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A Simple and Practical Approach to the Synthesis of the Marine Sponge Pigment Fascaplysin and Related Compounds

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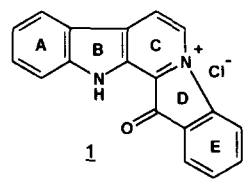
Abstract: Fascaplysin **1**, an antimicrobial and cytotoxic red pigment of the marine sponge *Fascaplysinopsis sp.*, has been synthesized in five steps from tryptamine **2** in 44% overall yield. The key steps in the synthesis are: (a) dehydrogenation of the dihydro-β-carboline intermediate **4** simultaneously with its benzylic oxidation on treatment with MnO_2 and (b) the thermal cyclization of the resulting β-carboline **7** into a quaternary salt **8**. Similarly, indoloisoquinolines **15** and **16**, the tetracyclic analogues of **1**, were prepared in six steps from α-amino ketone **9** in 59 and 55% overall yields, respectively.

Fascaplysin **1** was the first natural 12*H*-pyrido[1,2-*a*:3,4-*b'*]diindole isolated in 1988 from the marine sponge *Fascaplysinopsis sp.*[1]. This pigment, with dehydroluffariellolide diacid monoanion as the counterion, was subsequently isolated from the Fijian sponge *F. reticulata*, along with the other novel β-carbolines[2]. In 1992-1994 fascaplysin exhibiting antimicrobial and cytotoxic activities was synthesized by three groups, which used in these works the quite different approaches[3-5]. In Gribble's synthesis the keystone intermediate 12*H*-pyrido[1,2-*a*:3,4-*b'*]diindole was prepared from indole in six steps via acid-induced ring closure of the diindole intermediate[3]. Another approach to **1** was based on methodology which involved such reactions of the starting functionally substituted pyridine as metalation, heteroring cross-coupling and cyclization[4]. Lastly, a pivotal step of the iminophosphorane-mediated synthesis of **1** was the formation of the β-carboline part of its molecule via the tandem of aza-Wittig reaction / electrocyclic ring closure of 1,3-disubstituted indole[5].



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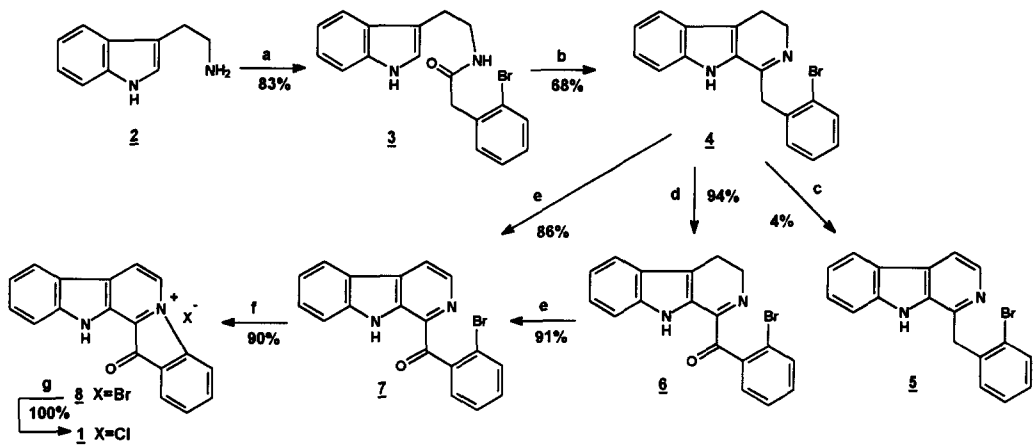
Unfortunately, the literature routes for the synthesis of fascaplysin are of limited utility for practical purposes, because of a large number of steps involved, the inaccessibility of most of starting materials

and the employment of some aggressive and hazardous reagents. We wish to report here a simple and practical synthesis of the title compound which is amenable to its large scale preparation.

Fascaplysin **1** was obtained in five steps from tryptamine **2** in 44% overall yield as outlined in Scheme 1. The shown yields have not been optimized. Acylation of tryptamine with *o*-bromophenylacetic acid gave the corresponding amide **3** which was converted into dihydro-β-carboline **4** by standard procedure. Our further plan was to realize successively dehydrogenation of the C ring of the intermediate **4** and benzylic oxidation of the resulting product. However, an attempt to dehydrogenate **4** by the action of Pd/C (10%) gave very low yield of β-carboline **5**. Treatment of **4** with usual black MnO_2 in $CHCl_3$ at room temperature led to the unexpected formation of ketone **6**. This result is very interesting owing to ease of oxidation of the substrate at the benzylic position that is commonly not characteristic of this reagent. At the same time reaction of **4** (or **6**) with MnO_2 in $CHCl_3$ under reflux produced α-acyl substituted β-carboline **7** with high yield. Short-run heating of **7** yielded the pyridodiindole quaternary salt **8** which was converted into fascaplysin **1** by treatment with dry HCl in MeOH. The main spectral characteristics (IR, UV, HMRS, ^1H and ^{13}C NMR) of synthetic fascaplysin are identical to those of the natural product. All the reagents used in this synthesis are commercially available and none of the steps involve chromatographic separation.

Scheme 1.

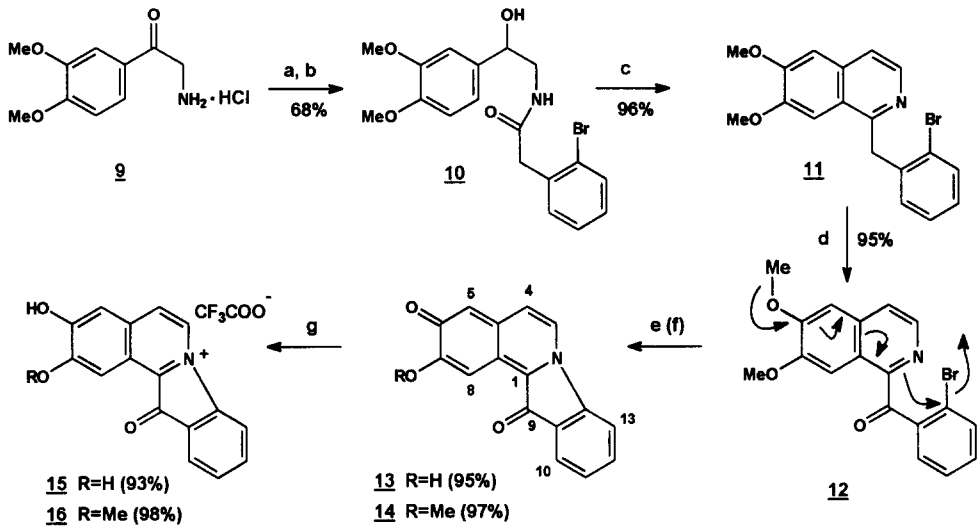


a: *o*-bromophenylacetic acid, tetralin, Ar, azeotropic distillation, 40 min; b: $POCl_3$, PhH, reflux, 30 min; c: Pd/C (10%), tetralin, reflux, 2 h; d: MnO_2, $CHCl_3$, r.t., 3 h; e: MnO_2, $CHCl_3$, reflux, 3 h; f: 220°C, 20 min; g: HCl/MeOH.

There are grounds to belive that the present approach provides a convenient and relatively simple route for synthesis not only of fascaplysin but also certain of pyrido[1,2-*a*:3,4-*b*']diindoles with substituents at the A

and E rings and other structurally related compounds. For example, indoloisoquinolines **15** and **16**, the tetracyclic analogues of fascaplysin having a C/D/E-ring system identical to that for **1**, were prepared in analogous manner as shown in Scheme 2. Compound **16** is a des-*O*-methyl analogue (OH at C-6 in place OMe) of the previously described indoloisoquinoline which was formed as a by-product in a synthesis of lysicamine[6].

Scheme 2.



a: *o*-bromophenylacetic acid, DCC, Py, DMF, 20°C, 3 h; b: $NaBH_4$, MeOH, 20°C, 30 min; c: $POCl_3$, PhH, reflux, 1 h; d: SeO_2, EtOAc, reflux, 4 h; e: 200°C, 20 min; f: PhBr, reflux, 6 h; g: TFAA, 20°C.

Acylation of α-amino ketone hydrochloride **9** with *o*-bromophenylacetic acid followed by reduction of the resulting amido ketone with $NaBH_4$ in MeOH afforded hydroxy amide **10** which was converted into isoquinoline **11** by treatment with $POCl_3$ in benzene. Oxidation of **11** with SeO_2 in EtOAc yielded ketone **12.** In contrast to the α-acyl substituted β-carboline **7** the heating of α-acylated isoquinoline **12** at 200°C produced not a quaternary salt of the type **8** but the tetracyclic compound **13** having a cyclohexadienone moiety[7]. This result is due to the easy elimination of MeBr from the molecule **12** when, as shown in Scheme 2, an N-C bond is formed. It is notable that under these conditions O-demethylation of MeO group at the 7-position also took place, whereas at reflux of a solution of **12** in PhBr this process was not observed and compound **14** was a single product[8]. Treatment of **13** and **14** with CF_3COOH at room temperature gave the quaternary salts **15**[9] and **16**[10]. The choice of trifluoroacetic acid as a solvent for compounds **13** and **14** was dictated by their very low solubility (especially **13**) in other solvents commonly used for ^1H NMR spectra measurements. The overall yields of **15** and **16** from α-amino ketone **9** were 55 and 59%, respectively, on six steps.

By this means, the outlined approach to the total synthesis of fascaplysin and related compounds of this type allows to prepare such products in large quantities that, in turn, opens up new possibilities for extensive study of the structure-activity relationships among these structurally very interesting compounds.

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7. Selected spectral data for **13**: EIMS (70 eV), m/z (rel. int., %): 265 (M^++2, 18), 264 (M^++1, 22), 263 (M^+, 97), 236 (19), 235 (100), 207 (14), 206 (24).
8. Selected spectral data for **14**: EIMS (15 eV), m/z (rel. int., %): 279 (M^++2, 100), 278 (M^++1, 19), 277 (M^+, 8), 265 (7), 264 (30), 263 (17), 249 (2), 248 (8), 247 (2), 237 (3), 236 (13). ^{1}H NMR (250 MHz, DMSO-d_6): 3.87 (s, 3H, OMe), 6.45 (s, 1H, H-5), 7.08 (d, 1H, J=7.0 Hz, H-4), 7.39 (dt, 1H, J=1.1, 7.2 Hz, H-11), 7.78 (dd, 1H, J=1.2, 7.4 Hz, H-13), 7.79 (dt, 1H, J=1.2, 7.4 Hz, H-12), 7.93 (s, 1H, H-8), 7.96 (dd, 1H, J=1.1, 7.2 Hz, H-10), 8.34 (d, 1H, J=7.0 Hz, H-3).
9. Selected spectral data for **15**: ^{1}H NMR (250 MHz, CF_3COOD): 7.67 (s, 1H, H-5), 7.77 (dt, 1H, J=1.6, 7.0 Hz, H-12), 7.98 (dt, 1H, J=1.4, 7.0 Hz, H-11), 8.04 (dd, 1H, J=1.6, 7.0 Hz, H-13), 8.10 (dd, 1H, J=1.4, 7.0 Hz, H-10), 8.31 (d, 1H, J=6.2 Hz, H-4), 8.79 (d, 1H, J=6.2 Hz, H-3), 8.81 (s, 1H, H-8). ^{13}C NMR (CF_3COOD), δ: 102.1, 106.4, 106.6, 108.0, 111.1, 111.3, 111.6, 115.6, 117.5, 118.4, 120.8, 121.5, 126.3, 132.5, 136.8, 208.8.
10. Selected spectral data for **16**: ^{1}H NMR (250 MHz, CF_3COOD): 4.36 (s, 3H, OMe), 7.67 (s, 1H, H-5), 7.78 (dt, 1H, J=1.2, 6.5 Hz, H-12), 7.99 (dt, 1H, J=1.2, 6.5 Hz, H-11), 8.06 (dd, 1H, J=1.2, 6.5 Hz, H-13), 8.12 (dd, 1H, J=1.2, 6.5 Hz, H-10), 8.33 (d, 1H, J=6.5 Hz, H-4), 8.73 (s, 1H, H-8), 8.83 (d, 1H, J=6.5 Hz, H-3).

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