Communications

Total Synthesis of (−)-Stemoamide Using Ruthenium-Catalyzed Enyne Metathesis Reaction

Atsushi Kinoshita and Miwako Mori*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

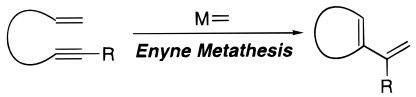
Received September 4, 1996

Stemoamide, which was first isolated from the roots and rhizomes of *Stemonaceous* plants, is a polycyclic alkaloid similar to stemonine, stenine, and stemospironine and possesses powerful insecticidal activity.[1,2] The first total synthesis of stemoamide was achieved by Williams.[3] We report here the total synthesis of (−)-stemoamide from (−)-pyroglutamic acid using a ruthenium-catalyzed enyne metathesis developed by Grubbs[4] and our group[5] that requires 14 steps.

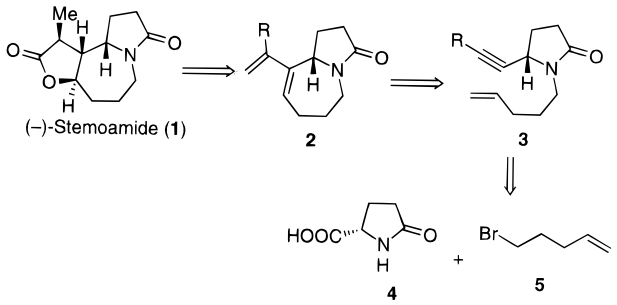
Intramolecular enyne metathesis[6] is a very attractive and unique tool for synthetic organic chemistry. We previously reported the enyne metathesis using a ruthenium catalyst developed by Grubbs.[4b,5] The important characteristic features of intramolecularly enyne metathesis are that the carbon−carbon bond formation between the alkene and alkyne occurs to give a cyclization product, and the alkylidene part of the alkene moiety migrates to the alkyne carbon (Scheme 1). The resultant diene moiety can be used for subsequent synthetic transformations.

Our retrosynthetic analysis of (−)-stemoamide is shown in Scheme 2. If the enyne metathesis of compound **3** is realized using a ruthenium catalyst, cyclized product **2** should be formed. Using the diene part of **2**, stemoamide (**1**) should be synthesized. The enyne **3** should be prepared from (−)-pyroglutamic acid (**4**) and 5-bromo-1-pentene (**5**).

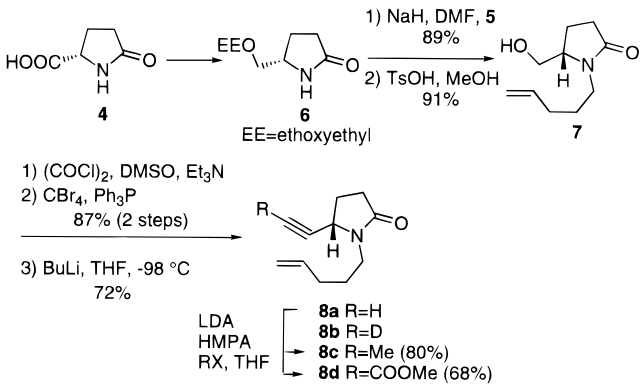
Scheme 1



Scheme 2. Retrosynthetic Analysis



Scheme 3. Synthesis of Enynes



The starting enyne was prepared from (−)-pyroglutamic acid, which was converted into compound **6** as described in the literature (Scheme 3).[7] Alkylation of the sodium salt of **6** with 5-bromo-1-pentene (**5**) proceeded smoothly in DMF and was followed by deprotection with TsOH in MeOH to give alcohol **7** in high yield. Oxidation of **7** with oxalyl chloride and DMSO was followed by treatment with CBr_4 and PPh_3 in a one-pot reaction.[8] The resultant dibromoalkene was treated with BuLi at −98 °C to give enyne **8a**, which was treated with an equimolar amount of LDA and then an excess amount of MeI to give enyne **8c** in 80% yield. Similar treatment of **8a** with LDA and then ClCOOMe at −98 °C gave enyne **8d** in 68% yield.

When a benzene solution of enyne **8c** and a catalytic amount of ruthenium catalyst **9a** (5 mol %) was stirred at 50 °C for 11 h, enyne metathesis proceeded smoothly to give a 5,7-fused compound in 73% yield (Scheme 4).

(1) Goetz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Eds.; Academic Press: New York, 1976; Vol. IX, pp 545−551 and references cited therein.

(2) (a) Harada, H.; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1967**, 460−462. (b) Irie, H.; Harada, H.; Ohno, K.; Mizutani, T.; Uyeo, S. *Ibid.* **1970**, 268−269. (c) Koyama, H.; Oda, K. *J. Chem. Soc. B* **1970**, 1330−1333. (d) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agr. Biol. Chem.* **1978**, *42*, 457−463. (e) Noro, T.; Fukushima, S.; Ueno, A.; Miyase, T.; Iitaka, Y.; Saiki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1495−1497. (f) Xu, R.-S.; Lu, Y.-J.; Chu, J.-H.; Iwashita, T.; Naoki, H.; Naya, Y.; Nakanishi, K. *Tetrahedron* **1982**, *38*, 2667. (g) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.

(3) Williams, D. R.; Reddy, P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417.

(4) (a) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073. (b) Fu, G. C.; Nugent, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (c) Schwab, P.; France, M. B.; Joseph, W. Z.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(5) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020.

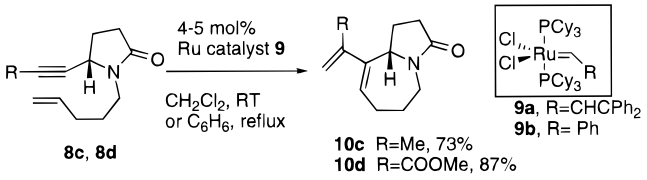
(6) (a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *109*, 737. Sivavec, T. M.; Katz, T. J.; Chiang, M. Y.; Yang, G. Xu-Q. *Organometallics* **1989**, *8*, 1620. Katz, T. J.; Chiang, M. Y.; Yang, G. Xu-Q. *Tetrahedron Lett.* **1991**, *32*, 5895. (b) Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1083. Watanuki, S.; Mori, M. *Heterocycles* **1993**, *35*, 679. Watanuki, S., Ochifuji, N.; Mori, M. *Organometallics* **1994**, *13*, 4129. (c) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294. Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824. (d) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. Chatani, N.; Yamaguchi, S.; Fukumoto, Y.; Murai, S. *Organometallics* **1995**, *14*, 4418.

(7) Saijo, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1449.

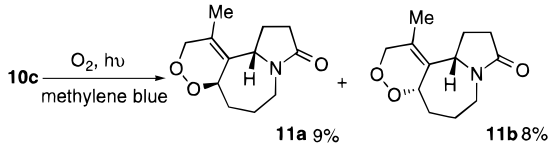
(8) Since the aldehyde was unstable, dibromolefination was carried out without isolation. To the CH_2Cl_2 solution of oxalyl chloride (2 equiv) and DMSO (4 equiv) was added **7** (1 equiv) at −78 °C, and then NEt_3 (10 equiv) was added at −50 °C, and the entire solution was stirred at 0 °C for 30 min. To this solution were added CBr_4 (4 equiv) and PPh_3 (8 equiv) at 0 °C, and the solution was stirred at room temperature for 3 h. After the usual workup, the desired dibromoalkene was obtained in 87% yield.

S0022-3263(96)01687-8 CCC: $12.00

Scheme 4. Cyclization of Enynes Using Ruthenium Catalysts



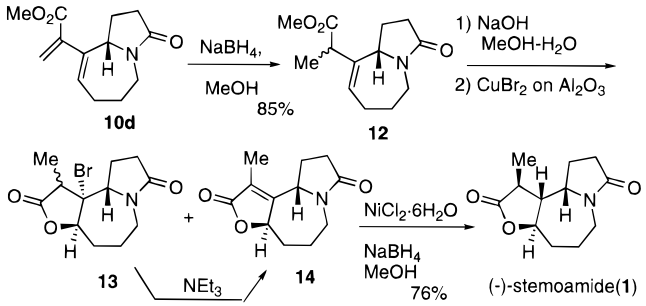
Scheme 5



Photoirradiation of **10c** in the presence of methylene blue under oxygen gave two products, **11a** and **11b**, in yields of 9% and 8%, respectively, along with the starting material (51%) (Scheme 5). The cause of the low yield of the desired products, **11a** and **11b**, is believed to be the fact that the two double bonds of **10c** are not conjugated. The chemical shifts of the vinylic protons of **10c** [4.90 (bs, 1 H), 4.95 (bs, 1 H), 5.92 (dd, J = 5.7, 9.1 Hz, 1 H)] appear at a higher field than those of the usual vinylic proton of the conjugated diene on the NMR spectrum. With regard to enyne metathesis, we previously reported the effects of the substituents on the alkyne. Enyne metathesis with a carbomethoxy group on the alkyne gives a cyclized product in low yield, since the conjugated diene with a carbomethoxy group generated in this reaction is unstable under these reaction conditions.[5] However, the diene of this cyclized product **10c** would not be conjugated because of the steric effect. We were very surprised to find that when a CH_2Cl_2 solution of enyne **8d** was stirred in the presence of a catalytic amount of ruthenium catalyst **9b**[4c] (4 mol %) at room temperature for 5 h the desired metathesis product **10d** was obtained in 87% yield.

Treatment of **10d** with $NaBH_4$ gave **12** as two inseparable isomers, which were hydrolyzed to give the corresponding carboxylic acid (Scheme 6). Bromolactonization[9] proceeded smoothly *via* 5-*endo*-*trig* cyclization, and two products, **13** and **14**, were obtained in yields of 25%

Scheme 6. Synthesis of (−)-Stemoamide



and 31%, respectively. Compound **13** could be easily converted into **14** by treatment with NEt_3.[10] The stereochemistries of these compounds were not determined at this stage. However, on the basis of a molecular modeling study, it was thought that the carboxylate would attack from the β-face of the olefin in bromolactonization because of the stability of the product, and the bromine was expected to be oriented *anti* to the oxygen. Treatment of enone **14** with $NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$ in MeOH[11] gave (−)-stemoamide (**1**), whose melting point, spectral data, and $[\alpha]_D$ value agreed with those reported.[2g,3] In this reaction, the hydride must be introduced to the β-face due to steric requirements, and the methyl group is placed *cis* to the ring-junction proton because of thermodynamic stability. The total synthesis of (−)-stemoamide was accomplished from (−)-pyroglutamic acid in 14 steps in 9% overall yield. Further studies are in progress.

Acknowledgment. This work was supported by a Grant-in Aid for Scientific Research on Priority Area of Reactive Organometallics (No. 05236106) from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Experimental procedures and characterization data for (−)-stemoamide and compounds **7**−**14** and an NMR spectrum for (−)-stemoamide (9 pages).

JO9616872

(9) Rood, G. A.; DeHaan, J. M.; Zibuck, R. *Tetrahedron Lett.* **1996**, *37*, 157.

(10) Since bromo lactone **13** was unstable, the crude bromolactonization product was treated with NEt_3 (2 equiv) at room temperature for 14 h to give unsaturated lactone **14** in 50% yield based on **12**.

(11) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.