Communication

A Convergent Formal Synthesis of (±)-Pumiliotoxin C

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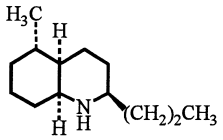
A short approach to a key precursor in the synthesis of (±)-pumiliotoxin C was achieved from [(6-9-η)-ethyl *cis*-6,8-nonadienoate]tricarbonyliron complex in five steps.

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 (^{1}H 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]



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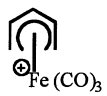

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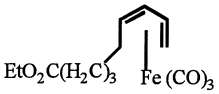

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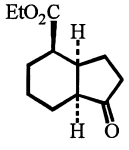

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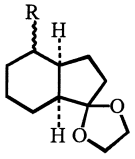

6 R = endo CO_2Et
7 R = exo CO_2Et
8 R = exo CH_2OH
2 R = exo CH_2Br

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Key Words

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

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