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A simple and effective approach to the synthesis of pyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine skeleton of arnoamines A and B, pentacyclic marine alkaloids from the ascidian *Cystodytes* sp.

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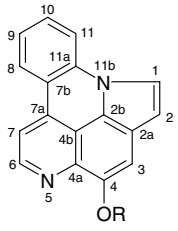
Dedicated to the memory of Professor George B. Elyakov, who has been an inspiration to us over the years

Abstract—Starting from ethyl 5-hydroxy-2-methyl-1-phenylindole-3-carboxylate, a simple and effective approach to the synthesis of pyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine skeleton of arnoamines A and B, unique pentacyclic alkaloids from the ascidian *Cystodytes* sp., has been developed. Synthesis of this ring system involves seven steps and produces ethyl 4-methoxy-1-methylpyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine-2-carboxylate in 41.5% overall yield.

Arnoamines A **1** and B **2** are the first members of a new family of marine cytotoxic alkaloids possessing a pyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine ring system which has not been previously observed in nature.[1] In 2000, Delfourne and co-workers accomplished the first synthesis of these alkaloids.[2]



1 R=H arnoamine A
2 R=Me arnoamine B

Starting from commercially available 2-methoxy-5-nitroaniline, arnoamine B **2** was obtained in 12 steps with a 5% overall yield. In this synthesis, a pentacyclic product, ethyl 4-methoxypyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine-1-carboxylate, having the ring system of arnoamines A and B, was formed in 10 steps with a 5.5% overall yield, using many expensive chemicals.

Now, we report a simple and effective approach to the synthesis of pyridopyrroloacridine ring system of arnoamines A and B.

The starting material in our sequence (Scheme 1) was the known indole **3** readily available by the condensation of *p*-benzoquinone with commercially available ethyl 3-anilinocrotonate.[3,4]

The treatment of **3** with dimethyl sulfate in the presence of base gave methyl ether **4** in 95% yield. Nitration of **4** with 75% nitric acid in acetic anhydride at −10 °C afforded a mixture of nitro derivatives **5** and **6** which was separated by flash chromatography[5] to give the desired nitro compound **5** with 63% yield.[6] The conversion of **5** to amine **7** was then achieved in almost quantitative yield using reduction on Raney nickel.[7]

Amine **7** was treated with 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione[8] to produce Meldrum's acid derivative **8** in 95% yield.[9] The thermal cyclization

Keywords: Synthesis; Marine alkaloids; Arnoamines A and B; Pyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridines; Ascidians; Cytotoxines.
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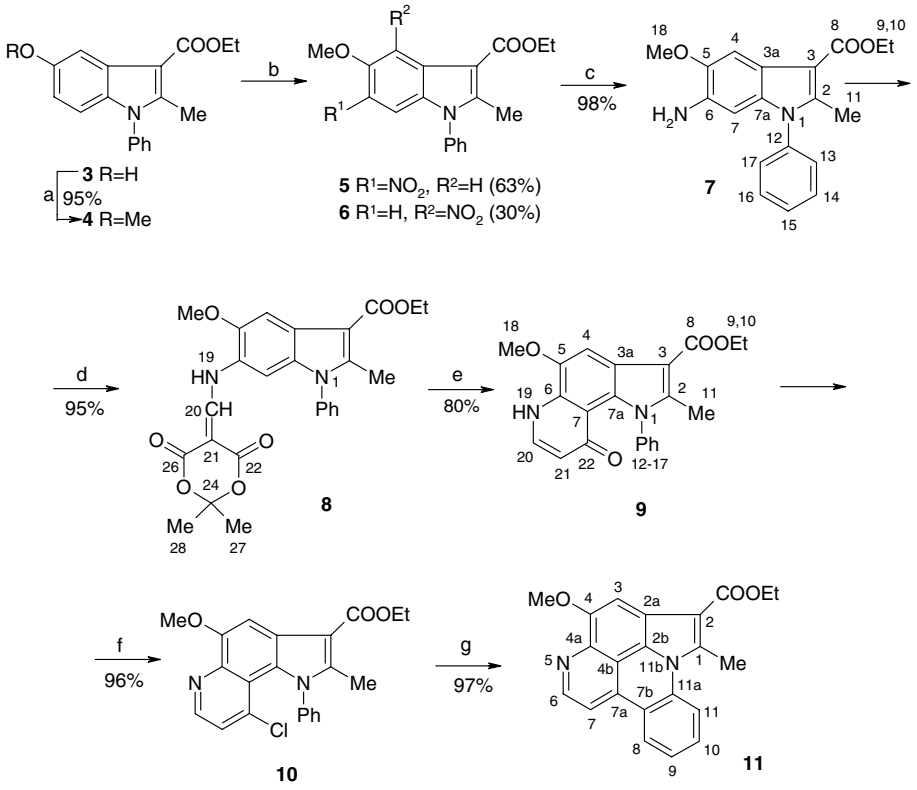

Scheme 1. Reagents and conditions: (a) Me_2SO_4, 2 N NaOH, H_2O, dioxane, rt, 30 min; (b) HNO_3 (75%), Ac_2O, −10 °C, 3 h; (c) Ni(Ra), H_2, *i*-PrOH, 60 °C, 2 h; (d) Meldrum's acid, $CH(OMe)_3$, reflux, 1 h; (e) Ph_2O, N_2, 220 °C, 30 min; (f) $POCl_3$, reflux, 30 min; (g) Bu_3SnH, AIBN, PhH, reflux, 24 h.

Table 1. ^{13}C and ^{1}H NMR data for **11** in $CDCl_3$ at 75 and 300 MHz, respectively

Atom	δ_C (mult)[a]	δ_H (mult, *J*, Hz)	HSQC, HMBC ($^{1}H \rightarrow {}^{13}C$)
1	138.4 s		
2	109.9 s		
2a	120.8 s		
2b	137.9 s		
3	102.6 d	7.69 s	H(3) → C(3) H(3) → C(2a) H(3) → C(2b) H(3) → C(2) H(3) → C(4) H(3) → C(4a) H(3) → C(4b)
4	150.8 s		
4a	113.3 s		
4b	116.2 s		
6	147.4 d	8.98 d, $J = 5.2$	H(6) → C(6) H(6) → C(7) H(6) → C(7a) H(6) → C(4a) H(6) → C(7b) H(6) → C(2b)
7	110.6 d	7.80 d, $J = 5.2$	H(7) → C(7) H(7) → C(6) H(7) → C(4a) H(7) → C(7b) H(7) → C(2b) H(7) → C(2a)
7a	132.1 s		
7b	122.0 s		
8	125.5 d	8.34 dd, $J_1 = 8.0$, $J_2 = 1.6$	H(8) → C(8) H(8) → C(10) H(8) → C(7a) H(8) → C(7b) H(8) → C(11a) H(8) → C(11)
9	124.7 d	7.46 ddd, $J_1 = 8.0$, $J_2 = 7.2$, $J_3 = 0.6$	H(9) → C(9) H(9) → C(11) H(9) → C(7b) H(9) → C(8) H(9) → C(11a)
10	130.5 d	7.61 ddd, $J_1 = 8.6$, $J_2 = 7.2$, $J_3 = 1.6$	H(10) → C(10) H(10) → C(11) H(10) → C(8) H(10) → C(7b) H(10) → C(11a)
11	117.5 d	8.23 dd, $J_1 = 8.6$, $J_2 = 0.6$	H(11) → C(11) H(11) → C(9) H(11) → C(11a) H(11) → C(7b) H(11) → C(7a)

Table 1 (*continued*)

Atom	δ_C (mult)[a]	δ_H (mult, *J*, Hz)	HSQC, HMBC ($^1H \rightarrow {}^{13}C$)
11a	136.2 s		
OCH_3	55.9 q	4.14 s	H(OMe) → C(4)
CO	166.0 s		
$O\underline{C}H_2CH_3$	60.1 t	4.50 q, $J = 7.1$	$H(O\underline{C}H_2CH_3) \rightarrow C(\underline{C}O)$ $H(O\underline{C}H_2CH_3) \rightarrow C(OCH_2\underline{C}H_3)$
$OCH_2\underline{C}H_3$	14.5 q	1.57 t, $J = 7.1$	$H(OCH_2\underline{C}H_3) \rightarrow C(O\underline{C}H_2CH_3)$
CH_3	15.9 q	3.26 s	$H(CH_3) \rightarrow C(CH_3)$ $H(CH_3) \rightarrow C(1)$ $H(CH_3) \rightarrow C(2)$ $H(CH_3) \rightarrow C(11)$ $H(CH_3) \rightarrow C(CO)$

[a] Carbon multiplicities were assigned on the basis of the results of DEPT-135, DEPT-90, HSQC, and HMBC experiments.

of **8** in diphenyl ether at 220 °C gave the cyclized product **9** in 80% yield.[10] When **9** was treated with phosphorus oxychloride at reflux, the chloro derivative **10** was obtained.[11] The thermal cyclization of **10** in benzene at reflux under the action of tri-*n*-butyltin hydride in the presence of α,α′-azoisobutyronitrile furnished ethyl 4-methoxy-1-methylpyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine-2-carboxylate **11** in 97% yield.[12] Thus, compound **11**, possessing the unique pentacyclic ring system of arnoamines A and B, was synthesized from ethyl 5-hydroxy-2-methyl-1-phenylindole-3-carboxylate **3** in seven steps in 41.5% overall yield. The structure of **11** was confirmed by ^1H and ^{13}C NMR measurements (Table 1).

In conclusion, our approach to the pyrido[4,3,2-*mn*]pyrrolo[3,2,1-*de*]acridine ring system could be used to synthesize various structural analogues of arnoamines A and B, that, in turn, has opened up fresh opportunities for detailed study of the structure-activity relationships among these potentially cytotoxic compounds.

Acknowledgement

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2. Delfourne, E.; Roubin, C.; Bastide, J. *J. Org. Chem.* **2000**, *65*, 5476–5479.
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4. This condensation was performed in 1,2-dichloroethane at reflux with removal of water by azeotropic distillation to produce **3** in 61% yield.
5. Flash chromatography was performed on flash silica gel 60 (Merck 0.015–0.040 mm), using *n*-hexane–acetone, 5:1.
6. Compound **5**: light yellow needles; mp 153–155 °C (EtOH); IR (CCl_4) ν_{max}: 1704, 1625, 1598, 1582, 1524, 1471, 1457, 1428, 1409, 1331, 1205, 1187, 1174, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (t, $J = 7.0$ Hz, 3H), 2.60 (s, 3H), 4.04 (s, 3H), 4.44 (q, $J = 7.0$ Hz, 2H), 7.28 (m, $2H_{arom}$), 7.60 (m, $3H_{arom}$), 7.62 (s, 1H, H-4), 7.87 (s, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.5 (q, C-11), 14.6 (q, C-10), 56.9 (q, C-18), 59.9 (t, C-9), 104.6 (d, C-4), 105.5 (s, C-3), 108.9 (d, C-7), 128.0 (d, C-13, C-17), 129.7 (d, C-15), 130.2 (d, C-14, C-16), 130.7 (s, C-6), 131.3 (s, C-3a), 135.4 (s, C-12), 136.2 (s, C-7a), 149.8 (s, C-5), 150.1 (s, C-2), 165.2 (s, C-8); EIMS (15 eV): *m*/*z* (%) = 354 (M^+, 22), 353 (M^+-1, 100), 352 (M^+-2, 87), 323 (14), 322 (68), 321 (53), 205 (10). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.38; H, 5.12; N, 7.91. Found: C, 64.52; H, 5.16; N, 8.07. Numeration of atoms is given in structural formulae of compounds **7**–**9**, and **11**.
7. Compound **7**: pale yellow prisms; mp 72–75 °C; IR (CCl_4) ν_{max}: 3481, 3391, 1696, 1634, 1598, 1544, 1503, 1491, 1475, 1396, 1301, 1197, 1151, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (t, $J = 7.1$ Hz, 3H), 2.51 (s, 3H), 3.94 (s, 3H), 4.41 (q, $J = 7.1$ Hz, 2H), 6.35 (s, 1H, H-7), 7.28 (m, $2H_{arom}$), 7.58 (m, $3H_{arom}$), 7.60 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.0 (q, C-11), 14.6 (q, C-10), 55.9 (q, C-18), 59.3 (t, C-9), 96.3 (d, C-7), 102.3 (d, C-4), 104.9 (s, C-3), 118.7 (s, C-3a), 128.2 (d, C-13, C-17), 128.5 (d, C-15), 129.6 (d, C-14, C-16), 132.7 (s, C-6), 133.4 (s, C-7a), 137.0 (s, C-12), 142.3 (s, C-2), 145.4 (s, C-5), 166.3 (s, C-8); EIMS (15 eV): *m*/*z* (%) = 324 (M^+, 21), 323 (M^+-1, 100), 322 (M^+-2, 93), 309 (7), 308 (33), 307 (28). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.34; H, 6.22; N, 8.64. Found: C, 70.50; H, 6.19; N, 8.74.
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9. Compound **8**: yellow prisms; mp 223–224 °C; IR ($CHCl_3$) ν_{max}: 3252, 3176, 1717, 1692, 1678, 1625, 1614, 1579, 1540, 1502, 1479, 1449, 1323, 1279, 1203, 1156, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (t, $J = 7.1$ Hz, 3H), 1.72 (s, 6H), 2.55 (s, 3H), 4.04 (s, 3H), 4.44 (q, $J = 7.1$ Hz, 2H), 6.89 (s, 1H, H-7), 7.31 (m, $2H_{arom}$), 7.62 (m, $3H_{arom}$), 7. 79 (s, 1H, H-4), 8.45 (d, $J = 14.8$ Hz, 1H, H-20), 11.71 (d, $J = 14.8$ Hz, 1H, H-19); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.2 (q, C-11), 14.6 (q, C-10), 26.9 (q, C-27, C-28), 56.4 (q, C-18), 59.7 (t, C-9), 86.7 (s, C-21), 97.4 (d, C-7), 103.1 (d, C-4), 104.8 (s, C-24), 105.1 (s, C-3), 123.8 (s, C-6), 125.3 (s, C-3a), 128.1 (d, C-13, C-17), 129.6 (d, C-15), 130.3 (d, C-14, C-16), 132.1 (s, C-7a), 135.9 (s, C-12), 146.3 (s, C-2), 146.4 (s, C-5), 150.2 (d, C-20), 164.1 (s, C-26), 165.3 (s, C-22), 165.6 (s, C-8); EIMS (15 eV): *m*/*z* (%) = 479 (M^++1, 10), 478 (M^+, 22), 477 (M^+-1, 52), 476 (M^+-2, 100), 375 (29), 374 (23), 205 (36), 185 (38). Anal. Calcd for $C_{26}H_{26}N_2O_7$: C, 65.25; H, 5.48; N, 5.86. Found: C, 65.32; H, 5.50; N, 5.80.
10. Compound **9**: a white solid; mp 267–268 °C; IR ($CHCl_3$) ν_{max}: 3423, 1695, 1685, 1631, 1600, 1584, 1549, 1509, 1475, 1426, 1404, 1387, 1375, 1348, 1290, 1218, 1176, 1142, 1096, 1076, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (t, $J = 7.1$ Hz, 3H), 2.49 (s, 3H), 4.09 (s, 3H), 4.44 (q, $J = 7.1$ Hz, 2H), 6.10 (d, $J = 7.4$ Hz, 1H, H-21), 7.18 (m, $2H_{arom}$), 7.38 (m, $1H_{arom}$), 7.43 (m, $2H_{arom}$), 7.47 (m, 1H, H-20), 8.13 (s, 1H, H-4), 9.04 (br s, 1H, H-19); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (q, C-11), 14.6 (q, C-10), 56.2 (q, C-18), 59.7 (t, C-9), 104.3 (d, C-4), 104.3 (s, C-3), 111.9 (d, C-21), 123.1 (s, C-3a), 127.1 (d, C-13, C-17), 127.4 (s, C-6),

127.5 (d, C-15), 128.2 (d, C-14, C-16), 129.8 (s, C-7a), 134.3 (d, C-20), 142.2 (s, C-12), 143.7 (s, C-5), 146.1 (s, C-2), 166.0 (s, C-8), 176.5 (s, C-22); EIMS (15 eV): m/z (%) = 376 (M^+, 7), 375 (M^+-1, 35), 361 (4), 345 (6), 331 (18), 170 (98), 169 (99), 168 (98), 142 (98), 141 (98), 140 (100). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.19; H, 5.36; N, 7.45. Found: C, 70.23; H, 5.37; N, 7.50.

11. Compound **10**: a yellow solid; mp 105–107 °C; IR (CCl_4) ν_{max}: 1703, 1607, 1570, 1561, 1537, 1498, 1467, 1428, 1389, 1326, 1285, 1215, 1153, 1123, 1101, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.50 (t, $J = 7.1$ Hz, 3H), 2.66 (s, 3H), 4.19 (s, 3H), 4.49 (q, $J = 7.1$ Hz, 2H), 7.11 (m, $2H_{arom}$), 7.25 (d, $J = 4.5$ Hz, 1H, H-21), 7.39 (m, $1H_{arom}$), 7.42 (m, $2H_{arom}$), 8.14 (s, 1H, H-4), 8.65 (d, $J = 4.5$ Hz, 1H, H-20); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2 (q, C-11), 14.5 (q, C-10), 56.2 (q, C-18), 59.9 (t, C-9), 103.0 (d, C-4), 107.7 (s, C-3), 117.3 (s, C-7), 118.8 (s, C-6), 122.6 (d, C-21), 123.8 (s, C-3a), 127.0 (d, C-13, C-17), 127.7 (d, C-15), 129.3 (d, C-14, C-16), 137.8 (s, C-22), 140.7 (s, C-7a), 142.0 (s, C-12), 145.5 (d, C-20), 147.1 (s, C-2), 151.6 (s, C-5), 165.6 (s, C-8); EIMS (15 eV): m/z (%) = 396 (M^+, 1), 395 (M^+-1, 3), 394 (M^+, 7), 393 (M^+-1, 9), 392 (M^+-2, 3), 381 (2), 379 (6), 351 (6), 349 (19), 252 (5), 224 (4), 223 (6), 171 (100), 170 (99). Anal. Calcd for $C_{22}H_{19}ClN_2O_3$: C, 66.99; H, 4.86; N, 7.11. Found: C, 67.10; H, 4.91; N, 7.05.
12. Compound **11**: yellow–green needles, mp 236–237.5 °C; IR ($CHCl_3$) ν_{max}: 1697, 1655, 1617, 1602, 1572, 1561, 1526, 1507, 1496, 1470, 1437, 1425, 1396, 1381, 1358, 1300, 1271, 1256, 1222, 1211, 1196, 1173, 1140, 1106, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/TFA-d, v/v = 20:1) δ: 1.63 (t, $J = 7.1$ Hz, 3H), 3.64 (s, 3H), 4.28 (s, 3H), 4.64 (q, $J = 7.1$ Hz, 2H), 7.89 (br t, $J = 8.3$ Hz, 1H, H-9), 8.15 (br t, $J = 8.3$ Hz, 1H, H-10), 8.50 (s, 1H, H-3), 8.53 (d, $J = 6.4$ Hz, 1H, H-7), 8.80 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz, 1H, H-11), 8.82 (br d, $J = 8.3$ Hz, 1H, H-8), 9.04 (d, $J = 6.4$ Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$/TFA-d, v/v = 20:1) δ: 14.2 (q, $OCH_2\underline{C}H_3$), 16.3 (q, C(1)-CH_3), 57.0 (q, OMe), 62.4 (t, $O\underline{C}H_2CH_3$), 109.8 (d, C-3), 111.1 (d, C-7), 112.8 (s, C-2), 113.6 (s, C-4a), 118.6 (d, C-11), 119.0 (s, C-4b), 119.5 (s, C-2a), 120.0 (s, C-7b), 126.3 (s, C-7a), 127.0 (d, C-9), 128.1 (d, C-8), 135.6 (d, C-10), 137.7 (s, C-11a), 139.2 (d, C-6), 142.4 (s, C-2b), 143.1 (s, C-1), 145.0 (s, C-4), 166.6 (s, CO). EIMS (15 eV) m/z (%) = 358 (M^+, 9), 357 (M^+-1, 9), 344 (12), 343 (41), 342 (32), 313 (15), 312 (22), 311 (19), 268 (60), 267 (30), 266 (39), 265 (28), 264 (32), 191 (88), 185 (100). Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.55; H, 4.90; N, 7.71.