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First enantioselective synthesis of (+)-quinolizidine 207I: determination of the absolute stereochemistry

Naoki Toyooka* and Hideo Nemoto

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan

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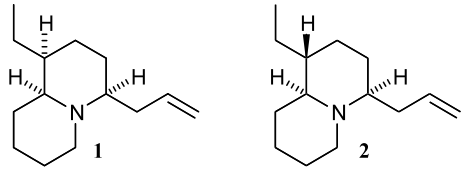
Abstract—First enantioselective synthesis of quinolizidine **207I** has been achieved and the absolute stereochemistry of natural quinolizidine **207I** was determined to be 1*S*,4*S*,10*S* by the present chiral synthesis using GC analysis with β-dextrin chiral column on co-injection with racemate.

The 5,8-disubstituted indolizidines and 1,4-disubstituted quinolizidines are the more common structural patterns found in amphibian skin.[1] None of these alkaloids has so far been reported from any other source. These dart-poison frog alkaloids continue to be of interest as synthetic targets[2] due to their intriguing biological activities. In addition, the biological activity of only a few 5,8-disubstituted indolizidines has been investigated due to the isolation in minute quantities from the skin. Among them, the relative stereochemistry of quinolizidine **207I** was anticipated to be **1** by our chiral synthesis of **2**[3] followed by stereocontrolled synthesis of **1**.[4] A sample of synthetic racemate of **1** had produced the best separations on GC analysis with β-dextrin chiral column.[4]



1

2

As part of a program directed at studying the synthesis of biologically active alkaloids,[5] we planed the enantioselective synthesis of **1** to determine the absolute stereochemistry of natural quinolizidine **207I**.

The synthesis began with enantiomerically pure triflate **3**,[6] which was converted to **4** using palladium catalyzed Sonogashira-type of coupling reaction[7] with propagyl ether in good yield. Catalytic hydrogenation of **4** over 5% Rh–C in EtOAc under the medium pressure (4 atm) gave the desired reduction product **5** in 90% yield. The stereochemistry of **5** was determined to be that of desired all *cis*-trisubstituted piperidine on the basis of the observation of NOE on the oxazolizinone **6** as shown in Scheme 1. After deprotection of silyl group with TBAF, carbon-chain at the 2 position was homologated by Swern oxidation followed by Wittig reaction of the resulting aldehyde to afford the homologated ether **7**. Hydrogenation and deprotection of the tetrahydropyranyl group with PPTS gave rise to alcohol **8**. This was transformed into the terminal olefin **9** using Sharpless'[8] and Grieco's[9] procedure. Finally, quinolizidine ring closure was performed by three-step sequence to provide the quinolizidine (+)-**1**.[10]

The GC analysis of our synthetic (+)-**1** revealed that the absolute stereochemistry of natural **207I** is 1*S*,4*S*,10*S* as shown in Scheme 1. On the GC analysis using a β-Dex-120 cyclodextrin-based column (Supelco Inc., Bellefonte, PA; 30 m, 0.25 mm i.d., 25 μm film thickness), synthetic (+)-**1** was coeluted with shorter retention time peak of racemate and natural product coeluted with the longer retention time peak of racemate.

In summary, we achieved the first chiral synthesis of quinolizidine **207I** and its absolute stereochemitry was determined to be 1*S*,4*S*,10*S* by the GC-coinjection analysis of (+)-**1**, (±)-**1**, and natural product unambiguously.

* Corresponding author.

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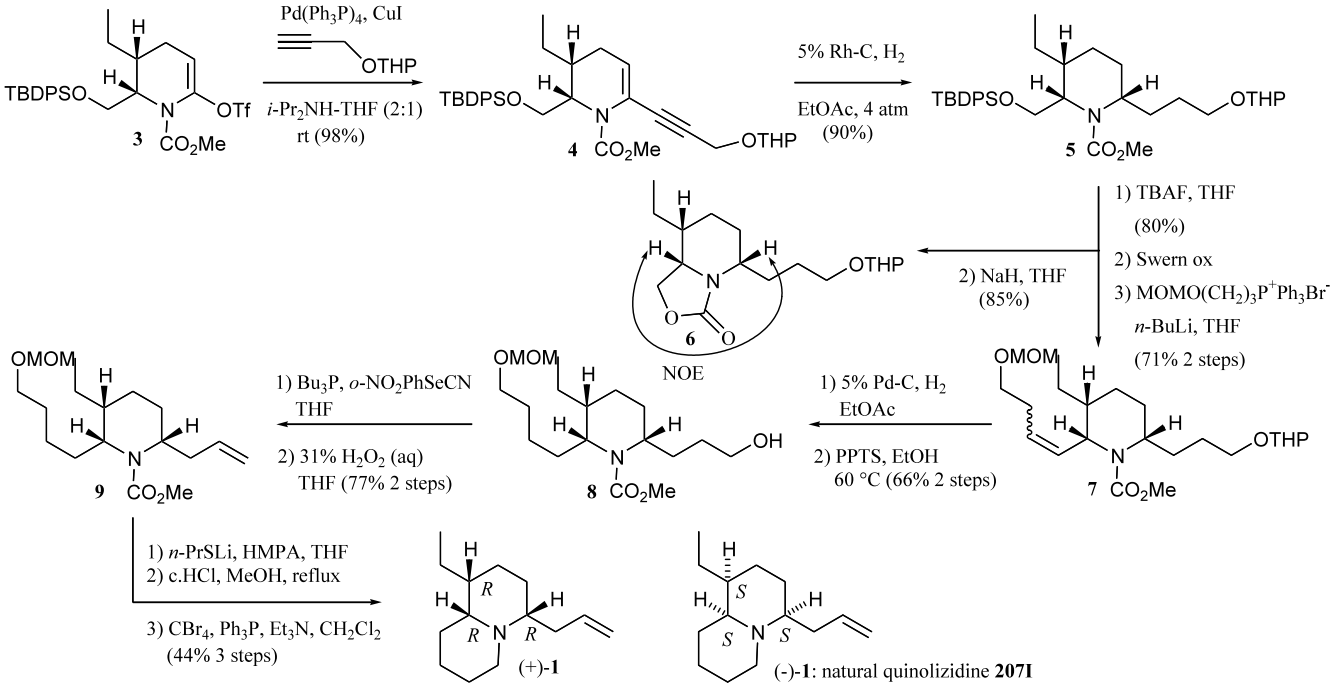

Scheme 1.

Acknowledgements

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10. The spectral data for synthetic (+)-**1** are as follows: IR (neat) 3071, 2929, 2862, 2786, 2757 cm^{-1}; ^1H NMR (500 MHz): δ 0.87 (3H, t, $J=7.3$ Hz), 1.25–1.66 (12H, br m), 1.73 (1H, dm, $J=12$ Hz), 1.79 (1H, dm, $J=12$ Hz), 1.88 (1H, br m), 1.96 (1H, d-like, $J=11$ Hz), 2.15 (1H, m), 2.42 (1H, dm, $J=12$ Hz), 3.33 (1H, dm, $J=11$ Hz), 5.03 (2H, m), 5.83 (1H, m); ^{13}C NMR (75 MHz): δ 12.53 (q), 18.46 (t), 25.06 (t), 26.28 (t), 26.34 (t), 27.17 (t), 31.09 (t), 38.36 (t), 40.62 (d), 53.10 (t), 64.24 (d), 66.75 (d), 115.98 (t), 136.35 (d); MS: 207 (M^+), 167 (100); $[\alpha]_D^{26}$ +29.5 (*c* 0.44, $CHCl_3$).