Synthesis of Pumiliotoxine C from Molecular Nitrogen as a Nitrogen Source

Masaya Akashi, Yoshihiro Sato, and Miwako Mori*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

mori@pharm.hokudai.ac.jp

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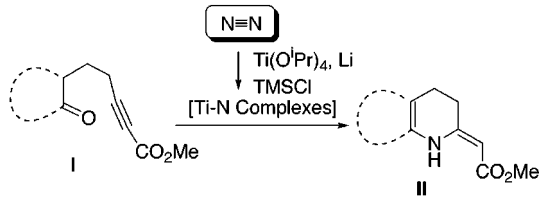
Nitrogen fixation is a very attractive and useful process in synthetic organic chemistry.[1] We have already reported the synthesis of indole derivatives[2f] using a titanium−nitrogen complex, which was synthesized from $TiCl_4$ or $Ti(O^iPr)_4$, Li, and TMSCl under an atmosphere of nitrogen.[2] In this reaction, a 2-substituted indole derivative was obtained in high yield from keto-alkyne, which has the electron-withdrawing group on the alkyne. If keto-alkyne **I** having the carbomethoxy group on the alkyne was reacted with titanium−nitrogen complexes, six-membered heterocycles would be formed. We report here the synthesis of (±)-pumiliotoxine C from ketoalkyne and molecular nitrogen. Our plan for the synthesis of the quinoline derivative is shown in Scheme 1.

When a THF solution of keto-alkyne **1a** (1 equiv) was added to a THF solution of titanium−nitrogen complexes, prepared from $Ti(O^iPr)_4$ (1.25 equiv), Li (12.5 equiv), and TMSCl (20 equiv) under nitrogen gas (1 atm), and the solution was stirred at room-temperature overnight, the desired quinoline derivative **2a** was obtained in 66% yield (Scheme 2).

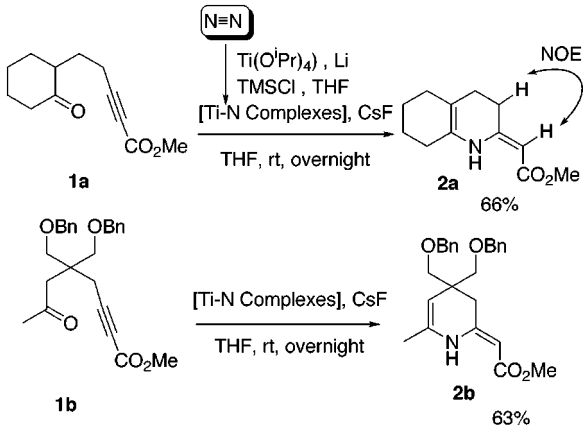
The result of an NOE experiment indicated that a *Z*-isomer was formed due to the stability of the hydrogen bond with carbonyl oxygen. In a similar manner, the desired piperidine derivative **2b** was obtained from keto-alkyne **1b** in 63% yield. These results are very interesting not only because molecular nitrogen was incorporated into the organic compounds in good yields but also because titanium−nitrogen complexes act as an agent for the introduction of an N-1 unit in the synthesis of heterocycles.

On the basis of these results, we attempted to synthesize (±)-pumiliotoxine C, which was isolated[3] from skin extracts of the Panamanian poisonous frog *Dendrobates pumilio*[4] as the first member of one major class of dendrobatid alkaloids.[5] Pumiliotoxin C has a *cis*-decahydroquinoline skeleton. Our retrosynthetic analysis is shown in Scheme 3. Pumiliotoxin C would be synthesized from quinoline derivatives **3**, which should be able to be synthesized from keto-alkyne **4** and molecular nitrogen using our method. From commercially available 3-methylcyclohexenone **5**, keto-alkyne **4** would be synthesized.

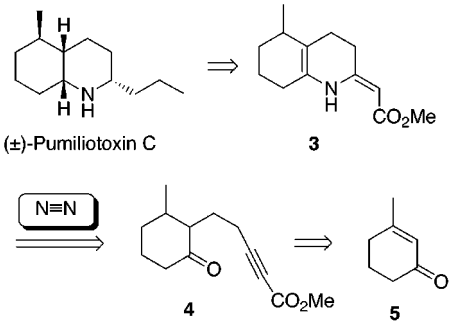
Scheme 1. Plan for Synthesis of Six-Membered Heterocycles



Scheme 2. Synthesis of Six-Membered Heterocycles



Scheme 3. Retrosynthetic Analysis of Pumiliotoxin C



Ketalization of compound **6**, which was obtained from **5**,[5] followed by hydroboration afforded alcohol **7**. Oxidation of **7** with PCC followed by treatment with CBr_4 and PPh_3 gave **8**. Treatment of **8** with BuLi gave lithium

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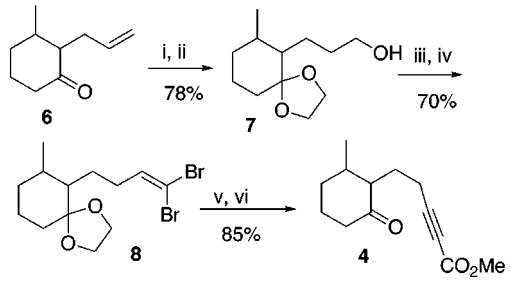
Scheme 4. Synthesis of Ketoalkyne[a]



[a] Key: (i) $(CH_2OH)_2$, PPTS; (ii) $(Sia)_2BH$, then H_2O_2, NaOH; (iii) PCC; (iv) CBr_4, PPh_3; (v) BuLi, then $ClCO_2Me$; (vi) 5% HCl.

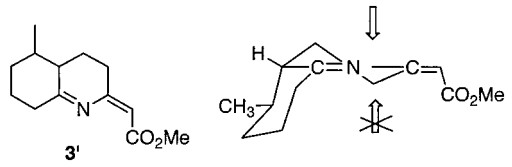


Figure 1.

acetylide, which was reacted with methyl chloroformate followed by deketalization to give keto-alkyne **4**. Synthesis of quinoline **3** was successfully achieved by the reaction of keto-alkyne **4** with titanium−nitrogen complexes using nitrogen gas in high yield. Dry air could be used for this reaction, and the desired quinoline derivative **3** was obtained in 58% yield. Hydrogenation and deprotection of compound **3** was carried out using 5 mol % of palladium on charcoal (STD-type).[3h,6] Protection of the secondary amine with carbobenzyloxy chloride afforded **9a** and **9b** in 57% yields in a ratio of 7 to 1.[7] The reason the desired product **9a** was obtained as a main product is thought to be that hydrogen approached from the convex face of **3′**, which is in a state of equilibrium with **3** in MeOH, as shown in Figure 1.

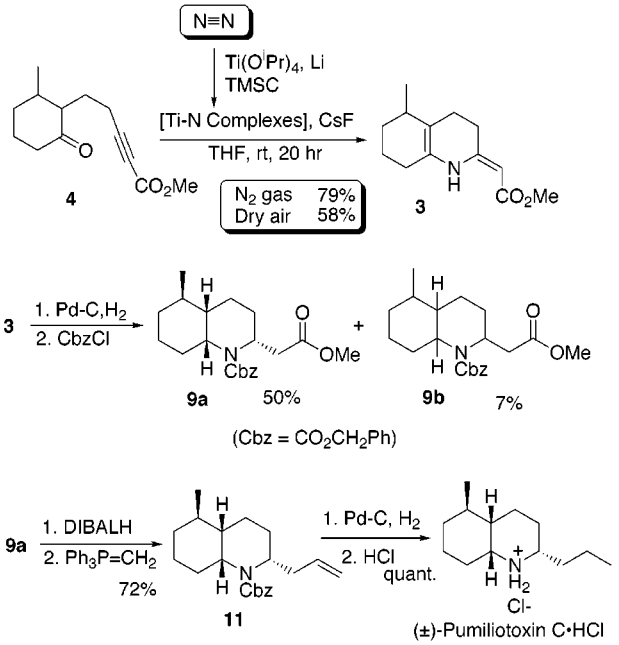
The major isomer **9a** was treated with DIBALH followed by reaction with a Wittig reagent to give compound **11**. Hydrogenation of **11** with 5% palladium on charcoal followed by treatment with Et_2O·HCl afforded pumiliotoxine C hydrochloride, whose spectral data agreed with those reported in the literature.[3a]

The fact that the stereochemistry of the synthetic product, which was confirmed by X-ray chrystallography,[8,9] agreed with that of the natural product indicated that we had succeeded in the synthesis of pumiliotoxin C from keto-alkyne and molecular nitrogen, namely, nitrogen gas or an atmospheric nitrogen.

Experimental Section

All manipulations were performed under an argon atmosphere. $Ti(O^iPr)_4$ was distilled and stored under argon atmosphere. THF and TMSCl were distilled just before using from sodium benzophenone (THF) and CaH_2 (TMSCl). Other solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70−230 mesh), and flash column chromatography was performed on silica gel 60 (230−400 mesh) using the indicated solvent. Melting points are uncorrected.

Scheme 5. Synthesis of Pumiliotoxin C



(*E*)-(5-Methyl-octahydroquinolin-2-ylidene)acetic Acid Methyl Ester (3). A solution of titanium−nitrogen complexes prepared from Li (70.4 mg, 10.1 mmol), $Ti(O^iPr)_4$ (0.30 mL, 1.02 mmol), and TMSCl (2.0 mL, 15.8 mmol) in THF (15 mL) under nitrogen was added to the THF (6.0 mL) suspension of **4** (176.9 mg, 0.796 mmol) and CsF (742.6 mg, 4.89 mmol) at −78 °C, and the whole mixture was stirred at room temperature for 20 h. Saturated aqueous $NaHCO_3$ was added at 0 °C, and the mixture was stirred at room temperature until the black precipitate disappeared. The mixture was filtered through Celite, and the filtrate was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/Et_3N = 100/3) to give **3** (138.8 mg, 79%) as a colorless oil: IR (neat) 3280 1658, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.95 (d, J = 6.8 Hz, 3 H), 1.32 (m, 1 H), 1.53−1.64 (m, 2 H), 1.91 (m, 1 H), 1.97−2.04 (m, 3 H), 2.10−2.22 (m, 2 H), 2.37 (ddd, J = 15.6, 6.6, 6.6 Hz, 1 H), 2.45 (ddd, J = 15.6, 10.5, 5.4 Hz, 1 H), 3.61 (s, 3 H), 4.47 (s, 1 H), 9.25 (brs, 1 H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 19.3, 19.6, 22.6, 27.1, 29.0, 31.1, 32.0, 50.1, 82.3, 114.0, 128.1, 156.7, 170.6; EI-LRMS m/z 221 (M^+), 206; EI-HRMS calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1414.

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Supporting Information Available: The spectral data and experimental procedure of **2a**,**b**, **4**, **7**, **8**, **9a**, **11**, and pumiliotoxin·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Palladium-charcoal was purchased from N.E. CHEMCAT Co.

(7) The stereochemistry of minor product **9b** was not determined.

(8) The melting point of the synthetic product [mp 246−248 °C (from EtOH−AcOEt)] did not agree with that (mp 232 °C) reported in the literature.[3a]

(9) Crystallographic data for the structural analysis have been deposited with the Cambridge Crystaallographic Data Centre, CCDC no. 165162 for pumiliotoxine C·HCl.