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LETTERS

Total Synthesis of Luotonin A

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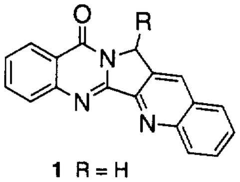
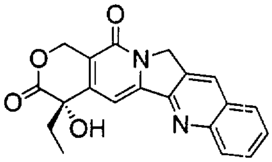
Abstract: The synthesis of the cytotoxic alkaloid luotonin A (**1**), which has been shown to possess anti-leukemic activity, has been achieved. The key step in the synthesis is a Friedländer condensation between 2-aminobenzaldehyde and dione **5**.

Chinese traditional medicine uses the plant *Peganum nigellastrum*, indigenous to northwest China, for the treatment of rheumatism, inflammation, abscesses, and other maladies.[1] A recent examination of the chemical components of the aerial parts of *P. nigellastrum* led to the isolation of two new alkaloids, luotonins A and B. Subsequent structure determination established luotonins A and B as **1** and **2**, the first known natural products to possess the heteroaromatic pyrroloquinazolinoquinoline ring system.[1] The pentacyclic ring system of **1** and **2** is strikingly reminiscent of camptothecin (**3**), an inhibitor of topoisomerase I, derivatives of which are clinically useful anticancer agents.[2] We now describe a short, biosynthetically patterned[1] synthesis[3] of **1** from the known tricyclic natural product vasicinone (**4**), which co-occurs with **1** in *P. nigellastrum.*[1]



1 R = H
2 R = OH



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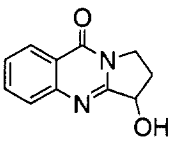

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Our brief synthesis of **1** begins with vasicinone (**4**), prepared in 5 steps and 22 % overall yield from anthranilic acid and 2-pyrrolidinone according to slightly modified literature procedures.[4] As outlined in Equation 1, conversion of **4** into **1** is accomplished in just 2 steps. Thus, oxidation of **4** using Jones reagent[5] gave dione **5**.[6] Friedländer

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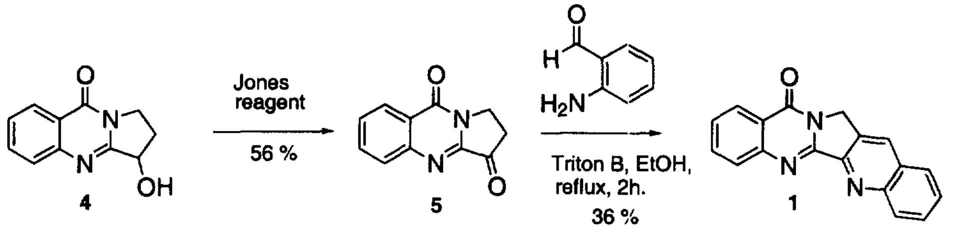
condensation[7] of **5** with 2-aminobenzaldehyde[8] then gave **1** directly.[9] Spectra of synthetic **1** are identical with those of the natural product.



(Eq. 1)

Conclusion. The two-step synthesis of luotonin A from vasicinone confirms the structure of **1**, supports its proposed[1] biosynthesis, and provides convenient access to **1** and, potentially, its analogs.

Acknowledgment. We thank Dr. Nomura[1] for helpful exchange of information and spectra of **1**.

References

[1] Ma, Z.; Hano Y.; Nomura T.; Chen, Y. *Heterocycles* **1997**, *46*, 541.

[2] Slichenmyer, W. J.; Rowinsky, E. K.; Donehower, R. C.; Kaufmann, S. H. *J. Nat. Cancer Inst.* **1993**, *85*, 271.

[3] For a very recent report of the synthesis of **1** (by a different route) that appeared after this synthesis was complete, see Wang, H; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097.

[4] a) Prepared by the method of Onaka, T. *Tetrahedron Lett.* **1971**, 4387. Our conversion of Onaka's **1f** to **1g** employed the procedure in Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles* **1985**, *23*, 2803. b) For the synthesis of the lactim ether used in the synthesis of **4**, see Onaka, T. *Tetrahedron Lett.* **1968**, 5711. c) See also Petersen, S.; Tietze, E. *Ann.* **1959**, *623*, 166.

[5] Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

[6] Preparation of **5**: To a cooled (0 °C) solution of vasicinone (**4**) (20 mg, 0.10 mmol) in acetone (10 mL) was added Jones reagent[5] (25.3 μL). The mixture was allowed to stir with warming to rt for 5 h. The reaction was then quenched with 10% $NaHCO_3$ (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and then evaporated to yield 15 mg of crude solid. Recrystallization from acetone yielded 11.1 mg of a tan solid (56%): "mp" 165-170 °C (darkens without melting), 205 °C (chars without melting); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.37 (1H, dd, *J* = 8.3, 1.5 Hz), 7.98 (1H, ddd, *J* = 8.3, 7.6, 1.5 Hz), 7.85 (dd, 1H, *J* = 7.8, 1.5 Hz), 7.63 (ddd, 1H, *J* = 7.8, 7.6, 1.5 Hz), 4.41 (2H, t, *J* = 6.7 Hz), 3.05 (2H, t, *J* = 6.7 Hz), ^{13}C NMR (100 MHz, DMSO-d_6) δ: 198.0, 160.3, 148.3, 148.0, 134.7, 128.9, 128.4, 125.9, 121.7, 79.2, 32.7; IR (KBr): 1744, 1656, 1600, 1468, 1386, 1285, 1103 cm^{-1}; UV λ_{max} (MeOH): 314, 300, 282, 228, 210 nm; HRMS for $C_{11}H_8N_2O_2$ (M^+): calcd, 200.0586; found, 200.0585. Anal. Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.74; H, 3.98; N, 13.77.

[7] For a review of the Friedländer condensation, see Cheng, C. C.; Yan, S. J. *Organic Reactions* **1982**, *28*, 37. For a particularly relevant precedent, see Shamma, M.; Novak, L. *Tetrahedron* **1969**, *25*, 2275.

[8] Smith, L. I.; Opie, J. W. *Organic Syntheses*, Wiley: New York, 1955; Collective Vol. III, p. 56.

[9] Preparation of **1**: To a solution of dione **5** (20.0 mg, 0.100 mmol) in absolute ethanol (5 mL) was added 2-aminobenzaldehyde (12.1 mg, 0.100 mmol). The solution was heated to a gentle reflux and Triton B (53 μL, 0.11 mmol, 40% in methanol) was added. The mixture was allowed to stir at reflux for 2.5 h. The ethanol was then removed in vacuo and the residue was taken up in chloroform. Partial purification was achieved on a 20 x 20 cm, 1000 μ silica gel preparative layer plate using 1:1 chloroform/ether as eluent. The resulting material was further purified by recrystallization from acetone to give 10.1 mg of **1** (36%), mp 254 °C (decomp), lit.[1] mp 252 °C (decomp). Spectra of synthetic **1** are identical with those of the natural product.