ORGANIC LETTERS

2008
Vol. 10, No. 2
197−199

Total Synthesis of (±)-Stemonamide and (±)-Isostemonamide Using a Radical Cascade

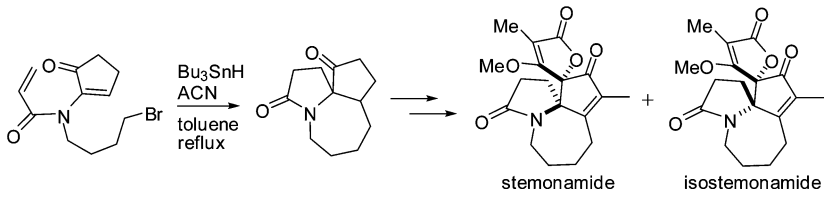
Tsuyoshi Taniguchi,[†] Genzo Tanabe,[‡] Osamu Muraoka,[‡] and Hiroyuki Ishibashi*,[†]

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan, and Faculty of Pharmaceutical Sciences, Kinki University, Higashi-osaka, Osaka 577-0818, Japan

isibasi@p.kanazawa-u.ac.jp

Received October 22, 2007

ABSTRACT



Total synthesis of stemonamide and isostemonamide is described. The concise construction of the tricyclic core of these alkaloids was achieved by radical cascade involving 7-*endo* and 5-*endo* cyclizations.

Stemona alkaloids such as stemonamide (**1**), isostemonamide (**2**), stemonamine (**3**), and isostemonamine (**4**) isolated from the roots of *Stemona japonica* that are used in Chinese and Japanese folk medicine as cough medicines and insecticides[1,2] provide attractive target molecules for total synthesis (Figure 1). These alkaloids have a complex tetracyclic structure containing two contiguous spirocyclic quaternary centers. Only one example was reported for the synthesis of (±)-**1** and (±)-**2**, which consisted of constuction of a seven-membered ring as a final step.[3] Herein, we describe a concise total synthesis of (±)-**1** and (±)-**2** using a radical cascade as a key step.[4]

Scheme 1 shows the retrosynthetic analysis of (±)-stemonamide (**1**). We envisioned that compound (±)-**1** could be synthesized by chemical transformation of the carbonyl group of cyclopentanone of the tricyclic skeleton **5**. Compound **5** may be obtained by a Bu_3SnH-mediated radical cascade of **7** that involves 7-*endo-trig* cyclization of alkyl radical and a subsequent 5-*endo-trig* cyclization of the resulting α-amidoyl radical **6**.[5]

Synthesis of **7** was begun by condensation of 1,2-cyclopentanedione[6] and 4-(*tert*-butyldimethylsiloxy)butylamine[7]

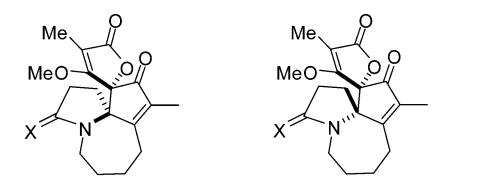


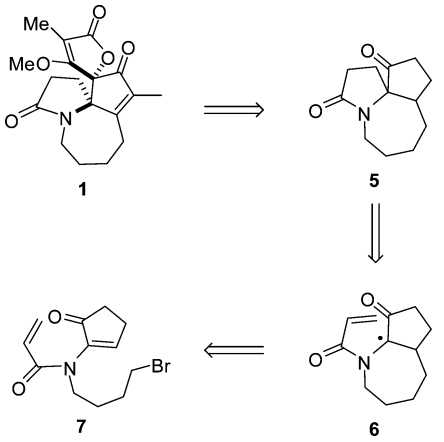
Figure 1. Stemonamide and related alkaloids.

[†] Kanazawa University.
[‡] Kinki University.

(1) Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep*. **2000**, *17*, 117.
(2) (a) Iizuka, H.; Irie, H.; Masaki, N.; Osaki, K.; Ueno, S. *J. Chem. Soc., Chem. Commun.* **1973**, 125. (b) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* **1994**, *57*, 665.
(3) (a) Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505. (b) Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61.
(4) For reviews on radical cascades, see: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224. (b) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215.

10.1021/ol702563p CCC: $40.75
Published on Web 12/20/2007

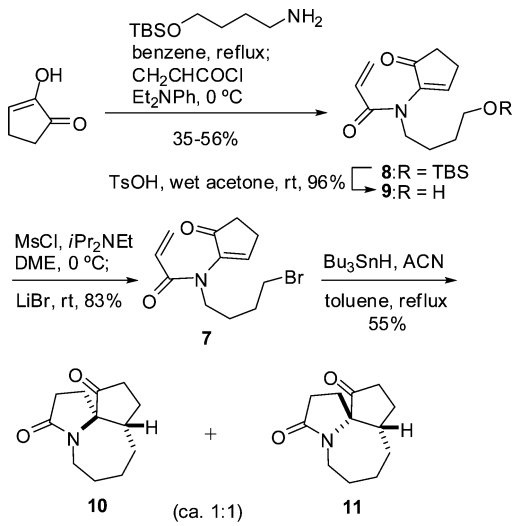
Scheme 1. Synthetic Strategy



followed by acylation of the resulting imine with acryloyl chloride in the presence of *N*,*N*-diethylaniline to give enamide **8**. After removal of the TBS group of **8**, mesylation of alcohol **9**, followed by bromination with lithium bromide, afforded the radical precursor **7**.

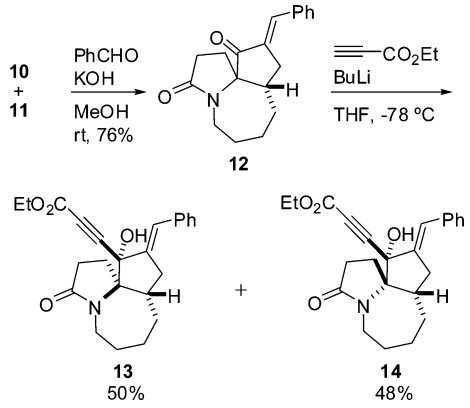
When a boiling solution of enamide **7** in toluene was treated with Bu_3SnH in the presence of 1,1′-azobis-cyclohexanecarbonitrile (ACN), a mixture of almost equal amounts of tricyclic compound **10** and its stereoisomer **11**, was obtained in 55% total yield (Scheme 2). The mixture of

Scheme 2



compounds **10** and **11** was converted to the mixture of α,*β*-unsaturated ketones **12** by aldol condensation with benzaldehyde (Scheme 3). A subsequent addition reaction of **12** with lithium ethyl propiolate afforded the adducts **13** and **14** in 50% and 48% yields, respectively. X-ray crystallographic analysis of **13** and **14** confirmed their structures, indicating that the phenyl groups of the mixture **12** have stereochemistries as depicted in Scheme 3. Treatment of the adducts **13** and **14** with magnesium methoxide in boiling MeOH[8] afforded methyl tetronates **15** and **18** in 85% and 75% yields, respectively (Scheme 4). Several attempts to introduce the methyl group to compound **15** (e.g., LDA then MeI) failed, but iodination compound **16** afforded methyl tetronate derivative **17** in high yield (Scheme 4).[9]

Scheme 3



Similar iodination of compound **18** with bis(trimethylpyridine)iodonium hexafluorophosphate/TfOH[10] followed by Suzuki−Miyaura coupling of the resulting compound **19** afforded compound **20** (Scheme 4).

Oxidative cleavage of alkenes **17** and **20** with OsO_4−$NaIO_4$ afforded ketones **21** and **23** in 88% and 62% yields, respectively (Scheme 5). α-Methylenation of ketone **21** with Eschenmoser's salt[11] in the presence of the various bases afforded the unsaturated ketone **22** in poor yield. Similar α-methylenation using paraformaldehyde/*N*-methylanilinium trifluoroacetate[12] also gave an unsatisfactory result. Fortunately, treatment of ketone **21** with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent)[13] followed by reduction of the resulting enaminone with DIBAL[14] and alkylation by MeI afforded α-methylenation ketones **22** in 67% yield. Similarly, compound **23** was converted to **24** in 74% yield. Finally, $RhCl_3$-mediated isomerization of the double bond[15] of *exo*-methylene ketone **22** furnished (±)-stemonamide (**1**)

(5) We previously reported the synthesis of a cephalotaxine skeleton by 7-*endo*-selective cyclization of aryl radical onto enamides followed by 5-endo cyclization of the resulting α-amidoyl radical, see: Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922. See also references cited therein.

(6) Tomari, K.; Machiya, K.; Ichimoto, I.; Ueda, H. *Agric. Biol. Chem.* **1980**, *44*, 2135.

(7) Ferraz, H. M. C.; Sasahara, R. M.; Losco, P. *Tetrahedron Lett.* **1992**, *33*, 8131.

(8) Witiak, D. T.; Tehim, A. K. *J. Org. Chem.* **1987**, *52*, 2324.

(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(10) Campos, P. J.; Tan, C.-Q.; Rodriguez, M. A. *Tetrahedron Lett.* **1995**, *36*, 5257.

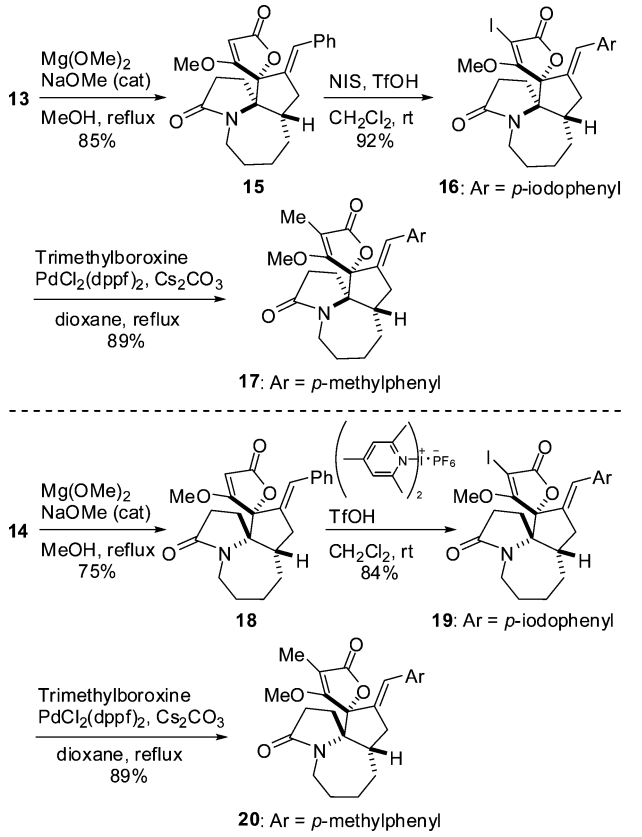
(11) For a recent review of the Mannich reaction, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(12) Gras, J. L. *Tetrahedron Lett.* **1978**, *19*, 2111.

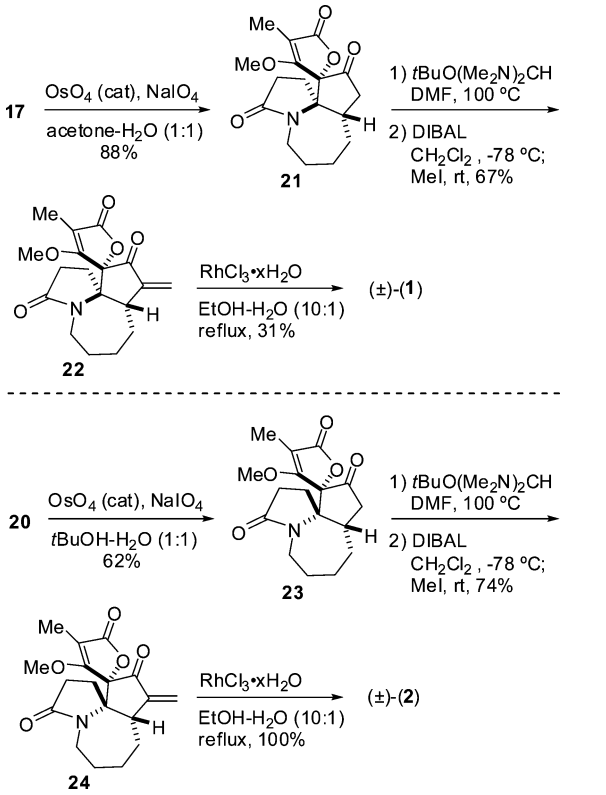
(13) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffman, H.; Grieshaber, P. *Ber.* **1968**, *101*, 41.

(14) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985.

Scheme 4



Scheme 5



(mp 232−233 °C, lit.[3] mp 240−241 °C) in 31% yield. Similar isomerization of **24** occurred smoothly to afford (±)-isostemonamide (**2**) (mp 223−224 °C, lit.[3] mp 225−227 °C) quantitatively (Scheme 5). Our spectral data were in accord with the literature values.[2,3]

In summary, we achieved an efficient total synthesis of (±)-stemonamide (**1**) and (±)-isostemonamide (**2**). The use of a radical cascade involving two *endo*-selective cyclizations allowed us to create the tricyclic core in one step. The present synthesis clearly demonstrates the usefulness of the radical cascade process for synthesis of nitrogen-containing polycyclic compounds.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan. We are grateful to Professor Yang Ye (Shanghai Institute of Materia Medica) for giving us the ^{1}H and ^{13}C NMR spectra of natural **1** and **2**.

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

OL702563P

(15) (a) Grieco, P.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. (b) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.