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Synthesis of Pterocellin A

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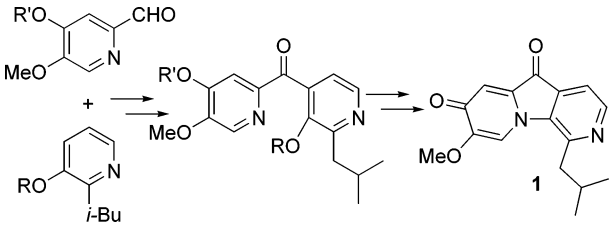
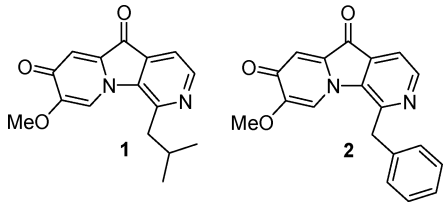
ABSTRACT

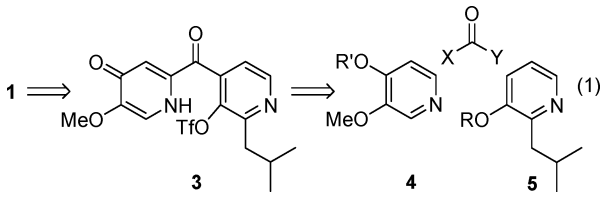


The first total synthesis of pterocellin A (1) was achieved in 10 linear steps from commercially available kojic acid (6) and 2-bromo-3-pyridinol (11) in a convergent sequence. The key constructive steps are a directed lithiation to couple two pyridines and an intramolecular nucleophilic aromatic substitution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

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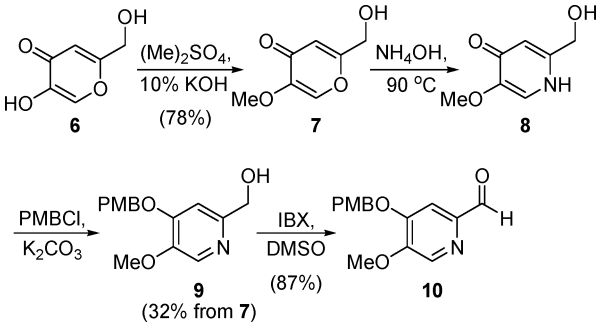
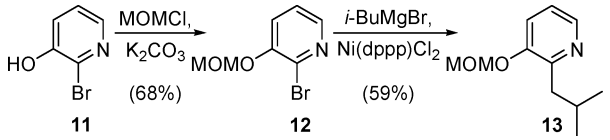
Scheme 1



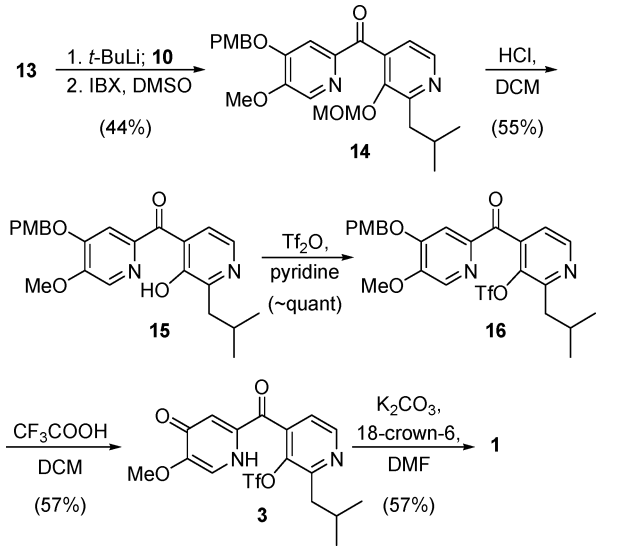
Preparation of the unit corresponding to **5** (Scheme 2) began with the methoxymethyl (MOM) ether protection of commercially available 2-bromo-3-pyridinol (**11**) to produce pyridine **12**. A Kumada cross-coupling[6] between bromopyridine **12** and isobutylmagnesium bromide using nickel catalysis[7] gave **13**.

Scheme 2



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

Scheme 3



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 ^{1}H NMR, ^{13}C 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, ^{1}H 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.

OL061002C

(6) For a leading reference, see: Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Amsterdam, 2005; pp 258−259.

(7) Ohta, A.; Takahashi, N.; Yuasa, K. *Heterocycles* **1990**, *30*, 875−884.

(8) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 7, 2101−2108.