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Total Synthesis of (+)-Homopumiliotoxin 223G

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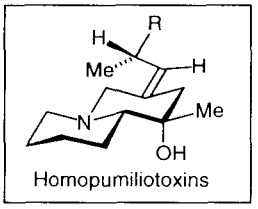
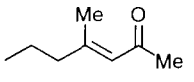
Abstract: A new practical route for the first total synthesis of (+)-homopumiliotoxin 223G is described, in which the palladium-catalyzed carbonylation of the vinyl iodide, leading to efficient construction of the quinolizidine nucleus incorporating the (*Z*)-alkylidene side chain, is the key strategic element. Another key feature of this synthesis involves the Lewis acid-induced chelation-controlled propargylation using the allenylsilane with complete diastereoselectivity.

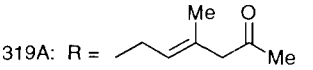
Neotropical poison-dart frogs of the family Dendrobatidae have been a rich source of a variety of structurally unique and pharmacologically significant alkaloids including those based on a simple bicyclic framework with tertiary nitrogen, many of which seem likely to be indolizidines.[1] In 1987 a simple bicyclic alkaloid of an unclassified type, namely, homopumiliotoxin 223G (**1**), was isolated in a trace quantity from

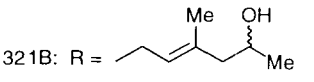


Homopumiliotoxins

223G (**1**): R = Me







Dendrobates pumilio,[2] which is the first example of an unusual class of dendrobatid alkaloids with a quinolizidine ring and appeared to be unique to this family of amphibians. However, the recent examination of skin extracts from nondendrobatid amphibians revealed that homopumiliotoxin 223G is also contained in the new world genus of bufonid toads *Melanophryniscus*[3] and the Madagascan genus of ranid frogs *Mantella*,[4] and the former genus contains new members of the homopumiliotoxin class alkaloids characterized as homopumiliotoxins 319A, 319B, and 321B.[3] The structure with relative configuration of these homopumiliotoxin alkaloids has been tentatively established (except for the configuration of the hydroxy group in the side chain in alkaloid 321B). However, because only trace quantities of the materials are available for study from natural sources, their absolute chemistry as well as optical rotations were not determined, although it has tentatively been assigned as shown (1*S*,9a*S*) based on the structural similarity of these homopumiliotoxins to the pumiliotoxin subclass alkaloids of known absolute configuration.

Owing to the scarcity of the substances available from natural sources, the absence of optical rotation data, and the intriguing biological activity, we became interested in the enantioselective total synthesis of the

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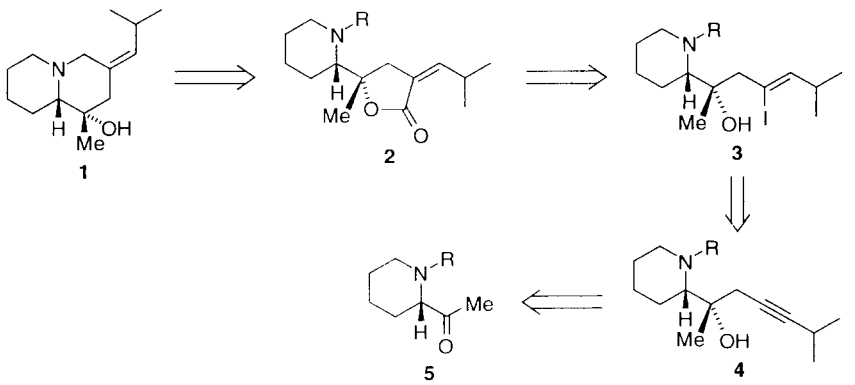
homopumiliotoxin alkaloids. Herein we disclose a new and facile approach to the first total synthesis of (+)-homopumiliotoxin 223G (**1**). Our strategy for the synthesis of **1** is outlined in the retrosynthetic pathway depicted in Scheme 1. The stereodefined generation of the exocyclic (*Z*)-olefin,[5] which is the salient common characteristic structural feature of the homopumiliotoxin alkaloids, is a fundamental requirement for achieving the synthesis of **1**. In this regard, our strategy capitalized on the palladium-catalyzed approach involving carbonylation[6] of a (*Z*)-vinyl halide **3**, which leads to lactonization allowing stereospecific incorporation of the (*Z*)-alkylidene side chain. This synthetic plan consists of another key step involving stereoselective direct construction of a homopropargylic alcohol **4** from a methyl ketone **5**, which is requisite for the preparation of **3**.

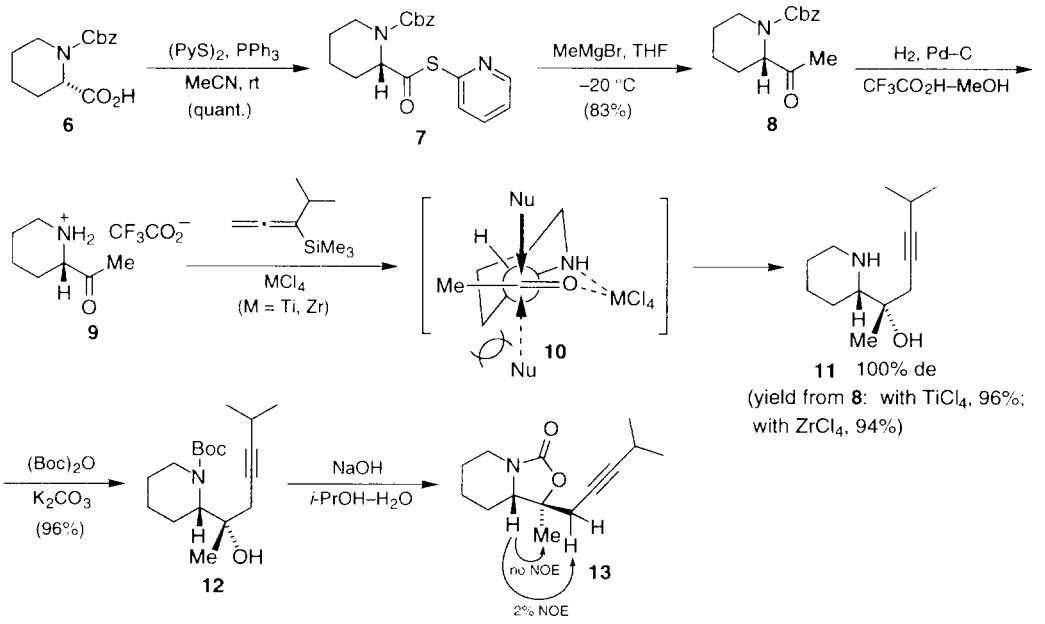
Scheme 1



Following this scheme, we began our investigations with the direct preparation of a homopropargylic alcohol **4** from *N*-protected (*S*)-2-acetylpiperidine (**5**). Thus, *N*-Cbz-L-pipecolinic acid (**6**) was treated, according to our previously described procedure,[7] with 2,2'-dipyridyl disulfide and triphenylphosphine affording the thioester **7**, which underwent Grignard reaction with MeMgBr (THF, –20 °C)[8] to give *N*-Cbz protected (*S*)-2-acetylpiperidine (**8**) in 83% overall yield from **6** (Scheme 2). Attempted propargylation of **8** by treatment with 4-methyl-2-pentynylmagnesium bromide under several reaction conditions resulted in intractable mixtures of products. This failure is most likely due to a tendency of the metallated propargylic anions to exist as an equilibrating mixture of allenic and propargylic anions.[9] We therefore decided to pursue an alternative strategy based on the method of Danheiser[10] involving $TiCl_4$-mediated addition of allenylsilanes to aldehydes and ketones. Thus, **8** underwent hydrogenolysis of the Cbz group in trifluoroacetic acid–methanol to afford the trifluoroacetate salt **9**, which was treated with $TiCl_4$ and then 1-isopropyl-1-(trimethylsilyl)allene[11] in dichloromethane at –78 °C to give the homopropargylic alcohol **11** with complete diastereoselectivity in 96% overall yield from **8**. Changing the Lewis acid from $TiCl_4$ to $ZrCl_4$ was also effective to furnish exclusively **11** in 94% overall yield from **8**. The configuration of the newly created chiral center of **11** was confirmed by examination of an NOE spectrum of the cyclic carbamate **13** derived by carbamoylation followed by alkaline treatment of **12**. The β-facial selectivity realized in the propargylation of **9** can be rationalized by invoking a Lewis acid-chelate cyclic intermediate **10**.

Radical hydrostannylation of the homopropargylic alcohol **12** using triethylborane and triphenyltin hydride stereoselectively afforded the (*Z*)-alkenyltin **14** along with the regioisomer **15** in a 3.6:1 ratio

Scheme 2

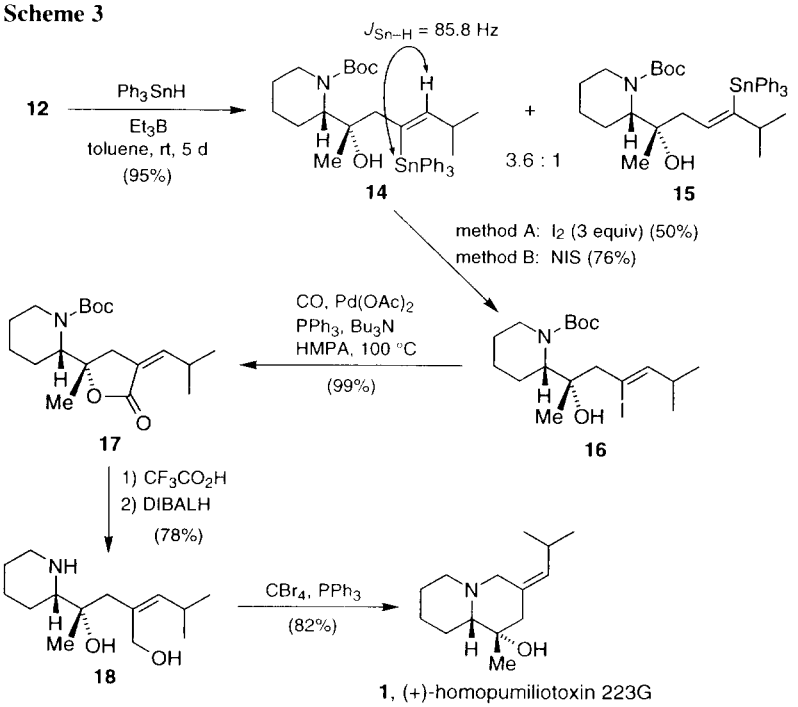


(Scheme 3). The assignment of the *Z* stereochemistry of **14** was made on the basis of the large coupling constant (85.8 Hz) between Sn and the vinylic proton. Upon exposure of **14** to iodine in dichloromethane, iododestannylation proceeded with retention of the *Z* configuration to give the vinyl iodide **16** in 50% yield. When the iododestannylation was carried out using *N*-iodosuccinimide instead of iodine, the yield of **16** could be remarkably enhanced up to 76%.

With the vinyl iodide **16** in hand, the palladium-catalyzed carbonylation was undertaken by treatment with carbon monoxide and tributylamine in the presence of a catalytic amount of $Pd(OAc)_2$ and triphenylphosphine in HMPA at 100 °C.[12] This procedure afforded the lactone **17** in 99% yield, which was converted to the diol **18** via deprotection followed by DIBALH reduction in overall yield of 78%. Dehydrocyclization of **18** was performed with CBr_4 and triphenylphosphine according to our previously described procedure[13] to provide (+)-homopumiliotoxin 223G (**1**) in 82% yield. The synthetic sample of **1** so obtained was shown, via spectral comparisons (MS, ^1H NMR), to be identical with natural homopumiliotoxin 223G.[2] The rotation observed for this product, $[\alpha]^{26}_D$ +1.6 (*c* 5.11, $CHCl_3$); for the hydrochloride salt (mp 183–184 °C), $[\alpha]^{25}_D$ +48.1 (*c* 0.505, MeOH), suggests the rotation of natural homopumiliotoxin 223G to be dextrorotatory, although at present no data on the optical rotation of the natural product have been reported.

In conclusion, a new practical approach to the first total synthesis of (+)-homopumiliotoxin 223G (**1**) has thus been developed in 11 steps and 27% overall yield from *N*-Cbz-L-pipecolinic acid (**6**). The key strategic element in this approach is the palladium-catalyzed carbonylation of the vinyl halide, leading to efficient construction of the quinolizidine nucleus incorporating the (*Z*)-alkylidene side chain. Another key feature of this synthesis involves the Lewis acid-induced chelation-controlled propargylation using the silylallene with complete diastereoselectivity for the direct construction of the homopropargylic alcohol. This work offers new general routes to a series of the homopumiliotoxin class alkaloids other than the alkaloids described here that are currently being investigated in this laboratory.

Scheme 3



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