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The first syntheses of 3-bromofascaplysin, 10-bromofascaplysin and 3,10-dibromofascaplysin—marine alkaloids from *Fascaplysinopsis reticulata* and *Didemnum* sp. by application of a simple and effective approach to the pyrido[1,2-*a*:3,4-*b*′]diindole system

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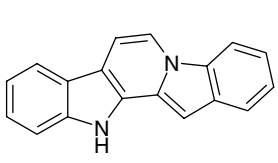
Abstract—A simple and practical approach for the synthesis of the marine sponge pigment fascaplysin was used for the total syntheses of its natural derivatives, the marine alkaloids 3-bromofascaplysin, 10-bromofascaplysin, and 3,10-dibromofascaplysin. The conditions of each step were revised, and as a result these compounds were produced by identical procedures with total yields of 40–43%.

The 12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole ring system **1** forms the framework of several marine alkaloids. The red pigment fascaplysin **2**, which was isolated in 1988 from the sponge *Fascaplysinopsis Bergquist* sp.,[1] is the most investigated representative. It exhibits a broad range of bioactivities including antibacterial, antifungal, antiviral, HIV-1-RT, p56 tyrosine kinase, antimalarial, potency to numerous cancer cell lines, specific inhibition of Cdk 4 and DNA intercalation.[2] These activities demonstrate the huge potential of fascaplysin derivatives for therapeutic assays and necessitates the elaboration of effective methods for their syntheses.

Recently, three bromosubstituted derivatives of fascaplysin were isolated: 3-bromofascaplysin **3**, 10-bromofascaplysin **4** and 3,10-dibromofascaplysin **5** from the sponge *Fascaplysinopsis reticulata* and the tunicate *Didemnum* sp.[3] We report here the first total syntheses of these compounds via a simple approach involving



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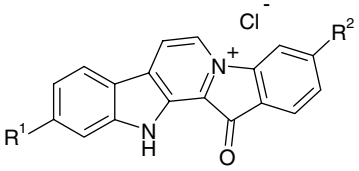

2 R^1=H, R^2=H
3 R^1=H, R^2=Br
4 R^1=Br, R^2=H
5 R^1=Br, R^2=Br

pyrido[1,2-*a*:3,4-*b*′]diindole formation, which we have elaborated for the synthesis of fascaplysin.[4] In the course of our work the conditions of each step were revised, and as a result the three bromofascaplysins were produced by identical procedures with total yields of 40–43% (Scheme 1 and Table 1).

The starting materials in our synthetic sequence were: tryptamine **6**, 6-bromotryptamine **7**, (2-bromophenyl)-acetic acid **8**, and (2,4-dibromophenyl)acetic acid **9**.[5] The latter substance was prepared in three steps from commercially available 3-bromo-4-methylaniline in 54% overall yield (Scheme 2). Each step was realized

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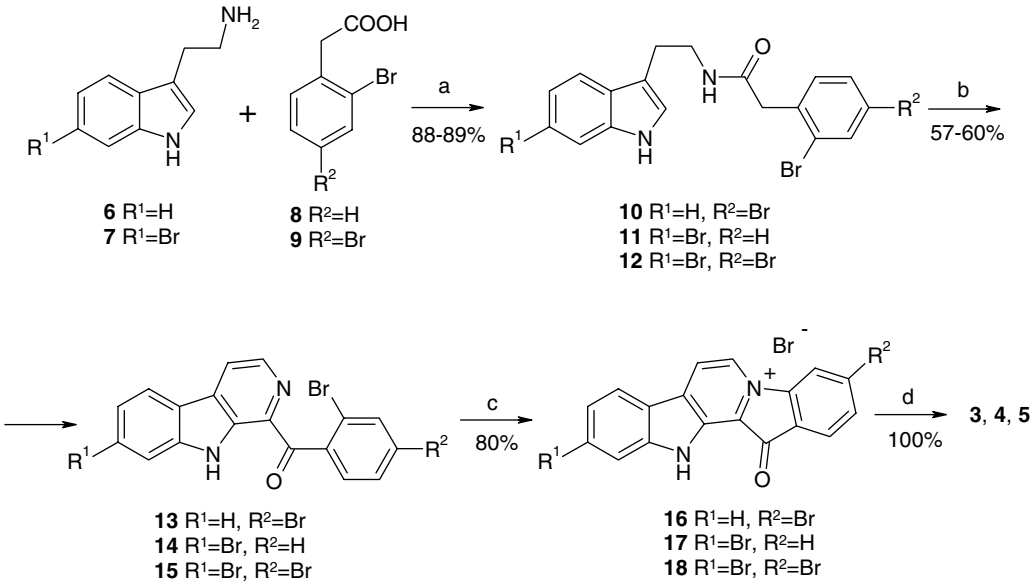
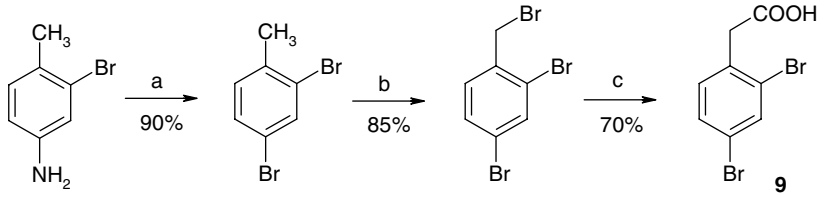


Scheme 1. Reagents and conditions: (a) **8** or **9**, DCC, CH_3CN, reflux, 30 min; (b) $POCl_3$, CH_3CN, Ar, reflux, 40 min, then MnO_2, PhH, reflux, 3 h; (c) 220 °C, 20 min; (d) HCl (dry), CH_3OH.

Table 1. Yields of the intermediates in the syntheses of **3**, **4**, and **5**

Target	Yield of acylation (step a), %	Yield of cyclization with oxidation (step b), %	Yield of quaternization (step c), %	Total yield, %
3-Bromofascaplysin **3**	89	60	80	43
10-Bromofascaplysin **4**	88	58	80	41
3,10-Dibromofascaplysin **5**	88	57	80	40



Scheme 2. Reagents and conditions: (a) $NaNO_2$, HBr (aq), 0 °C, then CuBr, HBr (aq), reflux, 40 min; (b) NBS, AIBN, CCl_4, reflux, 1 h; (c) NaCN, C_2H_5OH (aq), reflux, 1 h, then H_2SO_4 (aq), reflux, 12 h.

by standard procedures and was not optimized. This sequence can be used for obtaining a number of (2-bromophenyl)acetic acids, substituted at C-4 of the aromatic ring. Compounds **6** and **8** are commercially available, and the synthesis of 6-bromotryptamine **7** is described in the literature.[6]

To obtain amides **10**–**12** we attempted to use high-temperature azeotropic distillation as in the original fascaplysin synthesis, however, this synthetic method was ineffective. Acylation of tryptamines **6** and **7** with the acyl chlorides obtained from acids **8** and **9** was accompanied by secondary reactions, affording yields of the target products of about 20% after chromatographic separation. Use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a condensing agent allowed the preparation of amides **10**–**12** in 88–89% yield without additional purification.[7]

Compounds **10**–**12** were converted to α-acyl substituted β-carbolines **13**–**15** in two steps without isolation of the intermediate dihydro-β-carbolines.[8] Bischler–Napieralski cyclization was realized using $POCl_3$ in acetonitrile. The dihydro-β-carbolines were oxidized using MnO_2 (oxygen can be used instead without a decrease in yield).[9]

Finally, short-run heating of β-carbolines **13**–**15** yielded the pyridodiindole quaternary salts **16**–**18**, which were converted into compounds **3**–**5** by treatment with dry HC1 in MeOH. The overall yields of products were 40–43%. The spectral characteristics of synthetic fascaplysins **3**–**5** were identical to those of the natural products.[3,4]

At the present time, the biological activities of synthetic 3-bromofascaplysin **3**, 10-bromofascaplysin **4** and 3,10-

dibromofascaplysin **5** are being investigated thoroughly. It has already been shown by flow cytometry that compounds **3** and **4** induced apoptosis in human leukemia HL-60 cells at low concentrations of 0.25 μM: 35.8% and 36.1% of the apoptotic cells compared to untreated control cells.

We intend to apply this approach to the formation of 12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole ring systems to synthesize various fascaplysin derivatives, that, in turn, will open up fresh opportunities for detailed studies of the structure activity relationships among these potentially physiologically active substances.

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5. Compound **9**: white needles; mp 141–142 °C; IR (KBr) ν_{max}: 2965, 1708, 1658, 1581, 1468 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.75 (d, $J = 1.9$ Hz, 1H), 7.42 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.17 (d, $J = 8.3$ Hz, 1H), 3.79 (s, 2H, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.8, 135.2, 132.6, 132.5, 130.8, 125.7, 122.0, 40.7; MS (APCI): $m/z = 293/295/297$ (50.9:100.0:49.5) $(M+H)^+$. Anal. Calcd for $C_8H_6O_2Br_2$: C, 32.69; H, 2.06. Found: C, 32.62; H, 2.08.
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7. For example, compound **10**: white solid; mp 119–120 °C; IR (KBr) ν_{max}: 3366, 3284, 3081, 2944, 1650, 1627, 1614, 1580, 1563, 1468 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ: 10.81 (br s, 1H, NH), 8.14 (t, $J = 5.9$ Hz, 1H, NHCO), 7.82 (d, $J = 2.2$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.51 (dd, $J_1 = 8.1$ Hz, $J_2 = 2.2$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.26 (d, $J = 8.1$ Hz, 1H), 7.14 (d, $J = 2.2$ Hz, 1H), 7.06 (td, $J_1 = 6.8$ Hz, $J_2 = 8.1$ Hz, $J_3 = 1.2$ Hz, 1H), 6.97 (td, $J_1 = 6.8$ Hz, $J_2 = 8.1$ Hz, $J_3 = 1.2$ Hz, 1H), 3.56 (s, 2H, $-CH_2-CO$), 3.35 (q, $J_1 = 7.3$ Hz, 2H, CH_2-NH), 2.83 (t, $J = 7.3$ Hz, 2H, CH_2-CH_2-NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.4, 136.4, 134.9, 133.0, 131.7, 129.0, 127.9, 127.2, 124.9, 122.1, 122.0, 119.4, 118.6, 112.7, 111.2, 44.1, 39.8, 33.9; MS (APCI) $m/z = 435/437/439$ (50.5:100.0:50.7) $(M+H)^+$. Anal. Calcd for $C_{18}H_{16}N_2OBr_2$: C, 49.57; H, 3.70; N, 6.42. Found: C, 49.67; H, 3.72; N, 6.48.
8. For example, compound **13**: yellow solid; mp 174–175 °C; IR (KBr) ν_{max}: 3292, 3061, 1657, 1625, 1576, 1494, 1463 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ: 10.45 (br s, 1H, NH), 8.48 (d, $J = 4.9$ Hz, 1H), 8.44 (d, $J = 4.9$ Hz, 1H), 8.34 (d, $J = 7.9$ Hz, 1H), 8.02 (d, $J = 1.9$ Hz, 1H), 7.85 (d, $J = 8.3$ Hz, 1H), 7.77 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.64 (td, $J_1 = 7.2$ Hz, $J_2 = 8.0$, Hz, $J_3 = 1.0$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.34 (td, $J_1 = 7.2$ Hz, $J_2 = 7.9$ Hz, $J_3 = 1.0$ Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 195.9, 141.9, 140.5, 137.9, 135.3, 134.8, 134.3, 131.3, 131.0, 130.3, 129.2, 123.2, 121.9, 120.5, 120.0, 119.8, 113.1; MS (APCI) $m/z = 429/431/433$ (50.5:100.0:50.6) $(M+H)^+$. Anal. Calcd for $C_{18}H_{10}N_2OBr_2$: C, 50.27; H, 2.34; N, 6.51. Found: C, 50.37; H, 2.36; N, 6.60.
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