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Total synthesis of the cytotoxic alkaloid luotonin A

Haishan Wang and A. Ganesan*

Institute of Molecular and Cell Biology, National University of Singapore
30 Medical Drive, Singapore 117609

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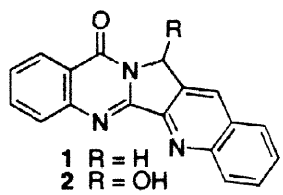
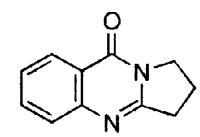
Abstract: The structure of luotonin A was unambiguously confirmed by total synthesis. Deprotonation of 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline gave an anion which was coupled with 2-sulfinylaminobenzoyl chloride (prepared by reaction of anthranilic acid with thionyl chloride) to afford the natural product in 85 % yield.

Keywords: natural products, alkaloids, quinazolinones, cytotoxins.

Two new pyrroloquinazolinoquinoline alkaloids, luotonin A (**1**) and B (**2**), were recently isolated[1] from the aerial parts of *Peganum nigellastrum* Bunge. The structures were assigned by NMR analysis, an isomeric ring skeleton being disfavoured by analogy to other natural products. The plant (Chinese name "Luo-Tuo-Hao") has a history of use in Chinese traditional medicine for treatment of conditions such as rheumatism, abcess, and inflammation. Luotonin A is cytotoxic against the murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL), while desoxyvasicinone (**3**, also isolated from the same extract) shows weaker activity (IC_{50} 79 μg/mL). This result highlights the importance of the quinoline ring for cytotoxicity. The same feature is also present in the topoisomerase I inhibitor camptothecin (**4**), derivatives[2] of which are in clinical use for cancer chemotherapy, as well as nothapodytine B[3] (**5**), an inhibitor of herpes simplex and human cytomegalovirus.



1 R = H
2 R = OH



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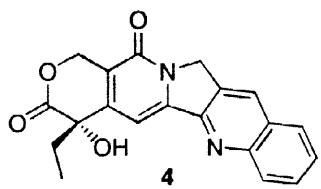

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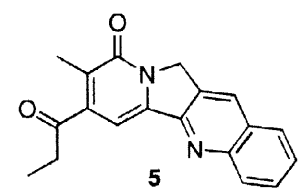

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The biological activity of luotonin A raises the intriguing possibility of obtaining camptothecin-like analogs where the lactone is replaced by simpler substituted benzene derivatives. These considerations, coupled with our interest[4] in quinazoline alkaloids, prompted us to embark on a synthesis of **1**. We were particularly attracted to a convergent retrosynthesis employing Kametani's "iminoketene"-amide condensation[5,6], leading back to anthranilic acid and the known lactone **6**. The latter was prepared (**Scheme**) in four steps from 2-nitrobenzaldehyde by a slight modification of Danishefsky's procedure[7].

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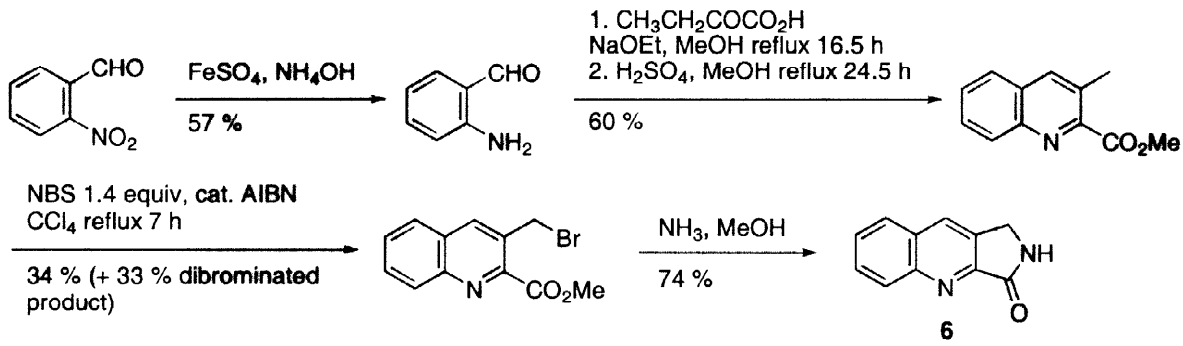
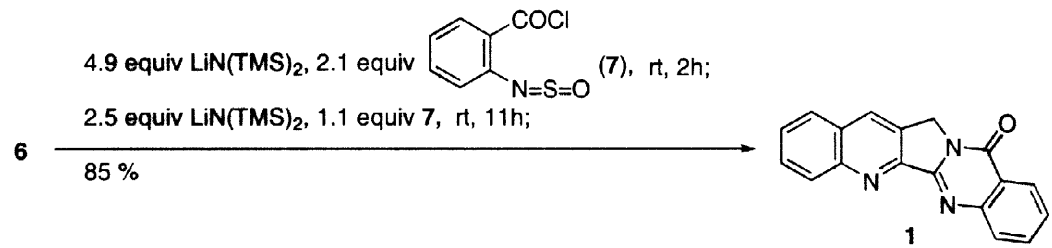


Scheme

Treatment of lactam **6** with 2-sulfinylaminobenzoyl chloride **7** under Kametani's conditions (benzene, rt) did not lead to any product, while only 6 % of **1** was isolated after refluxing for 13.5 h in acetonitrile, probably due to the poor solubility of **6** in these solvents. Instead, deprotonation of **6** with lithium bis(trimethylsilyl)amide gave an anion soluble in THF, which smoothly reacted with the acid chloride. As we used crude **7** which may contain acidic impurities, we found it advantageous to add it in two portions and use an excess of base.



Synthetic **1** matched the spectroscopic data reported in all respects, thus unambiguously confirming the structure of luotonin A. Since a wide variety of substituted anthranilic acids are available, our route is also readily adaptable to the preparation of analogs.

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References

1. Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541-546.
2. Slichenmyer, W. J.; Rowinsky, E. K.; Donehower, R. C.; Kaufmann, S. H. *J. Nat. Cancer Inst.* **1993**, *85*, 271-291.
3. (a) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623-2625; (b) Pendrak, I.; Wittrock, R.; Kingsbury, W. D. *J. Org. Chem.* **1995**, *60*, 3249-3251.
4. Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432-2433.
5. (a) Kametani, T.; Higa, T.; Loc, C. V.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186-6188; (b) Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306-2309.
6. Garín, J.; Merino, P.; Orduna, J.; Tejero, T.; Uriel, S. *Tetrahedron Lett.* **1991**, *32*, 3263-3264.
7. Danishefsky, S.; Bryson, T. A.; Puthenpurayil, J. *J. Org. Chem.* **1975**, *40*, 796-799.