Published in final edited form as:
Tetrahedron Lett. 2011 April 27; 52(17): 2048–2050. doi:10.1016/j.tetlet.2010.10.038.

Novel Entry to the Tricyclic Core of Stemofoline and Didehydrostemofoline

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Abstract

A novel approach to the tricyclic core of the *Stemona* alkaloids stemofoline and didehydrostemofoline has been discovered that features an intramolecular (3+2) dipolar cycloaddition of an unactivated carbon-carbon double bond with an azomethine ylide; the azomethine ylide was generated by an unprecedented reaction that occurred during a Swern oxidation of an α-(*N*-cyanomethyl)-β-hydroxy ester. In separate experiments, the efficacy of introducing the requisite oxygen functionality at C(8) and the 1-butenyl side chain at C(3) was established.

Keywords

Azomethine ylide; Dipolar cycloaddition; Alkaloid synthesis; Remote functionalization

The roots and leaves of the *Stemonacea* species have been used extensively in traditional oriental medicine as insecticides and to treat respiratory diseases and parasitic infestation.i Stemofoline (**1**) was the first alkaloid isolated from *Stemona japonica*, ii and didehydrostemofoline (**2**), which was originally named asparagamine A because the plant from which it was isolated was erroneously thought to be *Asparagus racemosus*, was reported afterwards.iii, iv Isostemofoline and isodidehydrostemofoline, the 11,12-*E* isomers of **1** and **2**, respectively, have also been isolated.v Both **1** and **2** exhibit powerful insecticidal activity as insect acetylcholine receptor antagonists.iv,vi Moreover, **2** exhibits nanomolar activity against different human carcinoma cell lines and possesses potent *in vivo* anti-oxytocin activity.iiib, vii These structurally intricate and biologically interesting targets have attracted considerable interest from the synthetic community.viii However, the only total syntheses that have been recorded for alkaloids of this family are of (±)-isostemofoline by Kendeix and of racemic **2** and (±)-isodidehydrostemofoline by Overman.x

In developing an approach to **1** and **2**, we were intrigued by the possibility of forming the tricyclic core embodied in **4** by a (3+2) dipolar cycloaddition involving an azomethine ylide **5** that might be generated *in situ* by silver ion promoted decyanation and deprotonation of

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Dedicated to my friend and colleague Harry Wasserman on the occassion of his 90th birthday.

Supplementary Data
Experimental procedures and characterization data for all new compounds are provided. Supplementary data associated with this article can be found in the online version at doi:(Insert doi).

the chiral amino nitrile **6** (Scheme 1).xi The subsequent transformation of **4** into the advanced intermediate **3** would then require a remote functionalization xii followed by introduction of the requisite lactone ring. A variety of options were then envisioned for converting **3** into the targeted alkaloids. We now report the details of some of our work in this area that has led to the discovery of a novel reaction to generate azomethine ylides and the successful preparation of the functionalized tricyclic core of **1** and **2**.

Inasmuch as we ultimately wished to complete enantioselective syntheses of **1** and **2**, we were attracted to a general entry to chiral pyrrolidines that had been developed by Davis.xiii However, in the interest of establishing the underlying efficacy of our plan, we elected to perform some preliminary experiments using racemic intermediates. In the event, benzenesulfinyl amide (**7**) was condensed with 4-pentenal (**8**), which was freshly prepared by Swern oxidation of 4-pentenol, in the presence of $Ti(OEt)_4$ to give the sulfinyl amine **9** in 92% yield (Scheme 2). When **9** was allowed to react with an excess of the enolate of methyl acetate, a tandem Mannich/cross-Claisen reaction ensued to provide the keto ester **10** in 52% yield. Although the dianion of methyl acetoacetate also reacted with **9** to give **10**, the yields were lower. Because Davis had shown that *N*-sulfinyl groups were incompatible with the impending cyclization,xiiia the *N*-sulfinyl group was replaced with an *N*-Boc group in 87% overall yield. Reaction of **11** with 4-carboxybenzenesulfonyl azide (4-CBSA) gave the intermediate diazo compound **12** that underwent facile Rh-catalyzed cyclization to give the protected pyrrolidine **13** in 84% overall yield.

We soon discovered that removal of the *N*-Boc protecting group from **13** gave an unstable intermediate keto ester that could not be further manipulated. Accordingly, we modified our plan and reduced the keto function in **13** and immediately transformed the intermediate alcohol into **14** by sequential removal of the *N*-Boc group and cyanomethylation (Scheme 3). We then envisioned that oxidation of the alcohol function in **14** would give **6** that would then be transformed into the tricyclic adduct **4** according to the plan outlined in Scheme 1. However, initial attempts to oxidize **14** under a variety of conditions afforded complex mixtures of unidentifiable products. Surprisingly, when **14** was subjected to oxidation under Swern conditions, we obtained a mixture (ca 5:1) of **15** and **16**. After separation of these two compounds by chromatography, **15** was isolated in 62% yield; the structures of **15** and **16** were confirmed by x-ray crystallography.xiv

The unexpected formation of a mixture of **15** and **16** upon Swern oxidation of **14** is consistent with the generation and cyclization of the azomethine ylide **18** (Scheme 4). A plausible mechanism for the formation of **18** might involve initial oxidation of **14** to give **6**, which might undergo reaction with an electrophilic species present during the Swern oxidation to give an intermediate of the general form **17**. Loss of either HCl or of a proton and dimethyl sulfide would furnish **18**. The formation of **18** from **6** under these conditions is unprecedented and merits further investigation as a novel entry to azomethine ylides.

We then explored several tactics for introducing the requisite functionality at C(8) of **15** by remote functionalization. Toward this objective, the ketone moiety of **15** was stereoselectively reduced with $NaBH_4$ to give **19** (Scheme 5). Irradiation of a solution of **19** in the presence of iodobenzene diacetate and iodine under conditions developed by Suaréz gave **20** in 85% yield.xv The formation of the iodo ether in this process is also unusual and appears to arise from two consecutive hydrogen-abstraction/iodination steps. In a parallel study, we discovered that an oxygen atom may be introduced at C(8) of **19** via a Barton reaction in the presence of oxygen to give the nitrate ester **21**.xvi The structures of both, **20** and **21**, were unequivocally proven by x-ray crystallography.xiv

Having established several viable tactics to introduce an oxygen function at C(8), we then turned our attention toward removing the undesired cyano group. In order to set the stage for this effort, the ester group was first transformed into the butenyl side chain at C(3) required for the synthesis of didehydrostemofoline (**2**). In the event, the alcohol moiety in **19** was first protected as a TES ether by reaction with TES–OTf to give **22** in 95% yield. Chemoselective reduction of the ester moiety to the primary alcohol followed by Swern oxidation gave the aldehyde **23** in 60% overall yield. Stereoselective olefination of **23** with the anion generated from **24** by the Julia-Kocienski protocol delivered **25**.[xvii] Unfortunately, we have been unable to effect the reductive decyanation of **25** to give **26** under a number of standard conditions.

In summary, we have developed a novel entry to the tricyclic core of the *Stemona* alkaloids stemofoline and didehydrostemofoline. The approach features the intramolecular (3+2) dipolar cycloaddition of an unactivated carbon-carbon double bond with an azomethine ylide; the azomethine ylide was generated by an unprecedented reaction that occurred during a Swern oxidation of an α-(*N*-cyanomethyl)-β-hydroxy ester. In separate experiments, the efficacy of introducing the requisite oxygen functionality at C(8) via a radical-mediated remote functionalization and the 1-butenyl side chain at C(3) via a Julia-Kocienski reaction was established. Although we have not yet identified conditions for removing the cyano group at C(5), this work validates our approach to these unusual alkaloids. The extension of the chemistry developed herein to the syntheses of stemofoline and didehydrostemofoline is under active investigation, the results of which will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (GM 25439 and GM31077), Pfizer, Inc., Merck Research Laboratories, and the Robert A. Welch Foundation (F-0652) for their generous support of this research. J. D. gratefully acknowledges a Feodor-Lynen postdoctoral fellowship from the Alexander von Humboldt Foundation. We also thank Dr. Christian Harcken for helpful discussions and conducting some preliminary experiments and Dr. Vince Lynch for performing the x-ray analyses.

References

i. Pilli RA, da Conceição Ferreira de Oliveira M. Nat. Prod. Rep. 2000; 17:117–127. [PubMed: 10714902]

ii. Irie H, Masaki N, Ohno K, Osaki K, Taga T, Uyeo S. J. Chem. Soc., Chem. Commun. 1970:1066–1068.

iii. (a) Sekine T, Fukasawa N, Kashiwagi Y, Ruangrungsi N, Murakoshi I. Chem. Pharm. Bull. 1994; 42:1360–1362. (b) Sekine T, Ikegami F, Fukasawa N, Kashiwagi Y, Aizawa T, Fujii Y, Ruangrungsi N, Murakoshi I. J. Chem. Soc., Perkin Trans. 1. 1995:391–393.

iv. (a) Brem B, Seger C, Pacher T, Hofer O, Vajrodaya S, Greger H. J. Agric. Food Chem. 2002; 50:6383–6388. [PubMed: 12381121] (b) Kaltenegger E, Brem B, Mereiter K, Kalchhauser H, Kahlig H, Hofer O, Vajrodaya S, Greger H. Phytochemistry. 2003; 63:803–816. [PubMed: 12877922]

v. Seger C, Mereiter K, Kaltenegger E, Pacher T, Greger H, Hofer O. Chem. & Biodiv. 2004; 1:265–279.

vi. Lind, RJ.; Greenhow, DT.; Blythe, J.; Goodchild, J.; Hirst, E.; Dunbar, SJ.; Earley, FGP. BCPC Conference—Pests & Diseases; 2002. p. 145-152.

vii. Tip–Pyang S, Tangpraprutgul P, Wiboonpun N, Veerachato G, Phuwapraisirisan P, Sup–Udompol B. ACGC Chem. Res. Commun. 2000; 12:31–35.

viii. For selected examples of approaches, see: (a) Beddoes RL, Davies MPH, Thomas EJ. J. Chem. Soc., Chem. Commun. 1992:538–540. (b) Kercher T, Livinghouse T. J. Am. Chem. Soc. 1996; 118:4200–4201. (c) Smith SC, Bentley PD. Tetrahedron Lett. 2002; 43:899–902. (d) Epperson MT, Gin DY. Angew. Chem. Int. Ed. 2002; 41:1778–1780. (e) Ye Y, Velten RF. Tetrahedron Lett. 2003; 44:7171–7173. (f) Baylis AM, Davies MPH, Thomas EJ. Org. Biomol. Chem. 2007; 5:3139–3155. [PubMed: 17878973] (g) Carra RJ, Epperson MT, Gin DY. Tetrahedron. 2008; 64:3629–3641. [PubMed: 18443655] (h) Thomas EJ, Vickers CF. Tetrahedron: Asymmetry. 2009; 20:970–979.

ix. Kende AS, Smalley TL Jr, Huang H. J. Am. Chem. Soc. 1999; 121:7431–7432.

x. Brüggemann M, McDonald AI, Overman LE, Rosen MD, Schwink L, Scott JP. J. Am. Chem. Soc. 2003; 125:15284–15285. [PubMed: 14664560]

xi. For example, see: (a) Grierson DS, Harris M, Husson H–P. J. Am. Chem. Soc. 1980; 102:1064–1082. (b) Overman LE, Jacobsen EJ. Tetrahedron Lett. 1982; 23:2741–2744.

xii. For reviews, see: Majetich G, Wheless K. Tetrahedron. 1995; 51:7095–7129. (b) Togo H, Katoghi M. Synlett. 2001:565–581.

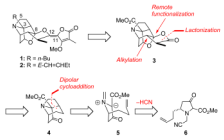
xiii. (a) Davis FA, Fang T, Goswami R. Org. Lett. 2002; 4:1599–1602. [PubMed: 11975638] (b) Davis FA, Yang B, Deng J. J. Org. Chem. 2003; 68:5147–5152. [PubMed: 12816469] (c) For a review, see: Zhou P, Chen B–C, Davis FA. Tetrahedron. 2004; 60:8003–8030.

xiv. X–ray data for compounds **15**, **16**, **20** and **21** have been deposited to the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 792740–792743.

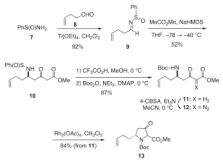
xv. Francisco CG, Freire R, Herrera AJ, Peréz–Martín I, Suárez E. Org. Lett. 2002; 4:1959–1961. [PubMed: 12027657] and references therein.

xvi. Boar RB, Copsey DB. J. Chem. Soc. Perkin Trans. 1. 1979:563–564.

xvii. Blakemore PR, Cole WJ, Kocienski PJ, Morley A. Synlett. 1998:26–28.



Scheme 1.



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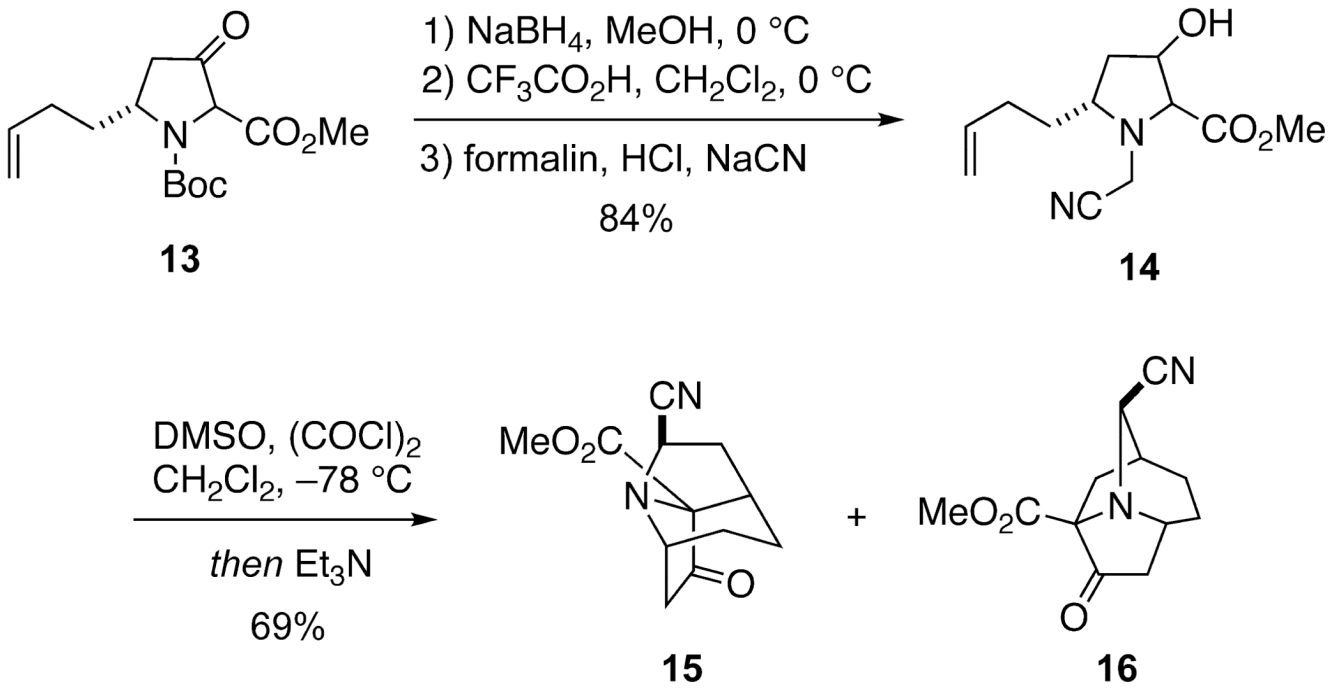

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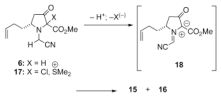
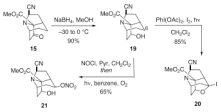


Scheme 4.



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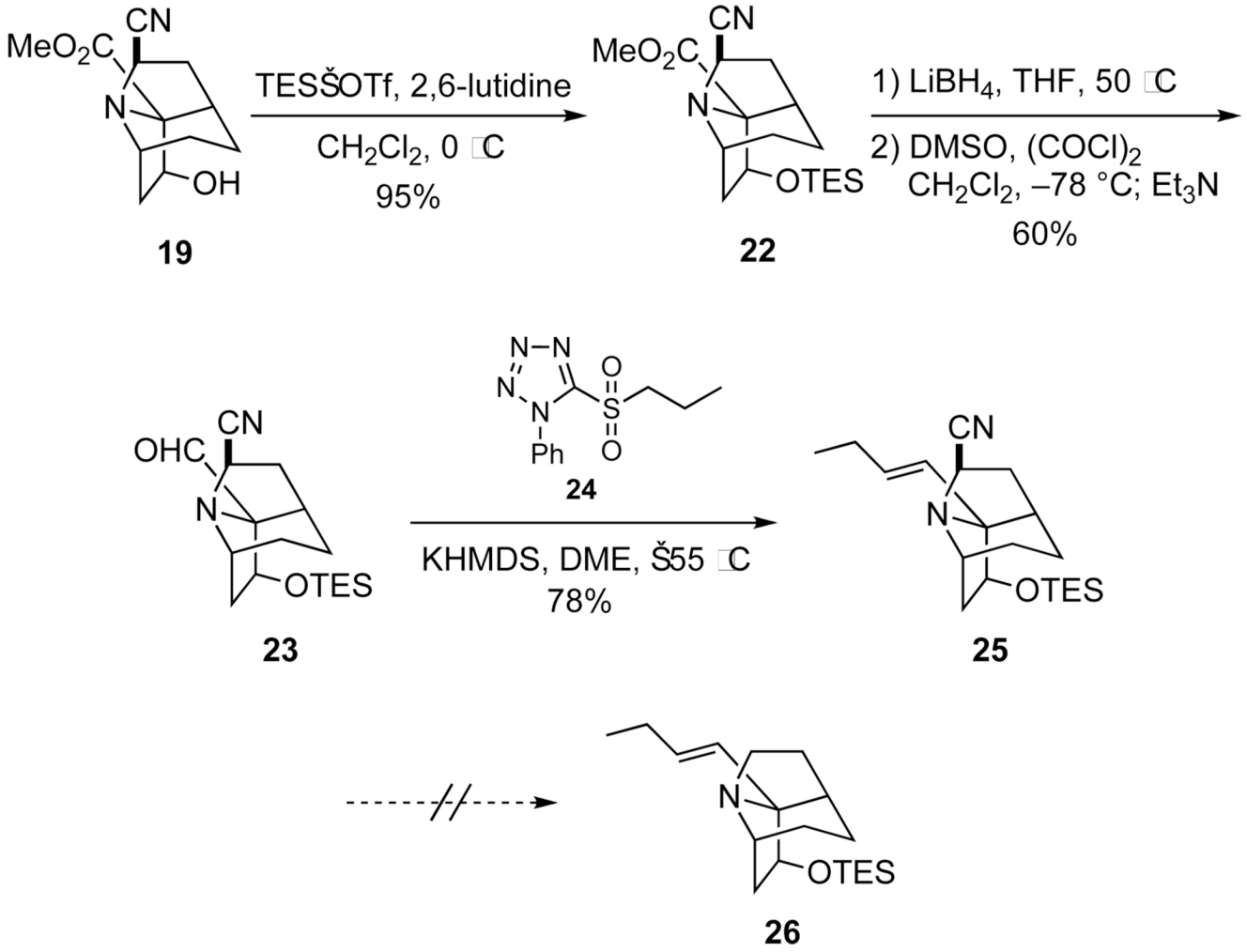

Scheme 6.