ORGANIC LETTERS

2011
Vol. 13, No. 18
4766–4769

Discovery of Hypoiodite-Mediated Aminyl Radical Cyclization Lacking a Nitrogen Radical-Stabilizing Group: Application to Synthesis of an Oxazaspiroketal-Containing Cephalostatin Analog

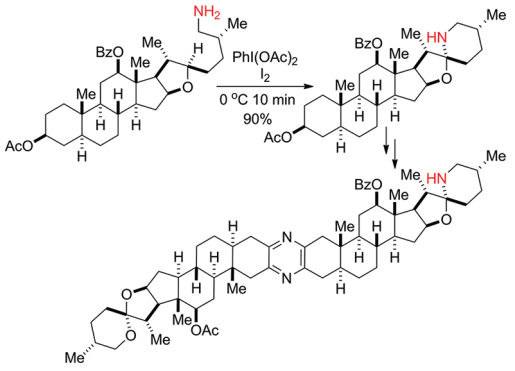
Myong Koag and Seongmin Lee*

The Division of Medicinal Chemistry, College of Pharmacy, University of Texas at Austin, Texas 78712, United States

SeongminLee@mail.utexas.edu

Received June 24, 2011

ABSTRACT



Synthesis of an oxazaspiroketal-containing bissteroidal pyrazine is described. The key transformation of this synthesis involves stereoselective formation of oxazaspiroketal via aminyl-radical cyclization of primary amine lacking a radical-stabilizing group by Suárez hypoiodite oxidation.

The cephalostatin/ritterazine[1] family is composed of 45 members of antineoplastic bissteroidal-pyrazine natural products, many of them (e.g., cephalostatin 1 **1**) displaying extreme antiproliferative activities with nanomolar cytotoxicity against the NCI 60-cancer cell line panel.[2] Currently, the mode of action of these anticancer agents is largely unknown. The fingerprint of cephalostatin bioactivities in the 60-tumor panel is quite different from those of known antitumor agents, potentially indicating a new mode of action. Semiempirical calculations[3] for rationalizing the SAR of natural cephalostatins/ritterazines and their analogues[4] show a strong correlation between bioactivity and enthalpy of oxacarbenium ion formation, implicating a potential role for the cephalostatins' spiroketal

(1) (a) Pettit, G. R.; Inoue, M.; Herald, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006. (b) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L. *J. Chem. Soc. Chem. Commun.* **1988**, 1440. (c) Pettit, G. R.; Xu, J. P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2027. (d) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1994**, *59*, 6164. (e) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484. (f) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484. (g) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *Tetrahedron* **1995**, *51*, 6707. (h) Flessner, T.; Jautelat, R.; Scholz, U.; Winterfeldt, E. *Prog. Chem. Org. Nat. Prod.* **2004**, *87*, 1. (i) Moser, B. R. *J. Nat. Prod.* **2008**, *71*, 487. (j) Lee, S.; LaCour, T. G.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2275.

(2) Full NCI-60 results for cephalostatins 1–9 (NSC# 363979–81, 378727–36) are on the Web at http://dtp.nci.nih.gov.

(3) LaCour, T. G. Ph.D. Thesis, Purdue University, 2001.

(4) (a) Jeong, J. U.; Sutton, S. C.; Kim, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 10157. (b) Guo, C.; Bhandaru, S.; Fuchs, P. L.; Boyd, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10672. (c) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692. (d) Lee, J. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2005**, *127*, 13122. (e) Phillips, S. T.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6589.

10.1021/ol2017033
Published on Web 08/12/2011

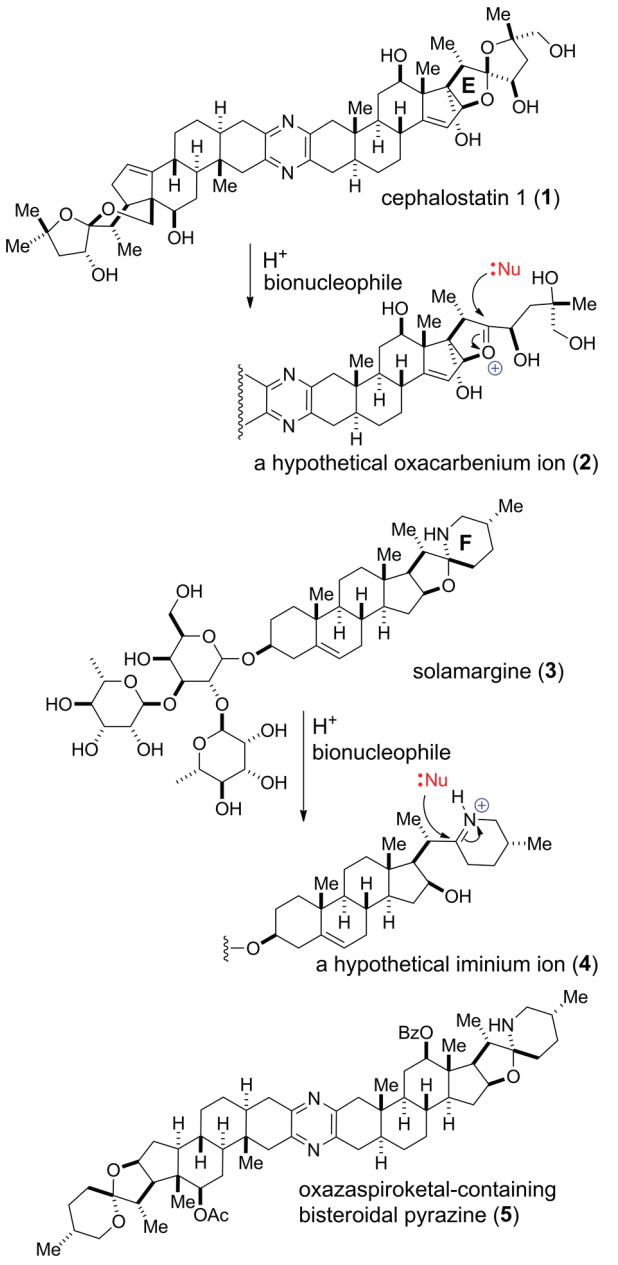
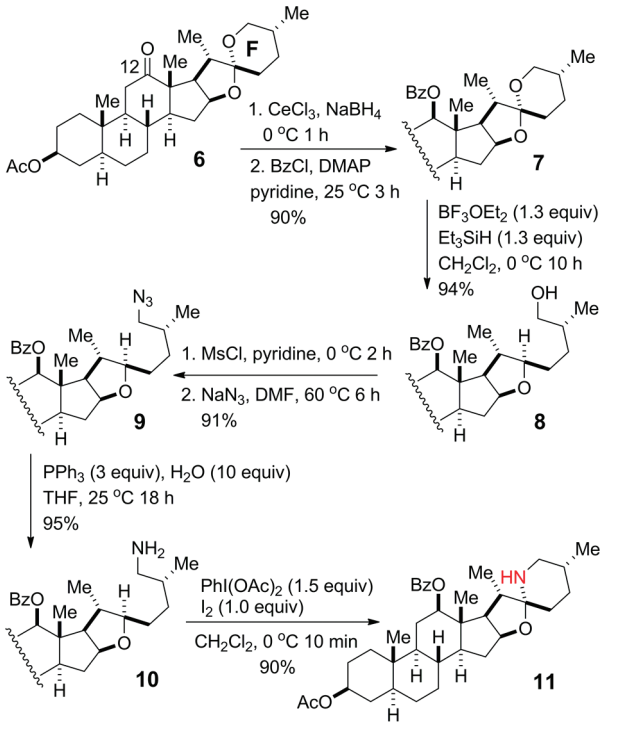


Figure 1. Steroidal alkaloids. Cephalostatin 1 (**1**) and solamargine (**2**) as potential alkylating agents.

moiety as a latent precursor of oxacarbenium ion (e.g., E-ring oxacarbenium ion **2**), which can react with bionucleophiles (e.g., DNA) to exert their bioactivities (Figure 1). Solamargine[5] **3** is a steroidal alkaloid glucoside that has shown to be highly effective at treating skin cancers with exceptional selectivity. The mechanism of action of solamargine **3** is poorly understood. Solasodine, the aglycon of solamargine **3**, has shown significant antitumor and DNA alkylating activities, and *N*-acetylation of oxazaspiro moiety in solasodine led to loss of bioactivity,[6] implying a role for solamargine's oxazaspiro moiety as a latent precursor of spiroaminal-derived iminium ion **4**. In our continuing efforts to discover potent cephalostatin analogues,[7] we wanted to prepare steroidal pyrazins bearing both oxazaspiro and dioxospiro moieties. Syntheses of solamargine-related compounds were accomplished using steroidal cyclic enolethers[8] and hemiacetal,[9] but oxazaspiroketal-containing bisteroidal pyrazine has not been reported. Herein, we report the first synthesis of an oxazaspiroketal-containing cephalostatin analog, where aminyl radical cyclization of primary amine lacking a radical-stabilizing group is employed as a key reaction.

Our synthesis of cephalostatin analog **5** started with the conversion of readily available hecogenin acetate **6** into C12 benzoate **7** via Luche reduction of C12 ketone followed by benzoylation of the corresponding C12 alcohol. The action of triethylsilane and borontrifluoride-etherate on the spiroketal **7** opened the F-ring stereoselectively to give a primary alcohol **8**, which was then converted into steroidal azide **9** by mesylation followed by azide formation. The Staudinger reduction of azide **9** produced a primary amine **10**, which set the stage for a crucial aminyl radical cyclization (Scheme 1).

Scheme 1. Synthesis of Steroidal Oxazaspiroketal **10**



With a primary alkyl amine **10** in hand, we explored formation of 5/6 oxazaspiroketal **11** via intramolecular

(5) (a) Cham, B. E.; Daunter, B. *Cancer Lett.* **1990**, *55*, 221. (b) Cham, B. E.; Meares, H. M. *Cancer Lett.* **1987**, *36*, 111. (c) Liu, L. F.; Liang, C. H.; Shiu, L. Y.; Lin, W. L.; Lin, C. C.; Kuo, K. W. *FEBS Lett.* **2004**, *577*, 67. (d) Cherney, E. C.; Baran, P. S. *Isr. J. Chem.* **2011**, *51*, 391. (e) Rahman, A.; Choudhary, M. I. *Nat. Prod. Rep.* **1999**, *16*, 619.

hydrogen abstraction of a nitrogen-centered radical. When steroidal alkyl amine **10**, which does not have a radical-stabilizing group, was subjected to Suárez hypoiodite oxidation[10] in the presence of iodobenzene diacetate and iodine, aminyl radical cyclization occurred smoothly (0 °C, 10 min, 90%) to afford the desired cyclization product **11** in a regio- and stereoselective fashion. Such a facile cyclization was quite surprising because hypoiodite-mediated aminyl radical cyclizations typically involve nitrogen radical-stabilizing groups,[11] such as cyanamide, amide, nitroamine, phosphoro amidate, and sulfonamide groups, to make the radicals more reactive toward hydrogen abstraction. The closest example to our study was establishment of 5/6 and 5/5 spiro moieties using an amide.[12] Therefore, our cyclization reaction would be among the first, if not the first, example of hypoiodite-mediated aminyl radical cyclization that does not utilize nitrogen radical stabilization. The THF moiety, which can stabilize carbon radical generated by transposition of nitrogen radical, appears to play a crucial role in the cyclization of nonstabilized nitrogen radical. Indeed, alkyl amines, such as octyl amine and isoamyl amine, that do not have carbon-radical stabilizing moiety did not undergo cyclization. This suggests that when a carbon radical-stabilizing group is positioned properly, hypoiodite-mediated radical cyclization can occur without amine modification, which is often cumbersome to install and remove.

Our attempts to capture or monitor reaction intermediates of the cyclization failed. A potential reaction mechanism for radical cyclization of primary amine **10** is shown in Figure 2. Action of iodobenzene diacetate and iodine on alkyl amine **10** produces *N*-iodoamine **12**, which generates nitrogen-centered radical **13**. 1,6-Transposition of the radical center from nitrogen to carbon by intramolecular hydrogen abstraction gives a carbon radical **14**, which is stabilized by adjacent oxygen atom through resonance. The carbon radical **14** reacts with iodine radical to form iodocyclic ether **15**. Oxygen atom-assisted removal of iodide produces oxacarbenium ion **16**, which is then quenched by the adjacent amine group to afford oxazaspiroketal **11**.

Having successfully prepared steroidal oxazaspiroketal **11**, we next investigated synthesis of bissteroidal pyrazine **21**. Removal of the C3 acetate group of

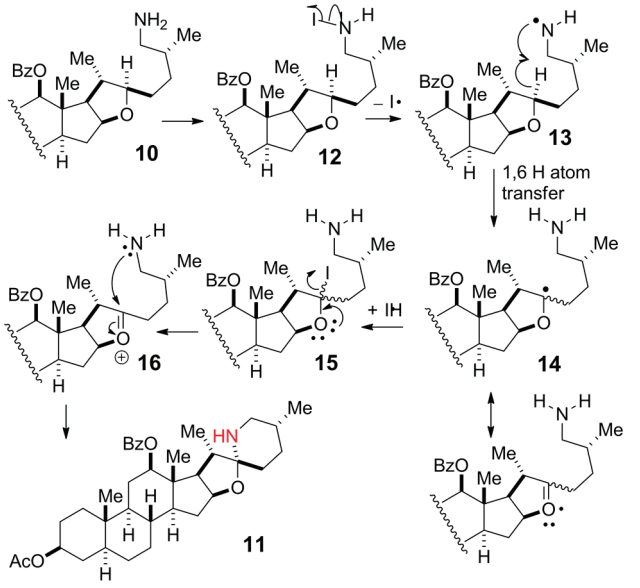
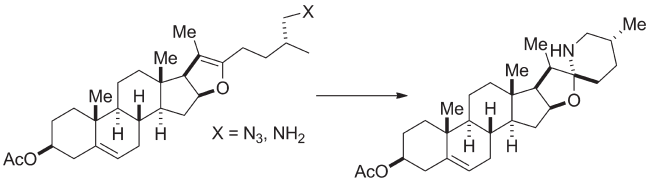


Figure 2. Proposed mechanism for oxazasprioketal formation via aminyl radical cyclization of alkylamine **10**.

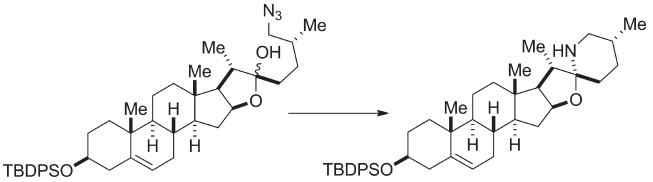
(6) Kim, Y. C.; Che, Q. -M; Gunatilaka, A. A. L.; Kingston, D. G. I. *J. Nat. Prod.* **1996**, *59*, 283.

(7) (a) Lee, S.; LaCour, T. G.; Lantrip, D.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 313. (b) Lee, S.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 317. (c) Lee, S.; Fuchs, P. L. *Org. Lett.* **2004**, *6*, 1437. (d) Lee, S.; Fuchs, P. L. *Org. Lett.* **2009**, *11*, 5.

(8) (a) Uhle, F. C. *J. Am. Chem. Soc.* **1953**, *75*, 2280. (b) Uhle, F. C. *J. Am. Chem. Soc.* **1961**, *83*, 1460. (c) Zha, X.; Sun, H.; Zhang, Y. *Chem. Biodiversity* **2007**, *4*, 25.



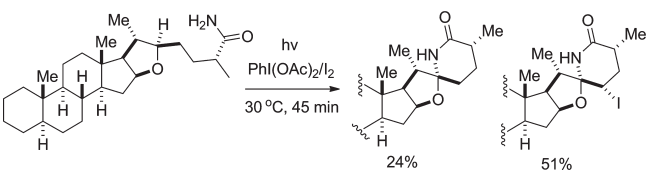
(9) Wei, G.; Wang, J.; Du, Y. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2930.



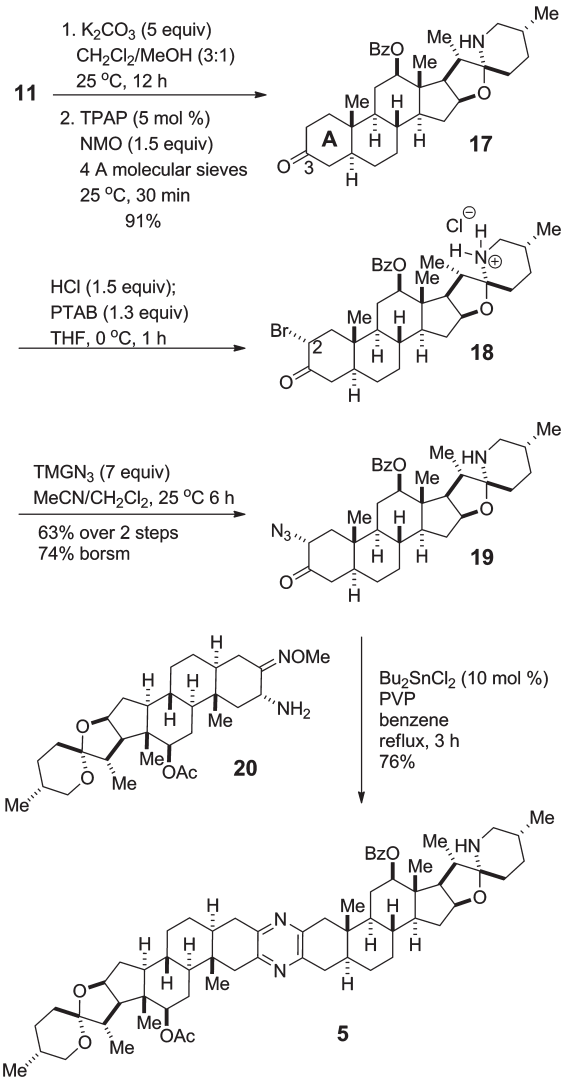
(10) (a) Meystre, C.; Heusler, K.; Kalvoda, J.; Wieland, P.; Anner, G.; Wettstein, A. *Helv. Chim. Acta* **1962**, *45*, 1317. (b) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117. (c) Hernandez, R.; Velazquez, S. M.; Suárez, E.; Rodriguez, M. S. *J. Org. Chem.* **1994**, *59*, 6395. (d) Betancor, C.; Freire, R.; Pérez-Martín, I.; Suárez, E. *Org. Lett.* **2002**, *4*, 1295. (e) Francisco, C. G.; Freire, R.; Herrera, A. J.; Martín, I. P.; Suárez, E. *Org. Lett.* **2002**, *4*, 1959–3337. (f) Lee, J. S.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2247.

(11) (a) Neale, R. S. *Synthesis* **1971**, 1. (b) Baldwin, S. W.; Doll, R. J. *Tetrahedron Lett.* **1979**, *20*, 3275. (c) Betancor, C.; Concepción, J. I.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1983**, *48*, 4430. (d) Armas, P.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Perkin Trans I* **1988**, 3255. (e) Carrau, R.; Hernández, R.; Suárez, E.; Betancor, C. *J. Chem. Soc., Perkin Trans I* **1987**, 937. (f) Dorta, R. L.; Francisco, C. G.; Suárez, E. *J. Chem. Soc., Chem. Comm.* **1989**, 1168. (g) Martín, A.; Pérez-Martín, I.; Suárez, E. *Org. Lett.* **2005**, *7*, 2027. Phosphoroamidate: (h) Armas, P.; Carrau, R.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1985**, *26*, 2493. (i) Togo., H.; Hoshina, Y.; Muraki, T.; Nakayma, H.; Yokoyama, M. *J. Org. Chem.* **1998**, *63*, 5193. (j) Nikishin, G. I.; Troyansky, F.; Lazareva, M. I. *Tetrahedron Lett.* **1985**, *26*, 1877. (k) Francisco, C. G.; Herrera, A. J.; Suárez, E. *J. Org. Chem.* **2003**, *68*, 1012.

(12) Hernández, R.; Medina, M. C.; Suárez, E. *Tetrahedron Lett.* **1987**, *28*, 2533.



Scheme 2. Synthesis of Bissteroidal Pyrazine **5**



oxazaspiroketal **11** followed by peruthenate oxidation of the corresponding alcohol produced C3 ketone **17** in 91% yield. Installation of bromine in the C2 position of ketone **17** turned out to be problematic. Bromination trials with phenyltrimethyl ammonium tribromide (PTAB) and other brominating agents generated mixtures of multiple unknown compounds. After many experiments, we found that protection of the secondary amine with hydrochloride prior to PTAB addition solved a such problem and provided α bromoketone **18**, which was then treated with tetramethylguanidium azide ($TMGN_3$) to give α azidoketone **19** in 63% over two steps. Lastly, under the conditions of the Guo-Fuchs unsymmetrical pyrazine coupling,[13] azidoketone **19** reacted smoothly with an aminomethoxime **20** prepared also from hecogenin acetate to yield the target bis-steroidal pyrazine **5** in 76% yield (Scheme 2).

In summary, our synthesis of oxazaspiroketal-containing steroidal pyrazine was accomplished in 12 steps and 28% overall yield starting from hecogenin acetate, where aminyl radical cyclization of primary amine established the requisite oxazaspirketal moiety. Currently, we are applying this modified Suárez cyclization to other substrates with functional groups that can stabilize transposed carbon radicals, and the results will be reported in due course.

Acknowledgment. The research was supported by the Robert A. Welch Foundation (Grant No. F-1741). We are grateful to Begoña Stevenson (Department of Chemistry and Biochemistry, The University of Texas at Austin), Charisse Crenshaw (Salk Institute), and Daniel Jamieson (Department of Chemistry, Purdue University) for helping with the manuscript preparation.

Supporting Information Available. Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) (a) Guo, C.; Bhandaru, S.; Fuchs, P. L.; Boyd., M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10672. (b) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692. (c) Li, W.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 4548.