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Toward a total synthesis of the stemofoline alkaloids: advancement of a 1,3-dipolar cycloaddition strategy

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ABSTRACT

Novel, intramolecular 1,3-dipolar cycloadditions of azomethine ylides have been applied to the synthesis of functionalized core structures of the stemofoline alkaloids. In an effort to maximize the efficiency of this key transformation in the context of an eventual total synthesis of these complex natural products, a number of strategic modifications to the cycloaddition substrate were investigated. The collective efforts have provided useful insights into the operative, regiochemical control elements for 1,3-dipolar cycloadditions leading to stemofoline alkaloids. A potential intermediate in the synthesis of these alkaloids was prepared.

The *Stemonacea* family contains approximately 30 different species of flowering plants native to various regions of Southeast Asia, from which a plethora of biologically active natural products have been isolated.[1,2] The ground-up leaves and tuberous roots of these plants have been used for centuries in traditional Asian medicine to prepare herbal teas for use in treating chronic cough symptoms associated with respiratory diseases, such as bronchitis and tuberculosis. Additionally, these extracts can be employed as pesticidal remedies for both human and agricultural infestations. Extensive investigations into the active principles of these plants have revealed a wealth of alkaloids that pose significant challenges to chemical synthesis, the most notable of which are the stemofoline alkaloids (Fig. 1). This complex group of alkaloids is characterized by a caged hexacyclic architecture varying only in the oxidation state of the C3 side chain and the geometry of the C11/C12 carbon–carbon double bond. These alkaloids exhibit powerful activity as insect acetylcholine receptor antagonists,[3,4] as well as activity against various human carcinoma cell lines and in vivo anti-oxytocin activity,[5] with didehydrostemofoline (**3**), which was the first of the stemofoline alkaloids to be isolated,[6] being the most potent. Despite numerous efforts toward the synthesis of these alkaloids,[7] only two total syntheses have been achieved. Kende reported the synthesis of (±)-**2** in 1999,[8] and compounds (±)-**3** and (±)-**4** were synthesized by Overman in 2003.[9]

Because of their structural complexity and biological activity, we became interested in the total synthesis of selected members

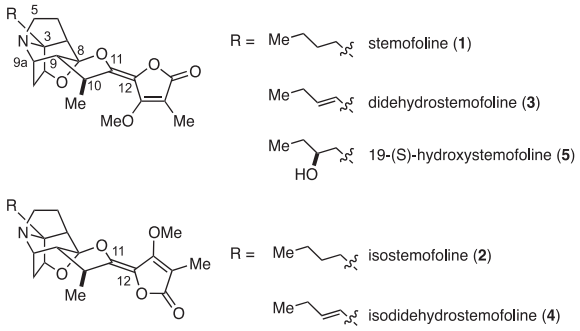
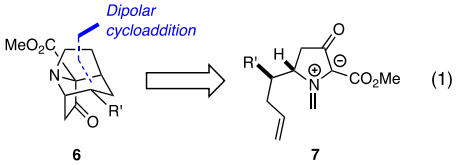


Figure 1.

of this family. The initial focus of our efforts centered on the construction of the functionalized tricyclic core **6** of these alkaloids using an intramolecular 1,3-dipolar cycloaddition reaction of an azomethine ylide of substrates of the general type **7** (Eq. 1). We recently reported some of our initial findings wherein we disclosed the successful construction of the tricyclic core **10** via a novel



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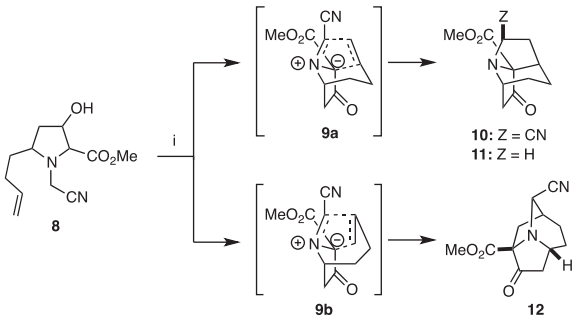
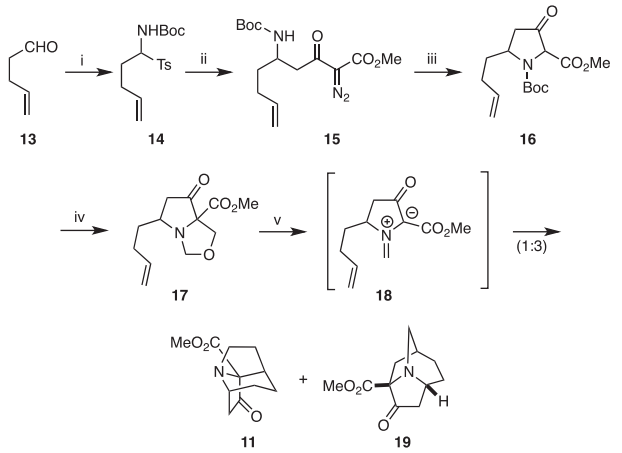


Scheme 1. Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; NEt_3; 16 h; 69%; regioisomeric ratio of **10**:**12** = 5:1.

process in which the azomethine ylide **9** was generated from **8** under the conditions of a Swern oxidation (Scheme 1).[10] Subsequent intramolecular 1,3-dipolar cycloaddition via the regioisomeric transition states **9a** and **9b** gave a mixture (ca 5:1) of **10** and **12**. This reaction granted access to the tricyclic core of the stemofoline alkaloids and provided essential proof of principle for our approach. However, we were unable to decyanate **10** to give **11** despite repeated efforts under a variety of conditions, so **10** is not a viable intermediate in a total synthesis of these alkaloids. Accordingly, we explored alternate avenues that would afford intermediates lacking superfluous substitution at C(5) (see Fig. 1). We now report some of our findings.

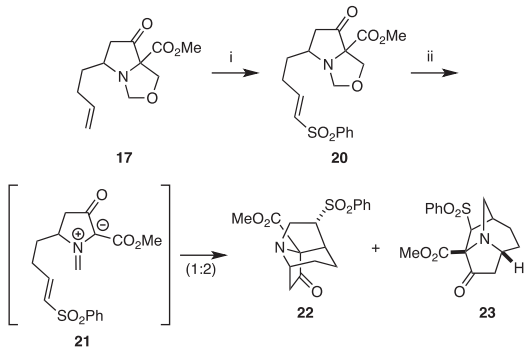
We were cognizant of the discoveries of Joucla, who had shown that azomethine ylides could be generated via thermolysis of 2,2-unsubstituted oxazolidines.[11] In order to apply this method to the problem at hand, we turned our attention to the synthesis of the oxazolidine **17**. Toward this end, α-amidosulfone **14** was prepared by condensing **13** with *tert*-butylcarbamate and *p*-toluenesulfinic acid sodium salt (Scheme 2). Compound **14** served as a masked acylimine that underwent a Mannich-type reaction with the enolate of methyl diazomethylacetoacetate to give diazo-β-ketoester **15** in 65% yield. Although the titanium enolate of methyl diazomethylacetoacetate was known to participate in Mannich-type reactions with sulfonimines,[12] the reaction of the corresponding lithium enolate anion with an α-amidosulfone was unknown. Upon exposure to catalytic amounts of rhodium acetate, **15** cyclized to give pyrrolidinone **16** in 96% yield. This route to **16** required only three steps and proceeded in 46% overall yield, whereas our previous synthesis required six steps, giving **16** in



Scheme 2. Reagents and conditions: (i) $H_2NCO_2{}^tBu$, *p*-$TolSO_2Na$, HCO_2H, THF:H_2O (4:1); 75%. (ii) $MeCOC(N_2)CO_2Me$, LDA, THF, -78 °C; 65%. (iii) $Rh_2(OAc)_4$ (1 mol %), CH_2Cl_2; 96%. (iv) $(MeO)_2CH_2$ (10 equiv), 10% CF_3CO_2H in CH_2Cl_2, rt, 7 h; 75%. (v) 160 °C, PhMe; 96%.

35% overall yield.[10] When **16** was treated with CF_3CO_2H and dimethoxymethane, oxazolidine **17** was formed in 75% yield. It should be noted that reaction times longer than 7 h resulted in the formation of appreciable amounts of **19** but none of the desired tricyclic compound **11**. Thermolysis of oxazolidine **17** presumably generated the azomethine ylide **18** that underwent dipolar cycloaddition to deliver a mixture (1:3) of cycloadducts **11** and **19** in 96% yield.[13] Although the ratio of regioisomers was poor relative to the desired cycloadduct **11**, this cycloaddition did provide the *nor*-cyano stemofoline core **11** in only five steps, considerably shorter than our earlier 10-step route to **10**.[10]

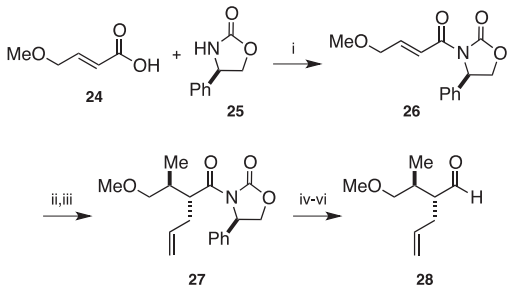
We reasoned that electronic factors might be partially responsible for the observed difference in regioselectivities in the cycloadditions of **9**. Accordingly, we queried whether a dipolar cycloaddition involving an electron deficient dipolarophile bearing a terminal electron withdrawing group might be more regioselective because of a better match with what we presumed was the inherent polarization of azomethine ylide. In order to explore this hypothesis, we converted **17** to **20** by a cross metathesis reaction with phenyl vinyl sulfone in the presence of Grubbs 2nd generation catalyst (Scheme 3). Unfortunately, thermolysis of **20** gave a mixture (1:2) of cycloadducts **22** and **23**—not significantly different from the cyclization of **18**.[13]



Scheme 3. Reagents and conditions: (i) phenyl vinyl sulfone, Grubbs II (5 mol%), CH_2Cl_2, reflux; 50%. (ii) 160 °C, PhMe; 97%.

The divergent regiochemical effects of having an electron-withdrawing group on the termini of the dipole and the olefin of the putative intermediates **9** and **21** are not readily interpretable. Although we considered the possibility of varying the nature and position of acceptors on the dipolarophile, we elected instead to turn our attention to examining steric effects that might be modulated by introducing substituents in the chain linking the dipole and dipolarophile. Such substituents would ideally correspond to those present in late-stage intermediates leading to the natural products themselves.

After considering various options, we decided to introduce a side chain at the eventual C(9) position (see Fig. 1) of an intermediate unsaturated azomethine ylide in anticipation that such a substituent would direct the cycloaddition to favor the desired regioisomer. This analysis led us to target the substituted aldehyde **28** as a starting material that would be processed along a path similar to that outlined in Scheme 2. The synthesis of **28** commenced with coupling the commercially available crotonic acid derivative **24** with the D-phenylglycine-derived Evans auxiliary **25** in the presence of Piv-Cl and LiClto give imide **26** (Scheme 4). We then employed a copper-mediated conjugate addition that was developed by Bergdahl to install a methyl group at the β-stereocenter;[14] α-alkylation of the imide enolate thus formed in situ with allyl iodide provided **27** in high (*dr* >15:1) diastereoselectivity. The chiral auxiliary was removed from **27** by the action of basic hydrogen



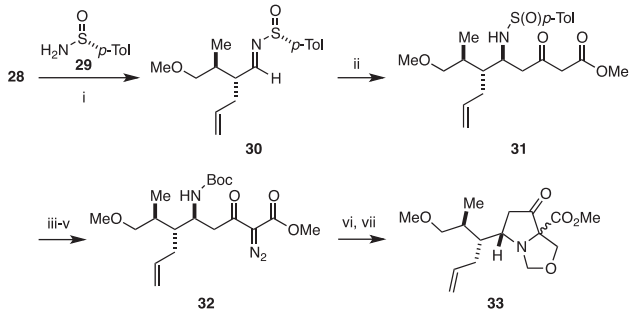
Scheme 4. Reagents and conditions: (i) Piv-Cl, NEt_3; then LiCl; 87%. (ii) $(CuI)_3(Me_2S)_4$, MeLi, TMS-I, Et_2O, -78 °C; 91% (*dr* = 7:1). (iii) LiHMDS, allyl iodide; 70% (*dr* >15:1). (iv) H_2O_2, LiOH, H_2O:MeOH (1:1); 83%. (v) $LiAlH_4$, THF; 99%. (vi) PCC/SiO_2, CH_2Cl_2; 99%.

peroxide,[15] the acid was reduced with $LiAlH_4$, and the resultant alcohol was oxidized to the corresponding aldehyde **28**.

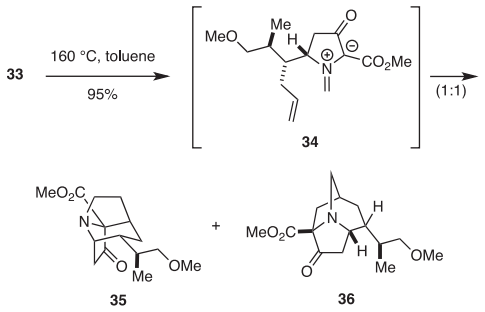
With enantiomerically-pure aldehyde **28** in hand, we employed a general protocol developed by Davis for preparing 5-substituted pyrrolidinones.[16] Namely, **28** was condensed with the chiral sulfonamide **29** in the presence of $Ti(OEt)_4$ to give sulfinimine **30** (Scheme 5). Compound **30** was then subjected to a tandem Mannich/cross-Claisen reaction using an excess of the enolate of methyl acetate to give β-ketoester **31** in excellent yield and diastereoselectivity (*dr* = 8:1).[17] In the first step of this sequence, the resident chirality of the sulfinimine controls the stereochemistry of the Mannich addition. The sulfonamide of β-ketoester **31** was then exchanged for a Boc-protecting group due to known incompatibility of the sulfonamide moiety to the impending NH-insertion reaction conditions.[18] Accordingly, treatment of β-ketoester **32** with CF_3CO_2H in methanol, followed by sequential reaction with Boc_2O and *p*-acetamidobenzenesulfonyl azide provided the diazo-β-ketoester **32** in 79% yield (3 steps). Cyclization of **32** via a rhodium acetate catalyzed NH-insertion, followed by reaction of the intermediate protected pyrrolidine derivative with dimethoxymethane and CF_3CO_2H gave oxazolidine **33** as an inconsequential mixture (ca 1:1) of diastereomers.

With the key oxazolidine **33** in hand, the stage was set for examining the pivotal dipolar cycloaddition. Although thermolysis of **33** did provide an improved ratio (1:1) of the regioisomeric cycloadducts **35** and **36** in excellent yield (Scheme 6),[13] the increased selectivity still falls short of what is synthetically optimal. It should be noted that thermolysis of the isolated cycloadducts **22**, **23**, **35,** and **36** under the original conditions did not result in any isomerization, suggesting that the observed regioisomeric ratios are kinetically controlled.

Despite the regiochemical outcome of this dipolar cycloaddition, it is noteworthy that enantiomerically-pure **35** is accessible



Scheme 5. Reagents and conditions: (i) $Ti(OEt)_4$, CH_2Cl_2, rt; 74%. (ii) NaHMDS, MeOAc, THF:Et_2O, −78 °C to 0 °C; 95%. (*dr* = 8:1).(iii) TFA, MeOH; (iv) Boc_2O, NEt_3, CH_2Cl_2; 81% (2 steps). (v) *p*-ABSA, NEt_3, MeCN; 97%. (vi) $Rh_2(OAc)_4$ (1 mol%), CH_2Cl_2; 87%. (vii) $(MeO)_2CH_2$, CF_3CO_2H, CH_2Cl_2, rt, 7 h; 67% (*dr* = 1:1).



Scheme 6.

in 15 synthetic operations and in 7% overall yield. These experiments also support our hypothesis that stereochemical and steric factors can be successfully exploited to enhance the regioselectivity of dipolar cycloadditions leading to the formation of compounds having the tricyclic core of the stemofoline alkaloids. We are currently exploring related tactics to access such compounds with improved selectivity, and the results of these efforts will be reported in due course.

Acknowledgments

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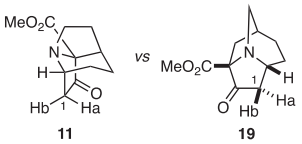
13. The ratio of **11** and **19** was based on a preliminary analysis of the ^1H NMR spectrum of the crude reaction mixture and confirmed by the isolated yields of both regioisomers. The ratio based on the ^1H NMR spectrum relies upon the relative integrations of the diagnostic *endo*-C(1)-Ha proton of **11** and the *endo*-C(1)-Ha proton of **19**. These protons appear as well resolved, sharp doublets between 1.5 and 2.2 ppm in all cycloadducts, with the signal from **11**, **22** and **35** always being upfield from the regioisomers **19, 23,** and **36**. The C(1)-Ha protons of **11**, **22** and **35** have geminal coupling constants of 18.0 Hz (±0.1 Hz),whereas the coupling constants for the C(1)-Ha protons of **19, 23,** and **36** are 15.6 Hz (±0.1 Hz).



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