First Synthesis of the Benzo[*f*]pyrido[2′,3′:3,4]-pyrrolo[2,1-*a*][2,7]naphthyridine Ring System

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The lithiated pyridine **7** on reaction with methyl 4-methylquinoline-3-carboxylate (**8**) gave the ketone **9**, which could be converted to the biaryl **11** *via* an effective two step anellation procedure. Treatment of **11** with dilute sulfuric acid resulted in an unexpected ring closure to give the title ring system.

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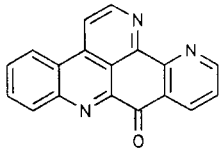
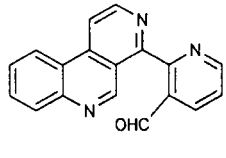
During our recent work on the total synthesis of the cytotoxic marine alkaloid ascididemin (**1**) [1] we made an attempt to prepare the heterocyclic aldehyde **2**. Thereby we found an easy access to the hitherto unknown benzo[*f*]-pyrido[2′,3′:3,4-]pyrrolo[2,1-*a*][2,7]naphthyridine ring system.

Scheme I



1

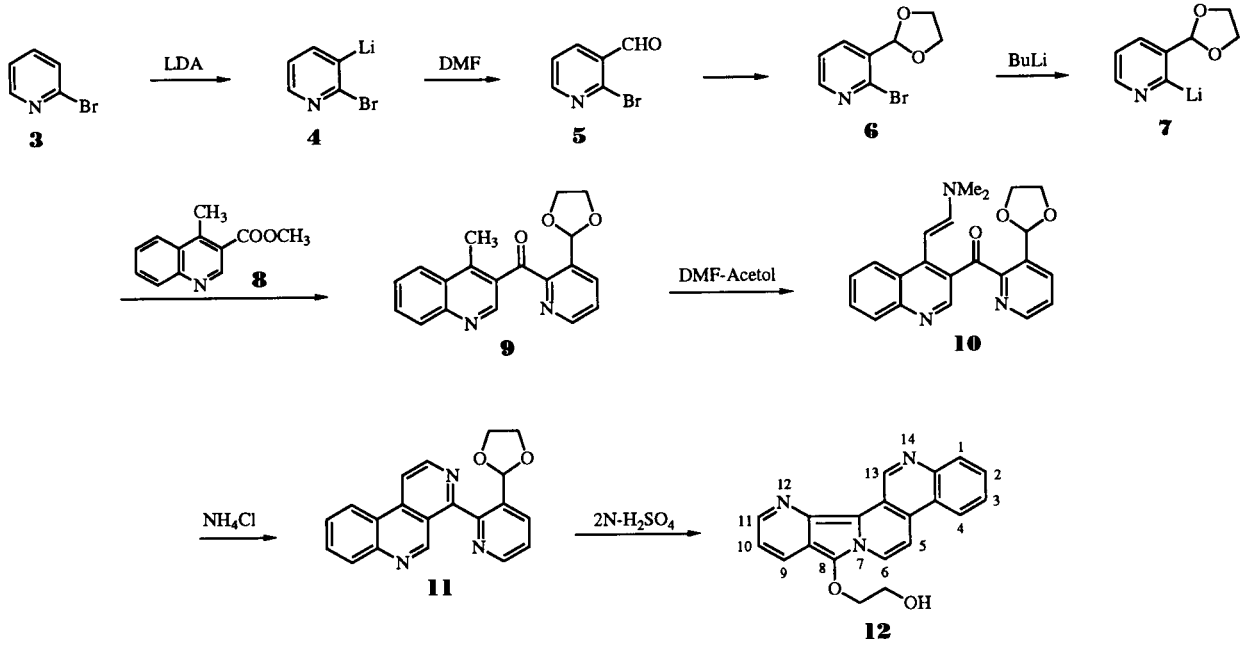


2

Direct lithiation of 2-bromopyridine (**3**) with lithium diisopropylamide following Queguiner's *ortho*-metalation procedure [2] and subsequent treatment of the intermediate 2-bromo-3-lithiopyridine (**4**) with DMF gave 2-bromopyridine-3-carbaldehyde (**5**) [3] in good yield. For further manipulations the formyl group was protected by acetalization with ethylene glycol under standard conditions. Halogen-metal exchange of the brominated pyridine **6** with *n*-butyllithium in THF at -78° gave a solution of the organolithium compound **7**. On addition of this solution to a precooled solution of methyl 4-methylquinoline-3-carboxylate (**8**) [4] the diaryl ketone **9** was obtained in 43% yield. On the other hand, addition of the ester to the aryllithium **7** gave the ketone in very poor yield. The aroyl quinoline **9** could be converted to an aryl benzo[*c*][2,7]-naphthyridine by a two step anellation procedure recently developed in this laboratory in the course of the synthesis of polycyclic alkaloids from *Annonaceae* [5]. Thus, on condensation of **9** with dimethylformamide diethylacetal in DMF at 125° the enamine **10** was formed. Heating of the crude **10** with ammonium chloride in ethanol gave **11** in high yield.

Our attempts to hydrolyze the dioxolane moiety in **11** to an aldehyde gave an unexpected product. The ir and nmr

Scheme II



spectra revealed, that the deep red compound obtained on treatment of **11** with dilute sulfuric acid did not bear an aldehyde function. The mass spectrum showed, that the molecular composition had not been changed by the reaction. The dioxolane ring, however, was cleaved to a hydroxyethoxy chain. Obviously, a carbenium ion formed by protonation and opening of the dioxolane ring had attacked a ring nitrogen of the benzo[*c*][2,7]naphthyridine. Subsequent aromatization by loss of a proton gave the pentacyclic compound **12**. This represents the first synthesis of the benzo[*f*]pyrido[2′,3′:3,4]pyrrolo[2,1-*a*][2,7]naphthyridine ring system.

EXPERIMENTAL

Melting points were determined on a Leitz HM Lux apparatus. Microanalyses were obtained on a Hewlett Packard CHN-Autoanalyser (nitrogen) and a Labormatic CH-Analyser. Mass spectra were recorded on a Vacuum Generators Spectrometer 7070H with EI (70 eV). The infrared spectra were run using a Perkin Elmer PE 398 instrument. The ^1H and ^{13}C nmr spectra were recorded on Jeol JNM-GX 400 or JNM-FX 100 spectrometers.

Flash column chromatography was carried out on silica gel (Merck Kieselgel 60, 230-400 mesh).

2-Bromopyridine-3-carbaldehyde (**5**).

To a stirred and cooled (-78°) solution of 9.0 ml of *n*-butyllithium (1.6 *M* in hexane, 14.4 mmoles) in 30 ml of anhydrous tetrahydrofuran under a nitrogen atmosphere, a solution of diisopropylamine (1.40 g, 13.9 mmoles) was added and the reaction mixture was stirred at -78° for 1 hour. Then a solution of 2-bromopyridine (**3**) (2.0 g, 12.7 mmoles) in dry tetrahydrofuran (5 ml) was added slowly and the mixture was stirred at -70° for 4 hours. After addition of dimethylformamide (3.0 ml) in dry tetrahydrofuran (5 ml) the mixture was allowed to warm up to -50° within 3 hours. Then 10% aqueous ammonium chloride solution (100 ml) was added and the mixture was extracted with ether (2 x 50 ml). The combined organic layers were dried over potassium carbonate and evaporated to give the crude product. Purification by flash chromatography (hexane-ether 8:2) gave **5** (1.20 g, 51%) as colorless needles, mp 65°; ir (potassium bromide): 1690, 1570, 1410, 1370, 835, 805; ^1H nmr (deuteriochloroform): δ 10.35 (s, 1H, CHO), 8.60 (dd, J = 4.5, 2.0 Hz, 1H, 6-H), 8.18 (dd, J = 8.0, 2.0 Hz, 1H, 4-H), 7.44 (dd, J = 8.0, 4.5 Hz, 1H, 5-H); ^{13}C nmr (deuteriochloroform): δ 190.9 (C=O), 154.4 (d), 145.3 (s), 137.9 (d), 130.6 (s), 123.4 (d); ms: m/z 187 (90, M^+), 185 (90, M^+), 158 (25), 156 (21), 105 (100), 77 (72); hrms: molecular ion at 184.9470 (theor. 184.9477 calculated for $C_6H_4{}^{79}BrNO$).

Anal. Calcd. for C_6H_4BrNO: C, 38.74; H, 2.17; N, 7.53. Found: C, 38.89; H, 2.31; N, 7.57.

2-Bromo-3-(1,3-dioxolan-2-yl)pyridine (**6**).

A solution of **5** (1.55 g, 8.3 mmoles), ethylene glycol (2.0 ml) and *p*-toluenesulfonic acid (0.1 g) in benzene (60 ml) was heated under reflux with azeotropic removal of water formed using a Dean-Stark apparatus. The solvent was then evaporated on the rotary evaporator and the residue purified by flash chromatography (ethyl acetate-hexane 8:2) to give **6** (1.73 g, 90%) as a colorless glass, mp 35-40°; ir (potassium bromide): 1580, 1560, 1425, 1370, 1095, 1045, 970; ^1H nmr (deuteriochloroform): δ 8.38 (dd, J = 4.7, 2.0 Hz, 1H, 6-H), 7.90 (dd, J = 7.5, 2.0 Hz, 1H, 4-H), 7.32 (dd, J = 7.5, 4.7 Hz, 1H, 5-H), 6.04 (s, 1H, -O-CH-O-), 4.18-4.08 (m, 4H, $-CH_2-CH_2-$); ^{13}C nmr (deuteriochloroform): δ 150.4 (d), 142.3 (s), 136.4 (d), 134.2 (s), 122.7 (d), 101.6 (d), 65.5 (t, 2C); ms: m/z 231 (32, M^+), 230 (32), 229 (32, M^+), 228 (30), 186 (13), 184 (13), 150 (25), 73 (100); hrms: molecular ion at 228.9720 (theor. 228.9738 calculated for $C_8H_8{}^{79}BrNO_2$).

Anal. Calcd. for $C_8H_8BrNO_2$: C, 41.77; H, 3.50; N, 6.09. Found: C, 41.83; H, 3.53; N, 5.90.

3-(4-Methylquinolyl) 2-[3-(1,3-Dioxolan-2-yl)pyridyl] Ketone (**9**).

A mixture of *n*-butyllithium (1.6 *M* in hexane, 2.91 ml, 4.65 mmoles) and dry tetrahydrofuran (10 ml) under a nitrogen atmosphere was cooled to -78° with stirring. Then a solution of **6** (1.05 g, 4.55 mmoles) in dry tetrahydrofuran (10 ml) was added and stirring was continued for 10 minutes. Then this solution was added slowly to a cooled (-78°) and stirred solution of methyl 4-methylquinoline-3-carboxylate (**8**) (0.804 g, 4.00 mmoles) in dry tetrahydrofuran (25 ml) *via* a teflon tubing. The mixture was stirred at -78° for 45 minutes, then hydrolyzed with 10% aqueous ammonium chloride solution (100 ml) and extracted with ether (2 x 70 ml). The combined organic layers were dried (potassium carbonate) and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane 1:1) to give **9** (0.63 g, 43%) as a white solid, mp 123°; ir (potassium bromide): 1660, 1565, 1320, 1280, 1220, 1090, 1075, 950, 935, 755; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.72 (s, 1H, 2-H quinoline), 8.62 (dd, J = 4.7, 1.6 Hz, 1H, 6-H pyridine), 8.29 (dd, J = 8.5, 0.6 Hz, 1H, ArH quinoline), 8.19 (dd, J = 7.9, 1.6 Hz, 1H, 4-H pyridine), 8.07 (d, J = 8.5 Hz, 1H, ArH quinoline), 7.89 (m, 1H, ArH quinoline), 7.73 (m, 1H, ArH quinoline), 7.68 (dd, J = 7.9, 4.7 Hz, 1H, 5-H pyridine), 6.39 (s, 1H, -O-CH-O-), 3.99 (m, 4H, $-O-CH_2-CH_2-O-$), 2.69 (s, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 196.3 (s), 154.0 (s), 149.8 (d), 148.9 (d), 147.6 (s), 145.4 (s), 135.5 (d), 133.8 (s), 131.0 (d), 130.6 (s), 129.4 (d), 127.4 (d), 127.0 (s), 125.9 (d), 125.0 (d), 99.0 (d), 64.9 (t, 2C), 15.1 (q); ms: m/z 320 (48, M^+), 275 (25), 248 (30), 247 (100), 220 (27), 219 (66), 170 (27), 142 (29), 115 (44); hrms: molecular ion at 320.1190 (theor. 320.1161 calculated for $C_{19}H_{16}N_2O_3$).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 70.61; H, 4.98; N, 8.62.

4-[3-(1,3-Dioxolan-2-yl)pyrid-2-yl]benzo[*c*][2,7]naphthyridine (**11**).

A mixture of **9** (0.31 g, 0.98 mmole), dimethylformamide diethylacetal (0.300 g, 2.04 mmoles) and dry dimethylformamide (2.0 ml) under a nitrogen atmosphere was heated with stirring at 125° for 30 minutes. Then the volatile compounds were evaporated under reduced pressure. To the red residue ammonium chloride (1.50 g) and ethanol (5.0 ml) were added and the mixture was refluxed for 10 minutes. After addition of water (50 ml) the mixture was extracted with ethyl acetate (2 x 50 ml). The combined organic layers were dried (potassium carbonate) and evaporated to give a crude product. Purification by flash chromatography (ethyl acetate-methanol 95:5) gave **11** (0.260 g, 80%) as a pale yellow solid, mp 179-182°; ir (potassium bromide): 2860, 1600, 1570, 1345, 1075, 940, 790, 770, 755, 620; ^1H nmr (deuteriochloroform): δ 9.25 (s, 1H, 5-H), 8.99 (d, J = 6.0 Hz, 1H, 2-H), 8.79 (dd, J = 4.7, 1.9 Hz, 1H, 6′-H), 8.63 (dd, J = 7.9, 1.9 Hz, 1H, 4′-H), 8.45 (dd, J = 6.0, 0.6 Hz, 1H, 1-H), 8.24-8.18 (m, 2H, 2ArH), 7.87 (m, 1H, ArH), 7.76 (m, 1H, ArH), 7.53 (dd, J = 7.9, 4.7

Hz, 1H, 5′-H), 6.05 (s, 1H, -O-CH-O-), 3.95 and 3.81 (2 m, 4H, $-CH_2-CH_2-$); ^{13}C nmr (deuteriochloroform): δ 159.1 (s), 155.2 (s), 151.9 (d), 149.3 (d), 147.3 (d), 145.4 (s), 138.3 (s), 135.6 (d), 134.1 (s), 130.9 (d), 130.4 (d), 127.7 (d), 123.8 (d), 122.8 (d), 122.0 (s), 120.1 (s), 115.3 (d), 100.3 (d), 65.3 (t, 2C); ms: m/z 329 (11, M^+), 285 (17), 284 (29), 257 (93), 256 (100), 143 (13), 43 (17); hrms: molecular ion at 329.1150 (theor. 329.1164 calculated for $C_{20}H_{15}N_3O_2$).

Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.64; H, 4.58; N, 12.67.

8-(2-Hydroxyethoxy)benzo[*f*]pyrido[2′,3′:3,4]pyrrolo[2,1-*a*][2,7]-naphthyridine (**12**).

A solution of **11** (0.150 g, 0.46 mmole) in 2*N* sulfuric acid (5.0 ml) was stirred at room temperature for 45 minutes. Then the mixture was diluted with water (50 ml), made basic with potassium carbonate and extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried (potassium carbonate) and evaporated to dryness. The residue was recrystallized from methanol to give **12** (0.065 g, 43%) as deep red needles, mp 183-185°; ir (potassium bromide): 3150, 1590, 1580, 1490, 1350, 1325, 1300, 1070, 1030, 1010, 875, 760, 720; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.82 (s, 1H, 13-H), 8.79 (d, J = 7.7 Hz, 1H, 6-H), 8.73 (dd, J = 3.9, 1.5 Hz, 1H, 11-H), 8.69 (m, 1H, ArH), 8.42 (dd, J = 8.8, 1.5 Hz, 1H, 9-H), 8.30 (d, J = 7.7 Hz, 1H, 5-H), 8.14 (m, 1H, ArH), 7.74 (m, 2H, 2ArH), 7.30 (dd, J = 8.8, 3.9 Hz, 1H, 10-H), 5.22 (t, J = 5 Hz, 1H, OH), 4.52 (t, J = 4.6 Hz, 2H, $-OCH_2-$), 3.84 (m, 2H, $-CH_2-OH$); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 147.7 (d), 146.5 (d), 143.7 (s), 130.4 (s), 129.7 (d), 128.6 (s), 127.7 (d), 127.5 (d), 126.1 (d), 123.3 (s), 123.0 (d), 122.7 (d), 122.5 (s), 119.9 (s), 118.2 (d), 109.5 (d), 109.3 (s), 105.3 (s), 77.4 (t), 60.0 (t); ms: m/z 329 (6, M^+), 285 (24), 284 (100), 256 (14), 128 (7); hrms: molecular ion at 329.1170 (theor. 329.1164 calculated for $C_{20}H_{15}N_3O_2$).

Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.20; H, 4.66; N, 12.48.

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REFERENCES AND NOTES

[1] F. Bracher, *Heterocycles*, **29**, 2093 (1989).

[2] F. Marsais, B. Laperdrix, T. Güngör, M. Mallet and G. Queguiner, *J. Chem. Res. (S)*, 278 (1982).

[3a] A. Ashimori, T. Ono, T. Uchida, Y. Ohtaki, C. Fukaya, M. Watanabe and K. Yokoyama, *Chem. Pharm. Bull.*, **38**, 2446 (1990); [b] M. Mallet, G. Branger, F. Marsais and G. Queguiner, *J. Organomet. Chem.*, **382**, 319 (1990); [c] Very recently, the preparation of **5** following the same strategy was mentioned in a footnote: X. Wang and V. Snieckus, *Tetrahedron Letters*, **32**, 4883 (1991).

[4a] N. D. Heindel, P. D. Kennewell and C. J. Ohnmacht, *J. Org. Chem.*, **34**, 1168 (1969); [b] A. Godard and G. Queguiner, *Tetrahedron Letters*, **22**, 4813 (1981); [c] **8** can more conveniently by prepared by esterification of 4-methylquinoline-3-carboxylic acid [6] with diazomethane in ether (84% yield).

[5a] F. Bracher, *Liebigs Ann. Chem.*, 87 (1989); [b] F. Bracher, *Arch. Pharm. (Weinheim, Ger.)*, **322**, 293 (1989).

[6] L. Marion, R. H. F. Manske and M. Kulka, *Can. J. Res.*, **24B**, 224 (1946); *Chem. Abstr.*, **41**, 767a (1947).