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TOTAL SYNTHESIS OF THE MARINE SPONGE PIGMENT FASCAPLYSIN

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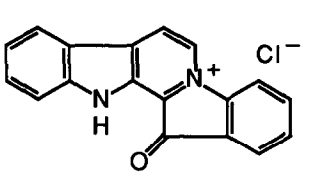
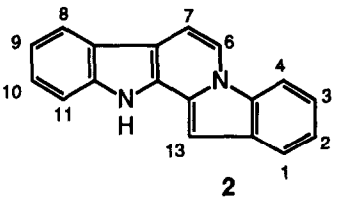
Summary: *Fascaplysin (1), an antimicrobial and cytotoxic red pigment from the marine sponge* Fascaplysinopsis *sp., has been synthesized in seven steps from indole (65% yield). The pivotal intermediate in the synthesis is diindole 3 which is induced to undergo acid-catalyzed cyclization and dehydrogenation to afford the desired pentacycle 2 in > 90% yield. Peracid oxidation of 2 yields fascaplysin.*

A red pigment, fascaplysin, was recently isolated from the Fijian sponge *Fascaplysinopsis* Bergquist sp. and characterized as the novel 12*H*-pyrido[1,2-*a*:3,4-*b*']diindole **1**, a ring system (**2**) that is apparently unique among natural products.[1] Fascaplysin (**1**) inhibits the growth of several microbes and is active against the L-1210 mouse leukemia system *in vitro*.[1] Herein we describe the first total synthesis of fascaplysin.

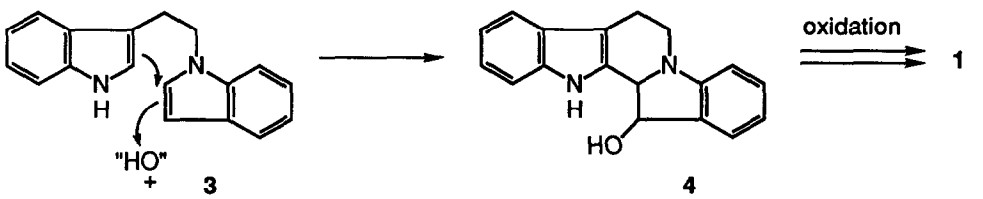


1



2

Our approach to the synthesis of **1** was predicated on the belief that diindole **3** would undergo regioselective electrophilic attack at the presumed more reactive unsubstituted indole-β-position[2] and concomitant cyclization to **4**. Subsequent oxidation would complete the synthesis.

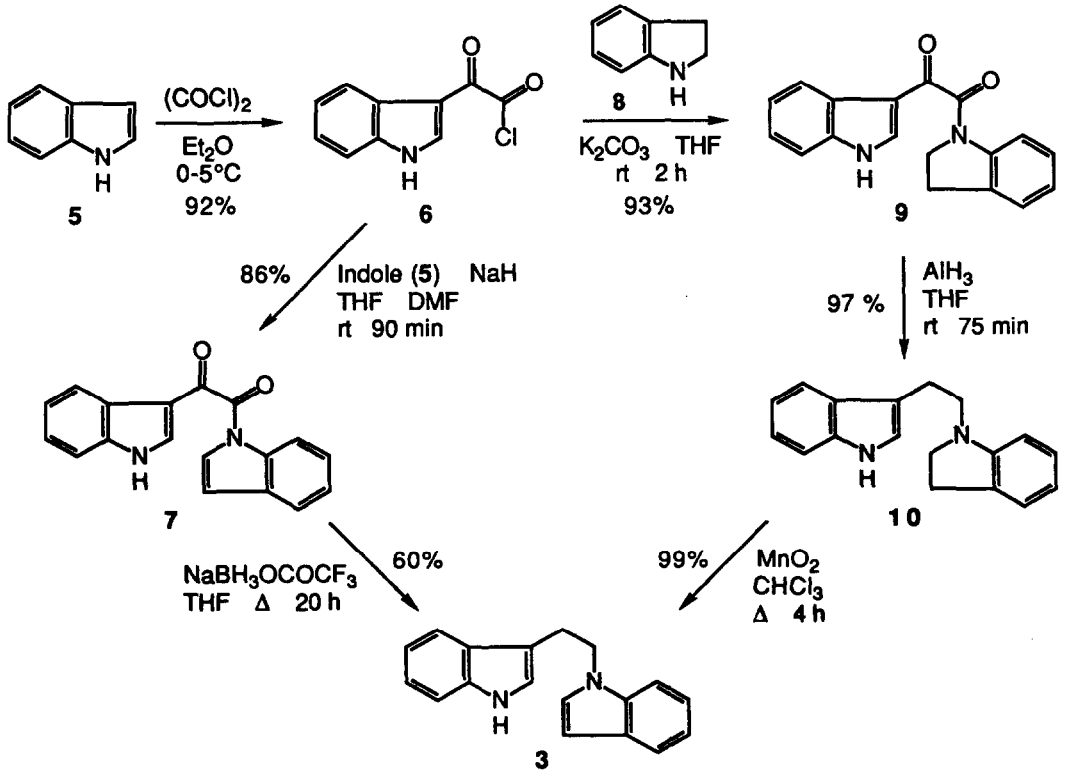


3 **4**

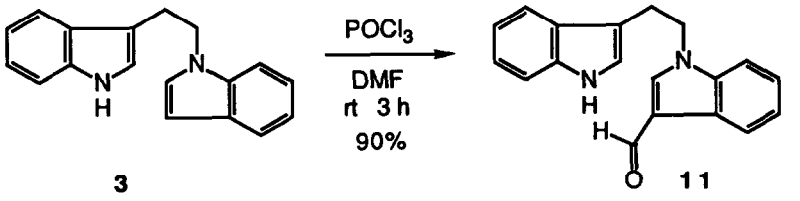
Diindole **3** was readily fashioned from indole (**5**) as shown in Scheme 1. Thus, the known 3-indolylglyoxylyl chloride[3] was allowed to react with 1-indolylsodium to form keto amide **7** (mp 228-9°C).[4,5] Attempted reduction of **7** with $LiAlH_4$ resulted in *N*-acyl cleavage[6] leading to tryptophol and indole. However, this cleavage reaction could be thwarted by the use of sodium (mono)trifluoroacetoxyborohydride,[7] which afforded **3** (mp 135.5-136°C)[4,5] in 47% overall yield from indole (**5**). To avoid the relatively poor reduction step (**7** → **3**), we

developed an improved synthesis of **3** which utilizes indoline (**8**) in place of indole (**5**) in the reaction with **6** (Scheme 1). Since indoline (**8**) is readily available from indole ($NaCNBH_3$, HOAc, 15°C, 94%),[8] this route also utilizes indole in the construction of both "halves" of **3**. Thus, acylation of indoline (**8**) with **6** gave keto amide **9** (mp 233.5-234°C).[4,5] Unfortunately, reduction of **9** with either $LiAlH_4$, $NaBH_4$, or B_2H_6 resulted in *N*-acyl cleavage or gave complex mixtures. After some experimentation, we found that AlH_3 (prepared *in situ* from $LiAlH_4$ and H_2SO_4)[9] smoothly transformed **9** into indolylindoline **10** (mp 135.5-136°C)[4,5] in excellent yield. Dehydrogenation of **10** was accomplished with MnO_2 to give **3** in 82% overall yield from indole. This alternative synthesis of **3** can be accomplished without the need for chromatography.

Scheme 1

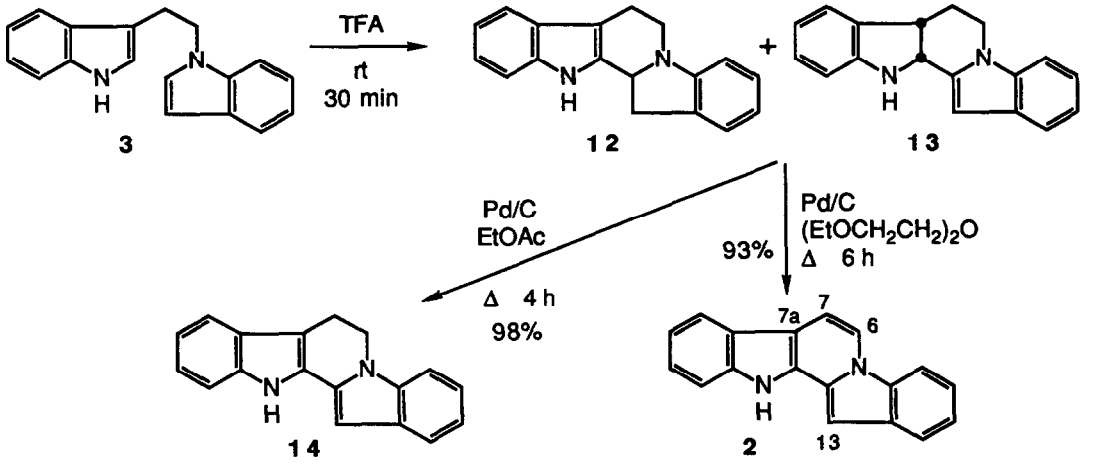


Preliminary attempts to oxidatively cyclize **3** to **4** with oxygen electrophiles[10] ($Pb(OAc)_4$; peracids; MoOPH; DDQ, HOAc) or their synthetic equivalents (NBS; *t*-BuOCl; $CuCl_2$, HOAc) have been discouraging. Furthermore, reaction of **3** with the Vilsmeier reagent ($POCl_3$/DMF) gave aldehyde **11** (mp 185.5-186.5°C)[5,11] in 90% yield, rather than the pentacyclic aldehyde. In any event, this latter result supports our contention that the unsubstituted indole-β-position would be the preferred site of electrophilic attack.

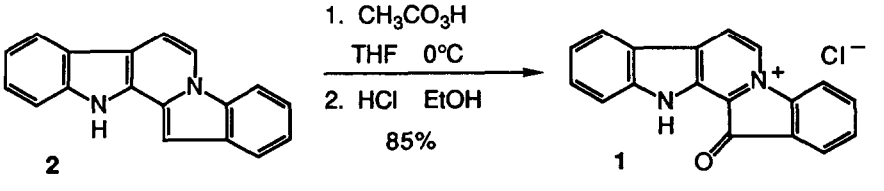


Since indoles undergo clean β-protonation in neat carboxylic acids,[12] we exposed **3** to trifluoroacetic acid (TFA) at room temperature (Scheme 2). To our delight, this treatment led to a mixture of the cyclized products **12** (mp 195-7°C)[4,5] and **13**[5] in a 10:1 ratio (88% yield after chromatographic separation).[13] Since it was more convenient not to separate **12** and **13**, direct oxidation of this mixture with 10% Pd/C in refluxing EtOAc afforded **14** (mp 263-5°C dec)[4,5] in 98% yield from **3**. A similar oxidation, but in refluxing 2-ethoxyethyl ether (180-190°C),[14] gave the fully aromatic pentacycle **2** as a pale green solid (mp 229-233°C dec)[5] in 93% yield from **3**.

Scheme 2



We anticipated that the C-13 position would be the preferred site of electrophilic attack in **2** since the resulting species would be a highly stabilized *N*-phenyl-β-carbolinium ion. In contrast, electrophilic attack at C-6, C-7, or C-7a would yield less stable intermediates. Indeed, treatment of **2** with *m*-CPBA, magnesium monoperoxyphthalate (MMPP),[15] or, better, peracetic acid in cold THF afforded fascaplysin (**1**) in 85% yield after vacuum liquid chromatography[16] (silica gel, Merck, 230-400 mesh, elution with HOAc/EtOH) followed by treatment with conc HCl/EtOH. This was identical in all respects (TLC, IR, MS, UV, ^{1}H NMR) with the natural product.



In summary, we have synthesized fascaplysin in 65% yield from indole (seven steps). The route should allow for the preparation of larger quantities of **1** as well as structural analogs for full biological evaluation of this natural product.

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4. This new compound gave a satisfactory elemental analysis (C, ± 0.12%; H, ± 0.12%; N, ± 0.28%).
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14. When old bottles of 2-ethoxyethyl ether were used, a dimer of **2** could be isolated along with **2**. For what may be a similar dimerization in the oxidation chemistry of tetrahydropapaveroline, see Mak, C.-P.; Brossi, A. *Heterocycles* **1979**, *12*, 1413.
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