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A Short Synthesis of the Antimicrobial Marine Sponge Pigment Fascaplysin.

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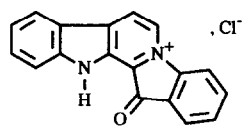
Abstract: *A short and convergent synthesis of Fascaplysin is reported. The approach is based on a recently developped methodology which involves such reactions as metalation, heteroring cross-coupling and cyclization.*

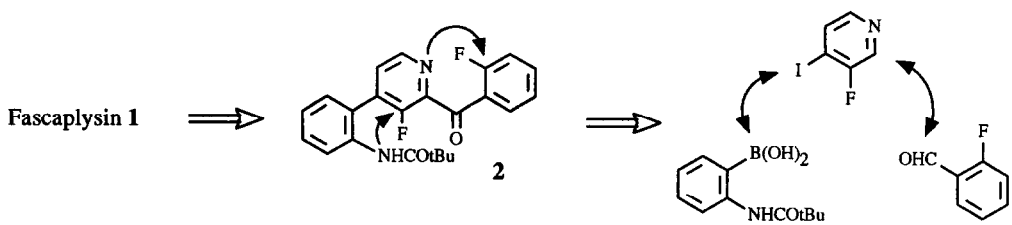
Fascaplysin (**1**) (Scheme 1), an antimicrobial and cytotoxic red pigment was isolated and characterized in 1988 by Ireland and Clardy from the Fijian sponge *Fascaplysinopsis Bergquist sp..*[1] Fascaplysin (**1**) inhibits the growth of several microbes and is active against the L-1210 mouse leukemia system in vitro.[1] In 1990, G.W. Gribble et al.[2] have prepared Fascaplysin (**1**) in 65% yield from indole (seven steps): the pivotal step of their strategy was the construction of the pyridine part of the molecule. A different approach to the synthesis of **1** is proposed based on our recent discovery of a new convergent route to carbolines[3] and α-substituted β-carbolines[4]. We wish to report here on the extension of this fruitful strategy to the total synthesis of Fascaplysin starting from simple benzene and pyridine derivatives.



Fascaplysin **1**

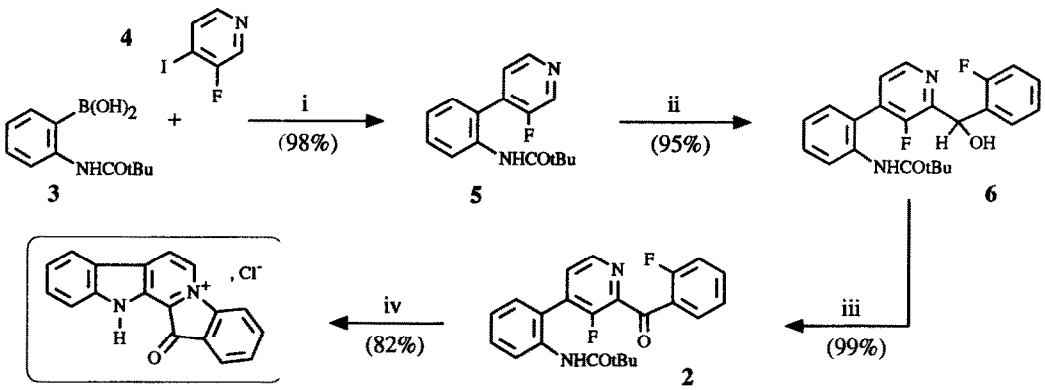
Scheme 1

A retrosynthetic analysis (Scheme 2) of Fascaplysin (**1**) suggests that it could be prepared by cyclization of the triaryl **2**. This latter compound could be obtained from two benzene and one pyridine building blocks via metalation[5] and cross-coupling reactions.[6]



Scheme 1

Palladium-catalyzed cross-coupling between boronic acid **3** and iodopyridine **4** using Suzuki's procedure gave the biaryl **5**[3]. Regioselective metalation[4] of **5** with n-butyllithium in THF at low temperature and reaction of the resulting lithio derivative with 2-fluorobenzaldehyde afforded the corresponding trisubstituted pyridine **6** in 95% yield. Oxidation[7] of **6** by MnO_2 in refluxing toluene led to the carbonyl derivative **2** in very high yield. The one-pot double cyclization of **2** to Fascaplysin (**1**) (dark red product) was best achieved by treatment with pyridinium chloride at 170°C followed by a basic workup (Scheme 2). The main physical data (IR, HRMS, ^1H NMR) of **1** are identical to those of the natural product.



i: $Pd(PPh_3)_4$/ 2M K_2CO_3/ toluene/ reflux (Ar) 48h; iii: MnO_2/ toluene/ reflux 2h
ii: 1) BuLi/ THF/ -75°C/ 1h3O 2) 2-F-PhCHO/ 1h/ -75°C iv: 1) Py, HCl/ 170°C 10 mn 2) NH_4OH/ ice

Scheme 2

The reported synthesis of Fascaplysin **1** relies on key steps such as metalation, cross-coupling and cyclization. It is fully convergent and regioselective and allows an interesting 76% overall yield (based on boronic acid **3** and iodopyridine **4**) in four steps.

REFERENCES and NOTES

1. Roll, D.M.; Ireland, C.M.; Lu, H.S.M. and Clardy, J. *J. Org. Chem.* **1988**, *53*, 3276.
2. Pelcman, B. and Gribble, G.W. *Tetrahedron Lett.* **1990**, *31*, 2381.
3. Rocca, P.; Marsais, F.; Godard, A. and Quéguiner, G. *Tetrahedron* **1993**, *49*, 49.
4. Rocca, P.; Marsais, F ; Godard, A. and Quéguiner, G. *Tetrahedron* **1993**, *49*, 3325.
5. For a comprehensive review on directed ortho metalation, see: Gschwend, H.W.; Rodriguez, H.R. *Org. React. (N.Y.)* **1976**, *26*, 1. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. For a recent review on π-deficient heterocycle metalation, see: Quéguiner, G.; Marsais, F.; Snieckus, V. and Epsztajn, *J. Advances Het. Chem.* **1991**, *52*, 187.
6. Miyaura, N.; Yanagi, T. and Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
7. Trécourt, F.; Marsais, F.; Güngör, T. and Quéguiner, G. *J. Chem. Soc. Perkin Trans.1* **1990**, 2409.

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