Tetrahedron Letters 52 (2011) 4076–4079

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 26 April 2011
Revised 21 May 2011
Accepted 24 May 2011
Available online 2 June 2011

Keywords:
Azomethine ylide
Dipolar cycloaddition
Stemofoline alkaloids
Natural product synthesis

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

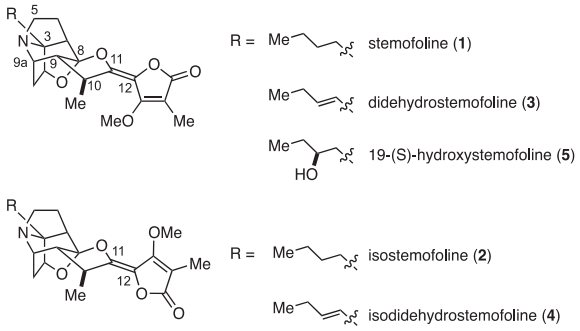
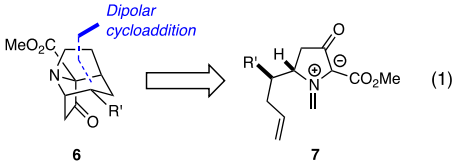


Figure 1.

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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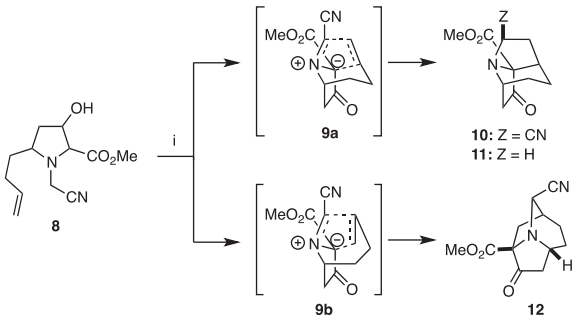
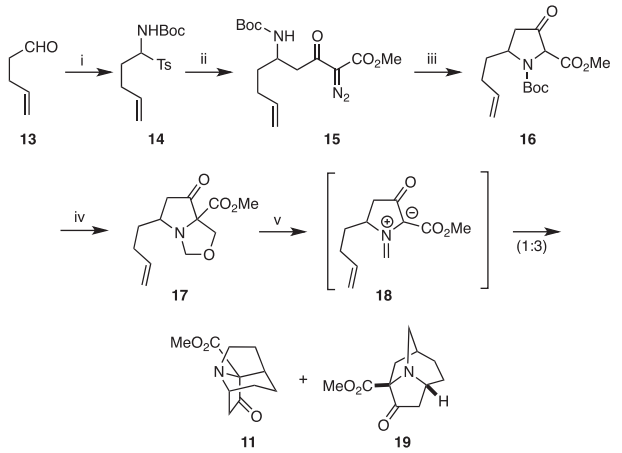
doi:10.1016/j.tetlet.2011.05.121



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.

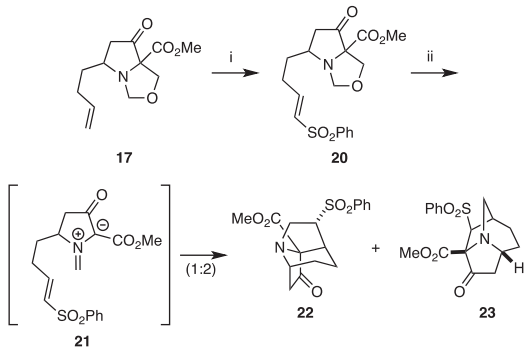
We were cognizant of the discoveries of Joucla, who had shown that azomethine ylides could be generated via thermolysis of 2,2-unsubstituted oxazolidines.[11] In order to apply this method to the problem at hand, we turned our attention to the synthesis of the oxazolidine **17**. Toward this end, α-amidosulfone **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