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 is an active alkaloid found in the skin secretions of neotropical poison arrow frogs. 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. Recently, Mehta and Fukumoto have successfully converted the cis-decahydridanone derivative 2 to pumiliotoxin C 1, in racemic and chiral form, respectively. Herein we report a facile synthesis of cis-decahydridanone derivatives via our recently developed method using (η^3-diene)Fe(CO) \(_3\) complexes. 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\(_2\))\(_2\)CO\(_2\)Et] to (η^5-pentadienyl)Fe(CO) \(_3\) cation 3 gave 4 in 97% yield. Intramolecular cyclization of 4 using LDA under an atmosphere of carbon monoxide gave the cis-decahydridanone derivative 5 with an endo carbethoxy at C-2 in 54% yield after acid quenching. 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 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\(_2\)Cl\(_2\) 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.

The reactions outlined herein demonstrate that the intramolecular iron-mediated cyclization can be an effective method for the diastereoselective synthesis of cis-decahydridanone 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. Moreover, the decahydroquinoline alkaloid (±)-5-epipumiliotoxin C could also be obtained in three steps starting from 5 using the same sequence.

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Key Words
- Pumiliotoxin C; Diene iron complex; cis-Decahydroquinoline; cis-Decahydrindanone.
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