

Synthesis of Pyrrolo-isoquinolines Related to the Lamellarins Using Silver-Catalyzed Cycloisomerization/Dipolar Cycloaddition

Shun Su and John A. Porco, Jr.*

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU),
Boston University, Boston, Massachusetts 02215

Received April 19, 2007; E-mail: porco@bu.edu

The lamellarin alkaloids are a family of novel marine natural products containing a highly substituted pyrrolo-isoquinoline core.¹ Lamellarin D **1** (Figure 1a) is a potent inhibitor of human topoisomerase I² and was recently shown to act on mitochondria to induce apoptosis.³ Another member of the family, lamellarin α -20-sulfate **2**, displays selective inhibition against HIV-1 integrase in vitro.^{4,5} We have considered development of methodology for rapid access to angular, pyrrolo-isoquinoline core structures⁶ related to the lamellarins⁷ using variants of the cycloisomerization of alkynyl imines⁸ involving dipolar cycloaddition of derived azomethine ylides.⁹ In this approach, treatment of alkynyl imines **3** with alkynophilic metal catalysts should afford azomethine ylides **4** which may undergo dipolar cycloaddition in the presence of dipolarophiles. Subsequent aromatization may lead to the formation of pyrrole frameworks **5** (Figure 1b).

To identify suitable conditions for the proposed metal-catalyzed domino cycloisomerization/dipolar-cycloaddition process, reaction screening¹⁰ involving alkynyl *N*-benzylidene glycinate **6**, dimethyl acetylene dicarboxylate (DMAD) **7**, and a series of alkynophilic metals was carried out in DCE using DIEA as base (50 °C).¹¹ Fortunately, a number of catalysts including the Au, Ag, and Cu salts shown in Figure 2 and Pd(OAc)₂ were able to facilitate the transformation. AgOTf and AgSbF₆ provided the best results in comparison to other metals investigated and were effective in catalytic quantities (10 mol %). Control experiments in the absence of metal salts led to decomposition ruling out the possibility of spontaneous formation of **8** under thermal conditions.¹²

To improve the efficiency of the cycloisomerization/dipolar-cycloaddition process, further optimization was carried out using imine **6**, DMAD **7**, and AgOTf (10 mol %). Parameters including solvents, bases, reaction temperature, and inclusion of external oxidants (e.g., DDQ, MnO₂) were investigated. Reactions conducted at 60 °C under ambient conditions in toluene using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base in the absence of oxidants afforded optimal results. Using this condition, select dipolarophiles were reacted with a number of alkynyl imines to generate diverse pyrrolo-isoquinolinone structures **8** and **24–37** (Table 1). Silver-mediated pyrrolo-isoquinoline formation was found to be workable with ortho alkynyl imines **9–17** bearing aryl, cyclopropane, propargyl ether, trimethylsilyl, terminal alkyne, and enyne functionality, as well as substrates with electron withdrawing and donating substituents on the aromatic backbone (entries 2, 5, and 7–9). In addition to DMAD, alkynes **19–23** were also investigated to provide lamellarin-type structures with unsymmetrical substituents on the pyrrolo-isoquinoline core. Reactions involving alkynes **19–23** typically afforded the desired products with lower yield compared to those using DMAD owing to diminished reactivity. The addition of Lewis acids¹³ to further activate the dipolarophiles led to only marginal improvement in reaction yields. Cycloisomerization/dipolar-cycloaddition was generally found to be highly

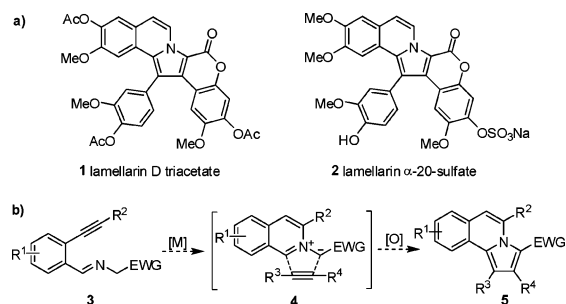


Figure 1.

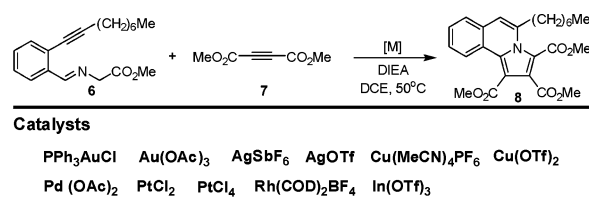


Figure 2. Reaction screening.

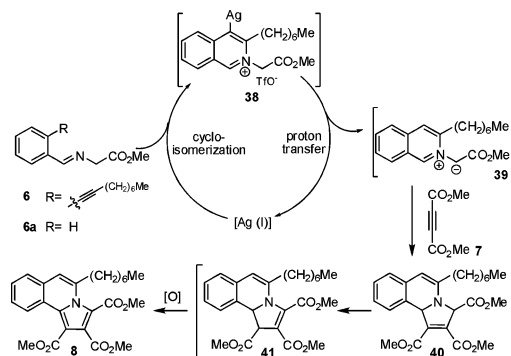


Figure 3. Proposed reaction pathway.

regioselective, providing **33–34** and **36–37** as single regioisomers.¹¹ However, reaction involving alkynoate **21** produced **35** as a 1.3:1 mixture of regioisomers¹⁴ and a desilylation product derived from **37** was observed when using alkyne **23** as dipolarophile. Thus far, alkynes lacking electron withdrawing groups have not been workable as dipolarophiles.

To probe possible reaction pathways for the cycloisomerization/dipolar-cycloaddition, we conducted a series of NMR experiments. Treatment of substrate **6** with AgOTf, DMAD, and DTBMP (toluene-*d*₈, room temperature, 6 min) afforded dihydropyrrole **41**, presumably via dihydropyrrole **40** (Figure 3). The structure of intermediate **41** was determined by extensive 2-D NMR experiments.^{11,15} Subsequent thermolysis of a solution of **41** at 60 °C under aerobic conditions led to the formation of **8**. Additional experiments were conducted to rule out a dipolar-cycloaddition/

Table 1. Reaction Scope^a

entry	R	R ¹ , R ²	R ³ , R ⁴	product	yield(%) ^{a,b}
1		H, H	MeO ₂ C, CO ₂ Me		72
2		H, F	MeO ₂ C, CO ₂ Me		59
3		H, H	EtO ₂ C, CO ₂ Et		83
4		H, H	MeO ₂ C, CO ₂ Me		78
5		OMe, OMe	MeO ₂ C, CO ₂ Me		78
6		H, H	MeO ₂ C, CO ₂ Me		63
7		OCH ₂ O	MeO ₂ C, CO ₂ Me		68
8		OMe, OMe	MeO ₂ C, CO ₂ Me		70
9		OMe, OMe	MeO ₂ C, CO ₂ Me		42
10		H, H	MeO ₂ C, CO ₂ Me		29
11		H, H	OHC, C ₆ H ₅		46
12		H, H	MeOC, Ph		56
13		H, H	MeO ₂ C, Ph		57 ^c
14		H, H	MeO ₂ C, H		52
15		H, H	EtO ₂ C, SiMe ₃		28 ^{c,d}

^a Yields based on the corresponding alkynyl benzylaldehydes.¹¹ ^b R⁵ = Me, for entries 7 and 10, R⁵ = ^tBu. ^c Yb(OTf)₃ (5 mol %) was added. ^d 16% of a desilylation product was also isolated.

cycloisomerization pathway. Reaction of *des*-alkyne substrate **6a** under conditions employed for formation of **8** led to recovered starting material. In the absence of DMAD, treatment of **6** with AgOTf and DTBMP (toluene-*d*₈, room temperature) led to the formation of a complex mixture by ¹H NMR analysis. Mass spectrograph analysis¹¹ of the mixture indicated the presence of **39** and the corresponding dimer.^{11,16} Subsequent addition of DMAD

also led to the formation of **41**. The available mechanistic data supports initial cycloisomerization of **6** to isoquinolinium species **38**.^{8e} Subsequent proton transfer and regeneration of Ag(I) affords azomethine ylide **39**, which may be followed by dipolar cycloaddition to dihydropyrrole **40**. Isomerization and final oxidation affords pyrrolo-isoquinoline **8**.

In summary, we have developed an efficient synthesis of pyrrolo-isoquinolines related to the lamellarin natural products involving domino cycloisomerization/dipolar-cycloaddition of readily available alkynyl *N*-benzylidene glycinate. Mechanistic studies revealed Ag(I)-catalyzed cycloisomerization to an azomethine ylide as a key step for formation of pyrrolo-isoquinoline structures. Further studies, including applications toward the syntheses of the lamellarin alkaloids, are currently in progress and will be reported in due course.

Acknowledgment. Financial support from the NIH-NIGMS CMLD initiative (Grant P50 GM067041) and Merck Research Laboratories is gratefully acknowledged. We thank Dr. Emil Lobkovsky (Cornell University) for X-ray crystal structure analyses and Dr. Aaron B. Beeler and Ms. Ji Qi (Boston University) for experimental assistance.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Bailly, C. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 363.
- Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796.
- Kluz, J.; Gallego, M.-A.; Loyens, A.; Beauvillain, J.-C.; Fernandez, Sousa-Faro, J.-M.; Cuevas, C.; Marchetti, P.; Bailly, C. *Cancer Res.* **2006**, *66*, 3177.
- Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901.
- Aubry, A.; Pan, X.-S.; Fisher, L. M.; Jarlier, V.; Cambau, E. *Antimicro. Agents Chemother.* **2004**, *48*, 1281.
- For the synthesis of pyrrolo-isoquinolines, see: (a) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (b) Yavari, I.; Sabbaghan, M.; Hossaini, Z. *Syn. Lett.* **2006**, 2501. (c) Kobayashi, M.; Tanabe, M.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 1469.
- Synthetic studies: (a) Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259. (b) Handy, S. T.; Zhang, Y.; Bregman, H. J. *Org. Chem.* **2004**, *69*, 2346. (c) Handy, S. T.; Zhang, Y. *Org. Prep. Proc. Int.* **2005**, *37*, 411. (d) Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Alvarez, M. J. *Org. Chem.* **2005**, *70*, 8231. (e) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440.
- (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920. (c) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Syn. Lett.* **2003**, 2265. (d) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339. (e) Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (f) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822.
- For metal-mediated azomethine ylide formation/dipolar cycloaddition, see: (a) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *114*, 593. For recent reviews on azomethine ylide cycloaddition, see: (b) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (c) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. For cycloadditions of metal-containing azomethine ylides from alkynyl imines, see: (d) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592. (e) Takaya, J.; Kusama, H.; Iwasawa, N. *Chem. Lett.* **2004**, 33, 16.
- Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413.
- See Supporting Information for complete experimental details.
- Asao, N.; Iso, K.; Yudha, S. *Org. Lett.* **2006**, *8*, 4149.
- See for example: Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836.
- Matsumoto, K.; Uchida, T.; Konishi, H.; Watanabe, Y.; Aoyama, K.; Asahi, M. *Chem. Lett.* **1987**, 807.
- For dihydropyrroles resembling compound **41**, see: Bacu, E.; Samson-Belei, D.; Nowogrocki, G.; Couture, A.; Grandclaudon, P. *Org. Biomol. Chem.* **2003**, *1*, 2377.
- (a) Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Heterocycles* **1989**, *29*, 57. (b) Gandasegui, M. T.; Alvarez-Builla, J.; Florencio, F. *Heterocycles* **1994**, *37*, 174.

JA072737V