

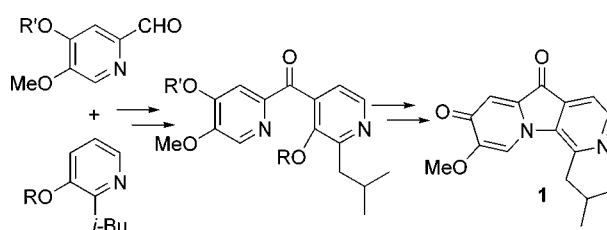
Synthesis of Pterocellin A

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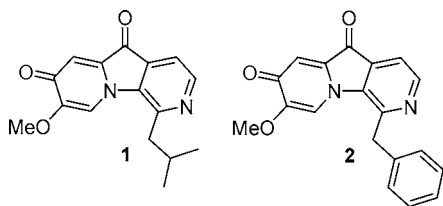
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ABSTRACT



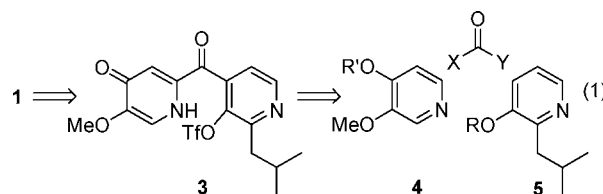
The first total synthesis of pterocellin A (**1**) was achieved in 10 linear steps from commercially available kojic acid (**6**) and 2-bromo-3-pyridinol (**11**) in a convergent sequence. The key constructive steps are a directed lithiation to couple two pyridines and an intramolecular nucleophilic aromatic substitution to form **1**.

In 2003, New Zealand scientists reported the isolation and characterization of two red natural products, pterocellin A (**1**) and B (**2**).^{1,2} The pterocellins exhibit in vitro anticancer activity against a variety of cancer cell lines. Since the pterocellins are the only known representatives of the tricyclic pyrido[4,3-*b*]indolizine ring system, and since no independent confirmation of the structure determination has been recorded, the synthesis of pterocellin A was undertaken. We now report the first synthesis of pterocellin A and the certification of the original structure assignment.³



Retrosynthetic analysis suggested (eq 1) that **1** might be achieved by cyclization of **3**. The latter should be available

in a convergent fashion from **4**, **5** and a carbonyl synthon. In principle, the carbonyl unit could be incorporated initially attached to either pyridine **4** or **5**. Both possibilities were examined, but in practice initial attachment to pyridine **4** provided the solution.



The synthesis began with the methylation of commercially available kojic acid (**6**) to yield pyrone **7**,⁴ which was then heated with concentrated ammonium hydroxide according to the procedure of Armit and Nolan to produce the known pyridone **8** (Scheme 1).⁵ Pyridone **8** was protected with *p*-methoxybenzyl (PMB) chloride to afford pyridine ether **9** in 32% overall yield from **7**; the low yield is attributed in part to difficulty in purifying pyridone **8**. Primary alcohol **9** was then oxidized using *o*-iodoxybenzoic acid (IBX) to aldehyde **10**.

[†] Undergraduate research participant; recipient of a Pfizer Summer Undergraduate Research Fellowship.

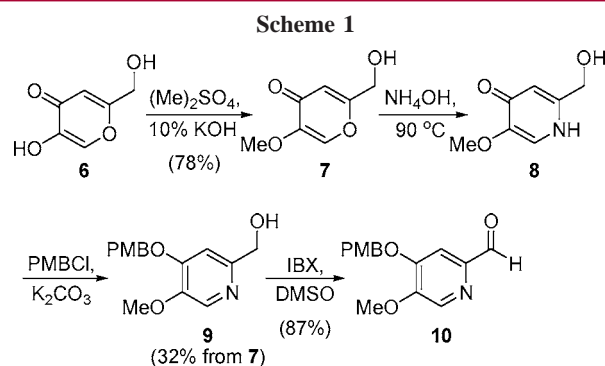
(1) Yao, B.; Prinsep, M. R.; Nicholson, B. K.; Gordon, D. P. *J. Nat. Prod.* **2003**, *66*, 1074–1077.

(2) Prinsep, M. R.; Yao, B.; Nicholson, B. K.; Gordon, D. P. *Phytochem. Rev.* **2004**, *3*, 325–331.

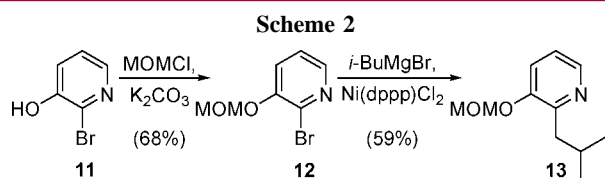
(3) For model studies leading to a monoaza counterpart of the ring system of **1** and **2**, see: Kende, A. S.; Henry, O.; Chen, Z. *Tetrahedron Lett.* **2004**, *45*, 7809–7812.

(4) Campbell, K. N.; Ackerman, J. F.; Campbell, B. K. *J. Org. Chem.* **1950**, *15*, 221–226.

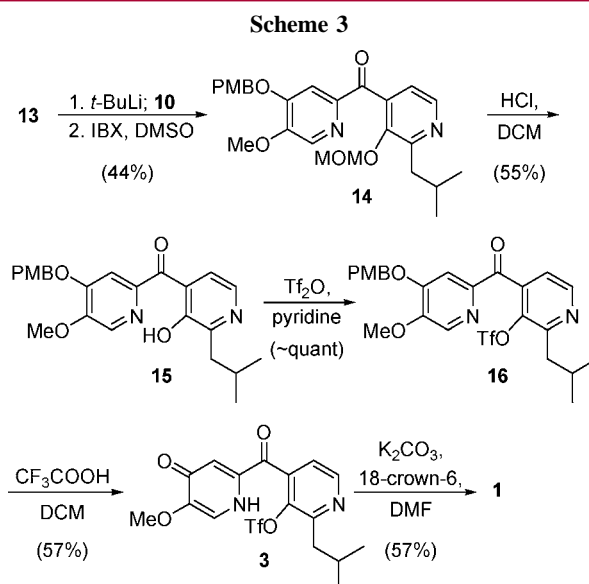
(5) Armit, J. W.; Nolan, T. J. *J. Chem. Soc.* **1931**, 3023–3031.



Preparation of the unit corresponding to **5** (Scheme 2) began with the methoxymethyl (MOM) ether protection of commercially available 2-bromo-3-pyridinol (**11**) to produce pyridine **12**. A Kumada cross-coupling⁶ between bromopyridine **12** and isobutylmagnesium bromide using nickel catalysis⁷ gave **13**.



Selective lithiation of pyridine **13** at the 4-position was achieved by using *t*-BuLi and enlisting the coordinating ability of the MOM group;⁸ the lithiated pyridine was then coupled to aldehyde **10** (Scheme 3). Since the purification of the resulting doubly benzylic alcohol proved problematic, it was oxidized without purification to dibenzylic ketone **14** using IBX. The MOM group was then removed from bicycle **14** using dilute hydrochloric acid to generate pyridinol **15**. The yield of this reaction is time dependent due to the competitive, but slower, removal of the PMB group. Esterification of pyridinol **15** using triflic anhydride and pyridine



in dichloromethane yielded triflate **16** in essentially quantitative yield. The facile removal of the PMB group using 10% TFA/DCM yielded pyridone **3**. As predicted, cyclization of **3** with potassium carbonate and 18-crown-6 in *N,N*-dimethylformamide afforded the desired **1** as a red solid in a 57% yield.

The ¹H NMR, ¹³C NMR, and UV–vis spectra (see the Supporting Information) of synthetic **1** are in excellent agreement with those reported for the natural material. Direct comparison of synthetic and natural **1** (TLC cospotting, ¹H NMR spiking experiments, and undepressed mixture melting point) verifies their identity.

In conclusion, we report the first synthesis of pterocellin A, a synthesis that confirms the initially reported structure.

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Supporting Information Available: Experimental procedures and characterization data for selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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