Communication

A Convergent Formal Synthesis of (±)-Pumiliotoxin C

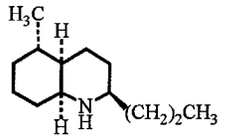
Ya-sheng Shieh (• • • •), Ming-Chang P. Yeh* (• • • •) and U. Narasimha Rao
Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan 117, R.O.C.

A short approach to a key precursor in the synthesis of (±)-pumiliotoxin C was achieved from [(6-9-η)-ethyl *cis*-6,8-nonadienoate]tricarbonyliron complex in five steps.

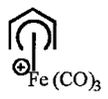
Pumiliotoxin C **1** is an active alkaloids found in the skin secretions of neotropical poison arrow frogs.[1] Due to the interesting structural and stereochemical properties, as well as the intriguing pharmacological aspects, this *cis*-decahydroquinoline based alkaloids have attracted considerable attention among synthetic organic chemists.[2] Recently, Mehta and Fukumoto have successfully converted the *cis*-decahydrindanone derivative **2** to pumiliotoxin C **1**, in racemic and chiral form, respectively.[3] Herein we report a facile synthesis of *cis*-decahydrindanone derivatives via our recently developed method using (η^4–diene)$Fe(CO)_3$ complexes.[4] This approach was readily adaptable for convergent synthesis of both (±)-pumiliotoxin C **1** and (±)-5-epipumiliotoxin C.

The addition of the functionalized zinc-copper reagent [$IZn(CN)Cu(CH_2)_3CO_2Et$] to (η^5-pentadienyl)$Fe(CO)_3$ cation **3** gave **4** in 97% yield.[4b] Intramolecular cyclization of **4** using LDA under an atmosphere of carbon monoxide gave the *cis*-decahydrindanone derivative **5** with an *endo* carbethoxy at C-2 in 54% yield after acid quenching.[4a] To achieve the synthetic route for the target molecule **2** from **5**, it is required to convert the *endo* carbethoxy into the *exo* position. Thus, the keto group of **5** was first transformed into the ketal **6** in 90% yield by treatment of **5** with ethylene glycol in refluxing benzene. Reaction of the ketal ester **6** with sodium ethoxide in ethanol furnished the epimer **7** as the major product in 66% yield together with 16% yield of the starting ketal **6** after aqueous work-up and flash column chromatography. The ketal ester **7** with the correct relative stereochemistry was reduced to alcohol **8** in 93% yield by reaction with LAH. Reaction of alcohol **8** with CBr_4 and PPh_3 in CH_2Cl_2 afforded the bromide **2** in 95%. The bicyclic compound **2** displays the same spectra (^1H NMR and ^{13}C NMR) with those provided by Mehta. We have thus completed a formal synthesis of (±) pumiliotoxin C **1**.[3a]

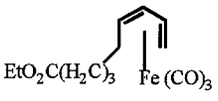
The reactions outlined herein demonstrate that the intramolecular iron-mediated cyclization can be an effective method for the diastereoselective synthesis of *cis*-decahydrindanone derivatives, which lead to the *cis*-decahydroquinoline based alkaloid with promising biological activities. It is important to mention that the present method towards the synthesis of **2**, an intermediate in the total synthesis of (±)-pumiliotoxin C **1** is more effective compared to those found in the literature.[2] Moreover, the decahydroquinoline alkaloid (±)-5-epipumiliotoxin C could also be obtained in three steps starting from **5** using the same sequence.[5]



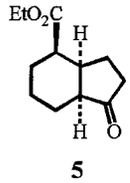
1



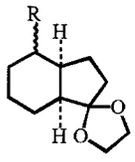
3



4



5



6 R = endo CO_2Et
7 R = exo CO_2Et
8 R = exo CH_2OH
2 R = exo CH_2Br

ACKNOWLEDGMENT

We thank Professor Mehta for providing spectral data of (±)-**2**. This research was supported by a grant from the National Science Council of Republic of China (Grant No. NSC 88-2113-M-003-010).

Received July 8, 1999.

Key Words

Pumiliotoxin C; Diene iron complex; *cis*-Decahydroquinoline; *cis*-Decahydrindanone.

REFERENCES

1. (a) Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205. (b) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives;* Pelletier S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chap. 1, p 1. (c) Daly, J. W.; Garraffo H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Acadamic Press: New York, 1993; Vol. 43; 185.
2. (a) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213. (b) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49*, 8805. (c) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521. (d) Comins, D, L.; Dehghani, A. *J. Chem. Soc. Chem. Commun.* **1993**, 1838. (e) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc. Perkin Trans 1* **1996**, 1113. (f) Bonin, M.; Royer, J.; Grierson, D. S.; Husson, H.-P., *Tetrahedron Lett.* **1986**, *27*, 1569. (g) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652. (h) Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103.
3. (a) Toyota. M.; Asoh. T.; Matsuura, M.; Fukumoto. K. *J. Org. Chem.* **1996**, *61*, 8687. (b) Mehta. G.; Praveen, M. *J. Org. Chem.* **1995**, *60*, 279.
4. (a) Yeh, M. C. P.; Sheu, B. A.; Fu, H. W.; Tau, S. I.; Chuang, L. W. *J. Am. Chem. Soc.* **1993**, *115*, 5941. (b) Yeh, M. C. P.; Sun, M. L.; Lin, S. K. *Tetrahedron Lett.* **1991**, *32*, 113.
5. Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673.