provides the lactone **40** in 73% yield, methylation of **40** via the lithium enolate gave **41** as the undesired stereoisomer at C10. We thus decided to employ an approach patterned after Overman's protocol for synthesizing a similar adduct.[10] Thus, the thioester **38** was transformed using our own method[25] to the aldehyde **42**, which was then converted to a saturated aldehyde via the Mannich reaction and

Scheme 5. Endgame toward the Construction of the Common Structural Motif of the Stemofoline Alkaloids



catalytic hydrogenation. Isomerization of the stereochemistry at the C10 methyl group through treatment with silica gel gave only the desired *S*-isomer **43**. Finally, selective desilylation with TBAF and cyclization generated lactol **44**, which was subjected to Swern oxidation to give the desired lactone **5** (P = TIPS) with all the desired stereochemistry. As a result of the incorporation of this methyl group, a pathway to the common core structural motif of the stemofoline alkaloids has been established. The key motif **5** bears seven stereocenters and has potentially provided access to the other stemona alkaloid members and their analogues.

In conclusion, we have developed a synthetic route to the common core motif of the stemofoline alkaloids. An intramolecular 1,3-dipolar cycloaddition reaction of the highly functionalized pyrrolidine intermediate successfully provided a set of stereochemistries on the core structure. We have also demonstrated the potency of a lithiated allylic sulfoxide as a homoenolate equivalent via an α-silylalkenyl sulfoxide precursor to the thioester. The sila-Pummerer reaction and acid-mediated cyclization enabled a powerful lactone formation strategy that eventually realized the formation of the complex caged structure of the stemofoline alkaloids. In combination with the elongation method to yield the γ-ylidene tetronate moiety and the C3 butenyl chain, this synthesis would open a route to a variety of derivatives of these biologically interesting stemofoline families.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02373.

Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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