[15] For dimerization of 1,2-allenyl ketones, see: a) A. S. K. Hashmi, J. -H. Choi, J. W. Bats, *J. Prakt. Chem.* **1999**, *341*, 342; b) A. S. K. Hashmi, T. L. Ruppert, T. Knöfel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295; c) A. S. K. Hashmi, *Angew. Chem.* **1995**, *105*, 1749; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581; d) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285.

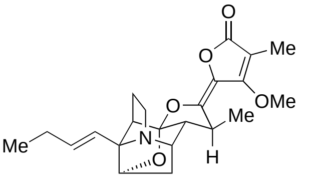
[16] For a recent highlight, see: A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590.

[17] For protonolysis of Pd enolate to regenerate divalent palladium, see: Z. Wang, X. Lu, *J. Org. Chem.* **1996**, *61*, 2254.

Enantiospecific Synthesis of the Bridged Pyrrolizidine Core of Asparagamine A: Dipolar Cycloadditions of Azomethine Ylides Derived from the Sulfonylation of Vinylogous Amides.**

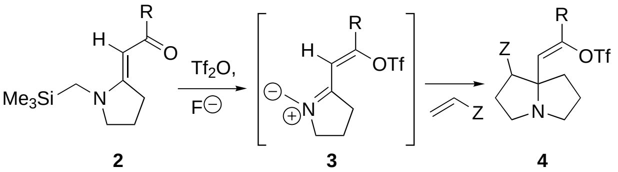
Matthew T. Epperson and David Y. Gin*

The efficient construction of highly functionalized pyrrolizidines is regarded as an important synthetic challenge owing to the diverse array of complex alkaloids that possess the necine skeleton. Asparagamine A (**1**) is a bridged pyrrolizidine alkaloid isolated from *Asparagus racemosus* that incorporates an intricate and rigid pentacyclic core[1] akin to the insecticidal stemofoline alkaloids,[2] natural products that have garnered considerable synthetic interest.[3] In vivo biological assays of **1** revealed potent antioxytocin activity,[4] despite its lack of structural homology with known oxytocin receptor antagonists.[5] We report herein an enantiospecific synthesis of the bridged pyrrolizidine skeleton of **1** that utilizes a complex intramolecular 1,3-dipolar cycloaddition as the key transformation.[6]



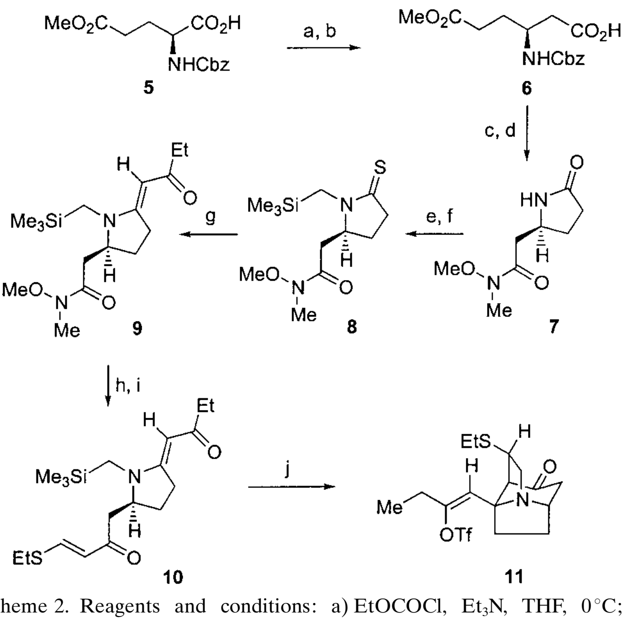
1

In the context of the synthesis of five-membered N heterocycles, azomethine ylides have proven to be valuable intermediates in a variety of 1,3-dipolar cycloadditions. A plethora of methods for the generation of these reactive intermediates exists and includes deprotonation, desilylation, or destannylation of imine or iminium salts, as well as the thermolysis or photolysis of aziridines.[7] However, in surveying the known procedures and substrates in the context of constructing the pyrrolizidine cage of **1**, a key challenge in this synthetic approach involves the direct installation of the angular C8 *E*-1-butenyl substituent during the cycloaddition reaction. As a result, vinylogous amides such as **2** (Scheme 1) were examined as potential precursors to azomethine ylides such as **3** through sequential O-sulfonylation[8] and desilylation.[9, 10] A 1,3-dipolar cycloaddition of **3** with a suitable dipolarophile would presumably lead to a pyrrolizidine that incorporates an enol triflate moiety at the angular position of **4**, a structure that maps directly onto the framework of **1**.



Scheme 1. Vinylogous amides (e.g. **2**) are suitable precursors to azomethine ylides (e.g. **3**).

Application of this strategy to the synthesis of **1** would necessitate an intramolecular mode of the cycloaddition to access the bridged azatricyclo[5.3.0.0^{4,8}]decane core of the alkaloid. *N*-Benzyloxycarbonyl-L-glutamic acid-5-methyl ester (**5**)[11] was employed as a readily available starting material whose sole stereogenic center dictates the enantiospecific course of the synthesis (Scheme 2). Arndt–Eistert reaction of



Scheme 2. Reagents and conditions: a) EtOCOCl, Et$_3$N, THF, 0 °C; CH$_2$N$_2$, Et$_2$O, 87 %; b) AgOAc, 1,4-dioxane, H$_2$O, 23 °C, 86 %; c) EDCl, MeONHMe, Et$_3$N, CHCl$_3$, 23 °C, 89 %; d) H$_2$, 10 % Pd/C, MeOH, 23 °C, atmospheric pressure, 99 %; e) NaH, TMSCH$_2$Cl, DMF, 23 °C, 49 %; f) Lawesson's reagent (0.51 equiv), PhMe, 23 °C, 88 %; g) BrCH$_2$COEt, then PPh$_3$, Et$_3$N, MeCN, 23 °C, 92 %; h) $CH\equiv CMgCl$, THF, 0 °C; i) EtSH, Et$_3$N, CH$_2$Cl$_2$, 23 °C, 75 %; j) Tf$_2$O (1.1 equiv), CHCl$_3$, 23 °C; TBAT (1.1 equiv), 65 °C, 24 h, 51 %. EDCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, TMS = trimethylsilyl, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, TBAT = tetrabutylammonium triphenyldifluorosilicate.

---

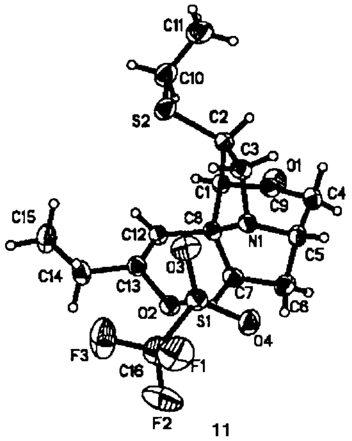
[*] Prof. D. Y. Gin, M. T. Epperson
Department of Chemistry, University of Illinois
Urbana, IL 61801 (USA)
Fax: (+1) 217-244-8024
E-mail: gin@scs.uiuc.edu

[**] This research was supported by generous gifts from Pfizer Inc., Glaxo Wellcome, Merck, Eli Lilly, Abbott, and Johnson & Johnson. Support from the Arnold and Mabel Beckman Foundation (BYI), the Alfred P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation are gratefully acknowledged. M.T.E. thanks the NSF and AstraZeneca for predoctoral fellowships.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

the carboxylic acid functionality within **5** proceeded smoothly and provided the homologous glutamic acid **6**. Coupling of **6** with *N*,*O*-dimethylhydroxylamine in the presence of EDCl afforded the corresponding Weinreb amide in 89 % yield. Subsequent hydrogenolysis of the benzyl carbamate and concomitant spontaneous lactamization led to the formation of the 2-pyrrolidinone intermediate **7**. N-Alkylation of lactam **7** with chloromethyltrimethylsilane, followed by chemoselective thionation with Lawesson's reagent gave thiolactam **8** in 88 % yield. S-Alkylation of **8** with 1-bromo-2-butanone followed by Eschenmoser sulfide contraction afforded the vinylogous amide (*E*)-**9** as a single stereoisomer in 92 % yield. The configuration of the trisubstituted double bond was established through NOE enhancement (9.5 %) of the methylene protons adjacent to the trimethylsilyl group upon irradiation of the vinyl proton. Addition of ethynylmagnesium chloride to the Weinreb amide, followed by hydrolysis and conjugate addition of ethanethiol provided the cycloaddition substrate **10** in 75 % yield as a 6:1 mixture of *E* and *Z* isomers.

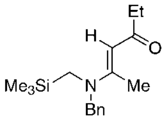
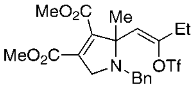
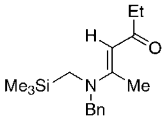
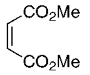
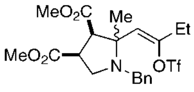
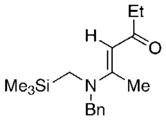
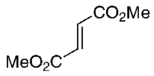
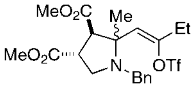
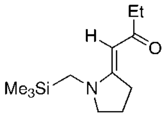
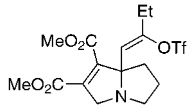
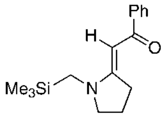
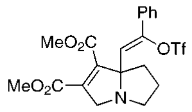
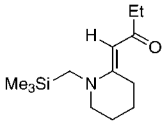
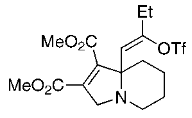
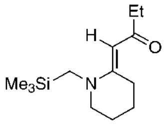
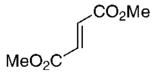
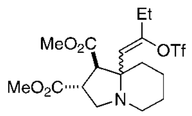
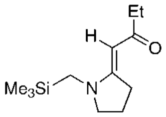
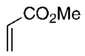
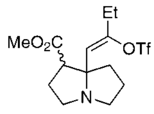
The azomethine ylide intermediate was generated by treatment of **10** with Tf_2O in chloroform at room temperature followed by the addition of TBAT[12] at room temperature. After heating the reaction at 65 °C for 24 h, the bridged pyrrolizidine **11** was isolated in 51 % yield as a single regio- and stereoisomer. The constitution and configuration of **11** were unambiguously established by single-crystal X-ray diffraction (Figure 1). The formation of the *Z* enol triflate is consistent with the initial sulfonylation step, which proceeds via the *s-cis* conformer and ultimately provides the desired precursor to the *E*-1-butenyl substituent in **1**. Moreover, the intramolecular cycloaddition process occurred with complete regiochemical control. When the reaction was carried out in CD_3CN with cesium fluoride (1.1 equiv) as the silicon scavenger and monitored by ^1H NMR spectroscopy, the only product detected was **11**.



11

Figure 1. ORTEP diagram of **11**.

Table 1.

Entry	Substrate	Dipolarophile[a]	Product	Yield	*endo*/*exo*
1		DMAD		68 %	
2				62 %	1:1
3				71 %	1:1
4		DMAD		70 %	
5		DMAD		75 %	
6		DMAD		63 %	
7				63 %	1:1
8				69 %	2.9:1

[a] DMAD = dimethylacetylene dicarboxylate.

Neither the cycloadduct derived from the Z isomer nor the azatricyclo[5.2.1.0^{4,8}]decane regioisomer was observed in the reaction mixture.

The success of the dipolar cycloaddition reaction with a relatively complex substrate **10** to form **11** prompted an investigation into the utility of the sulfonylation of vinylogous amides as azomethine ylide precursors for the synthesis of functionalized *N*-heterocycles in general. Thus, a series of intermolecular cycloadditions were performed with DMAD, dimethyl maleate, or dimethyl fumarate as the dipolarophile and a variety of vinylogous amides to serve as 1,3-dipole precursors. Acyclic vinylogous amides (see Table 1, entries 1–3) undergo the transformation efficiently, generating highly substituted pyrrolidines. As seen in the synthesis of **11**, vinylogous amides derived from 2-pyrrolidinones (Table 1, entries 4 and 5) provide facile access to pyrrolizidines. Furthermore, highly functionalized indolizidines can be prepared from vinylogous amides derived from 2-piperidinones (Table 1, entries 6 and 7).

In summary, the first enantiospecific synthesis of the bridged pyrrolizidine core of asparagamine A has been accomplished. The synthetic approach highlights an intramolecular 1,3-dipolar cycloaddition of an azomethine ylide derived from the sulfonylation of a vinylogous amide. This strategy allows concomitant installation of the angular *E*-1-butenyl side chain during the assembly of the azatricyclo[5.3.0.0^{4,8}]decane skeleton of **1**. The use of vinylogous amides in this capacity can be extended to the preparation of a variety of highly functionalized pyrrolidines, pyrrolizidines, and indolizidines.

Received: February 7, 2002 [Z18668]

---

[1] T. Sekine, N. Fukasawa, Y. Kashiwagi, N. Ruangrungsi, I. Murakoshi, *Chem. Pharm. Bull.* **1994**, *42*, 1360–1362.

[2] H. Irie, N. Masaki, K. Ohno, K. Osaki, T. Taga, S. Uyeo, *J. Chem. Soc. Chem. Commun.* **1970**, 1066.

[3] For racemic syntheses of the pyrrolizidine core of stemofoline, see: a) R. L. Beddoes, M. P. H. Davies, E. J. Thomas, *J. Chem. Soc. Chem. Commun.* **1992**, 538–540; b) T. Kercher, T. Livinghouse, *J. Am. Chem. Soc.* **1996**, *118*, 4200–4201; for a synthesis of (±)-isostemofoline, see: c) A. S. Kende, T. L., Smalley, Jr., H. Huang, *J. Am. Chem. Soc.* **1999**, *121*, 7431–7432.

[4] a) S. Tip-Pyang, P. Tangpraprutgul, N. Wiboonpun, G. Veerachato, P. Phuwapraisirisan, B. Sup-Udompol, *ACGC Chem. Res. Commun.* **2000**, *12*, 31–35; b) T. Sekine, F. Ikegami, N. Fukasawa, Y. Kashiwagi, T. Aizawa, Y. Fujii, N. Ruangrungsi, I. Murakoshi, *J. Chem. Soc. Perkin Trans. 1* **1995**, 391–393.

[5] a) P. D. Williams, D. J. Pettibone, *Curr. Pharm. Des.* **1996**, *2*, 41–58; b) T. M. Goodwin, A. Zograbyan, *Clin. Perinatol.* **1998**, *25*, 859–871.

[6] The absolute configuration of **1** has not been established.

[7] Reviews: a) J. W. Lown in *1,3-Dipolar Cycloaddition Chemistry*, *Vol. 1* (Ed.: A. Padwa), Wiley, New York, **1984**, p 663; b) E. Vedejs, F. G. West, *Chem. Rev.* **1986**, *86*, 941–955; c) Y. Terao, M. Aono, K. Achiwa, *Heterocycles* **1988**, *27*, 981–1008; d) R. Grigg, *Chem. Soc. Rev.* **1987**, *16*, 89–121; e) K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863–909; f) O. Tsuge, S. Kanemasa, *Adv. Heterocycl. Chem.* **1989**, *45*, 231–349; g) E. Vedejs in *Advances in Cycloaddition*, *Vol. 1* (Ed.: D. P. Curran), JAI, Greenwich, **1988**, pp. 33–51; h) A. Padwa in *Comprehensive Organic Synthesis*, *Vol. 4*, (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 1069–1109; i) P. A. Wade in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 1111–1168; for related 2-azaallylanion cycloadditions, see: j) W. H. Pearson, Y. Mi, I. Y. Lee, P. Stoy, *J. Am. Chem. Soc.* **2001**, *123*, 6724–6725, and references therein.

[8] For a recent review on the activation of amides and vinylogous amides with triflic anhydride, see: a) I. L. Baraznenok, V. G. Nenajdenko, E. S. Balenkova, *Tetrahedron* **2000**, *56*, 3077—3119, and references therein; for the activation of *O*-silylhydroxamic acids with triflic anhydride to generate nitrile oxides, see: b) D. Muri, J. W. Bode, E. M. Carreira, *Org. Lett.* **2000**, *2*, 539–541.

[9] For an example of the generation of azomethine ylides from the N-alkylation of vinylogous imidates, see: A. Padwa, G. Haffmanns, M. Tomas, *Tetrahedron Lett.* **1983**, *24*, 4303–4306.

[10] For the use of amides and thioamides as azomethine ylide precursors, see: a) E. Vedejs, G. R. Martinez, *J. Am. Chem. Soc.* **1980**, *102*, 7993–7994; b) F. G. West, E. Vedejs, *J. Org. Chem.* **1983**, *48*, 4773–4774, and references therein.

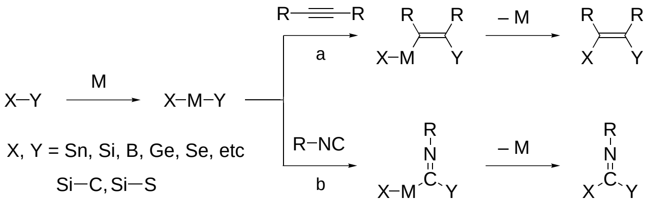
[11] a) X. Feng, E. D. Edstrom, *Tetrahedron: Asymmetry* **1999**, *10*, 99–105; b) commercially available from Bachem.

[12] A. S. Pilcher, H. L. Ammon, P. DeShong, *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167.

Cyanamide Synthesis by the Palladium-Catalyzed Cleavage of a Si–N Bond[**]

Shin Kamijo, Tienan Jin, and Yoshinori Yamamoto[*]

Studies on the transition-metal-catalyzed reaction of main-group-element–element bonds with unsaturated bonds have spread widely and extensively because of the synthetic utilities of the resulting products.[1] Various element–element bonds (X–Y) add to unsaturated C–C bonds, such as alkynes, 1,3-dienes, and allenes, in the presence of a transition-metal catalyst (route a in Scheme 1, vicinal addition). Among the bismetallic compounds, perhaps the most well-studied



Scheme 1. Transition-metal-catalyzed addition of X–Y bonds to unsaturated bonds.

---

[*] Prof. Dr. Y. Yamamoto, S. Kamijo, T. Jin
Department of Chemistry
Graduate School of Science, Tohoku University
Sendai 980-8578 (Japan)
Fax: (+81) 22-217-6784
E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp

[**] We thank collaborators at the Instrumental Analysis Center, Department of Chemistry at Tohoku University, for measurements of mass spectra and elemental analyses. S.K. is also thankful for a fellowship from the Japan Society of Promotion of Science for Young Scientists.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.