

**THREE-STEP TOTAL SYNTHESIS OF PYRROLOQUINAZOLINO-
QUINOLINE ALKALOID, LUOTONIN A, BY INTRAMOLECULAR
HETERO DIELS-ALDER REACTION[#]**

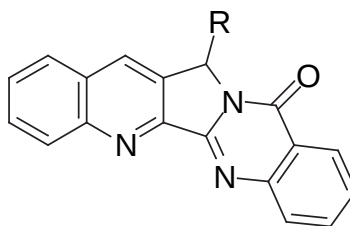
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Abstract - Total synthesis of luotonin A (**1**) was accomplished, starting from 3-aminomethyl-2-bromoquinoline (**4**) in three steps *via* intramolecular hetero Diels–Alder reaction.

We have been exploring intramolecular hetero Diels–Alder reactions of 1-azadienynes for the construction of biologically active heterocycles such as nothapodytine B.¹ In order to demonstrate the flexibility of our protocol, we envisioned a novel one-pot generation of quinazolinone ring systems by using cyano group as a Diels–Alder dienophile.² Since luotonins A (**1**) and B (**2**) possess quinazolinone framework as their partial structures, luotonin A (**1**) was adopted as our present target molecule. Luotonins A (**1**) and B (**2**) were originally isolated by Nomura and his coworkers in 1997 from the aerial parts of *Peganum nigellastrum* (Figure 1).³ Because these alkaloids have unique pyrroloquinazolinoquinoline ring system and luotonin A (**1**) shows cytotoxic activity against mouse leukemia P-388 cells, luotonin A (**1**) has attracted significant attention in recent years.⁴ In this communication, we report a three-step synthesis of luotonin A (**1**) employing intramolecular hetero Diels–Alder reaction.

Figure 1



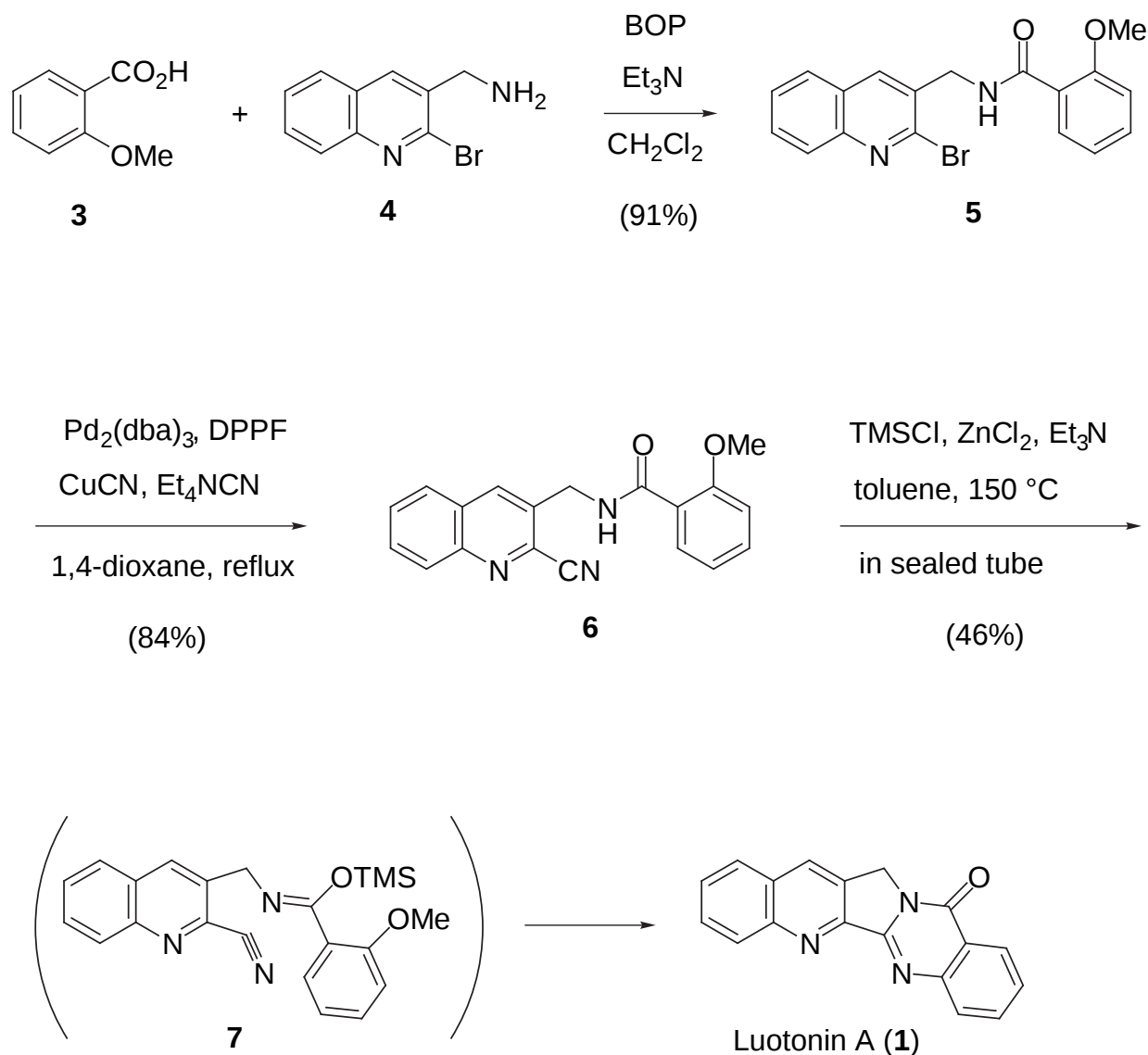
Luotonin A (**1**): R=H

Luotonin B (**2**): R=OH

The requisite substrate (**6**)⁵ for the pivotal hetero cycloaddition was easily prepared in two steps as depicted in Scheme 1. Condensation of 2-methoxybenzoic acid (**3**) with 3-aminomethyl-2-bromoquinoline (**4**)⁶ in the presence of BOP and Et₃N provided the amide (**5**) in 91% yield. To introduce cyano group into the C-2 position of **5**, palladium-catalyzed coupling reaction of **5** with CuCN was investigated.⁷ As a result, the reaction proceeded smoothly in the presence of 4 mol % of Pd₂(dba)₃, 16 mol % of DPPF and stoichiometric amounts of Et₄NCN, giving the cyanide (**6**) in 84% yield.

With the efficient synthesis of **6** established, the compound (**6**) was next subjected to intramolecular hetero Diels–Alder reaction. Heating of **6** with TMSCl and Et₃N at 150 °C in the presence of ZnCl₂ produced luotonin A (**1**) in 46% yield. The synthetic **1** thus obtained was spectroscopically identical with that reported.³

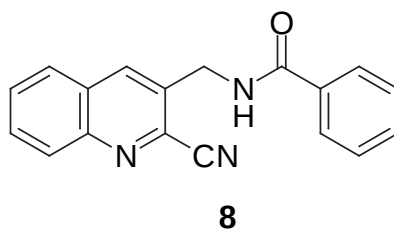
Scheme 1



REFERENCES AND NOTES

Dedicated to Professor James P. Kutney on the occasion of his 70th birthday.

1. (a) M. Toyota, C. Komori, and M. Ihara, *J. Org. Chem.*, 2000, **65**, 7110. (b) M. Toyota, C. Komori, and M. Ihara, *Heterocycles*, 2000, **52**, 591.
2. Although the ability of a nitrile to act as a heterodienophile has been known, the requirement of very high reaction temperature has made nitrile unattractive as a heterodienophile. D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, Inc., New York, 1987.
3. Z.-Z. Ma, Y. Hano, T. Nomura, and Y.-J. Chen, *Heterocycles*, 1997, **46**, 541.
4. (a) P. Molina, A. Tarraga, and A. Gonzalez-Tejero, *Synthesis*, 2000, 1523. (b) T. R. Kelly, S. Chamberland, and R. A. Silva, *Tetrahedron Lett.*, 1999, **40**, 2723. (c) Z.-Z. Ma, Y. Hano, T. Nomura, and Y.-J. Chen, *Heterocycles*, 1999, **51**, 1593. (d) H. Wang and A. Ganesen, *Tetrahedron Lett.*, 1998, **39**, 9097.
5. The intramolecular hetero Diels–Alder reaction of **8** afforded neither the corresponding cycloadduct nor luotonin A (**1**).



6. K. Mekouar, Y. Ganisson, S. Leue, and A. G. Greene, *J. Org. Chem.*, 2000, **65**, 5212.
7. T. Sakamoto and K. Ohsawa, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2323.