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The Total Synthesis of UK-1

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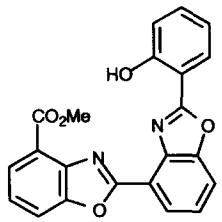
Abstract: A concise, five-step total synthesis of UK-1, a novel bis(benzoxazole) metabolite of *Streptomyces* sp. 517-02, was accomplished. The methyl ether of UK-1 was also synthesized in 3 steps using the same methodology. Both syntheses are accomplished by the sequential construction of two benzoxazole rings derived from 3-hydroxyanthranilic acid. Copyright © 1996 Elsevier Science Ltd

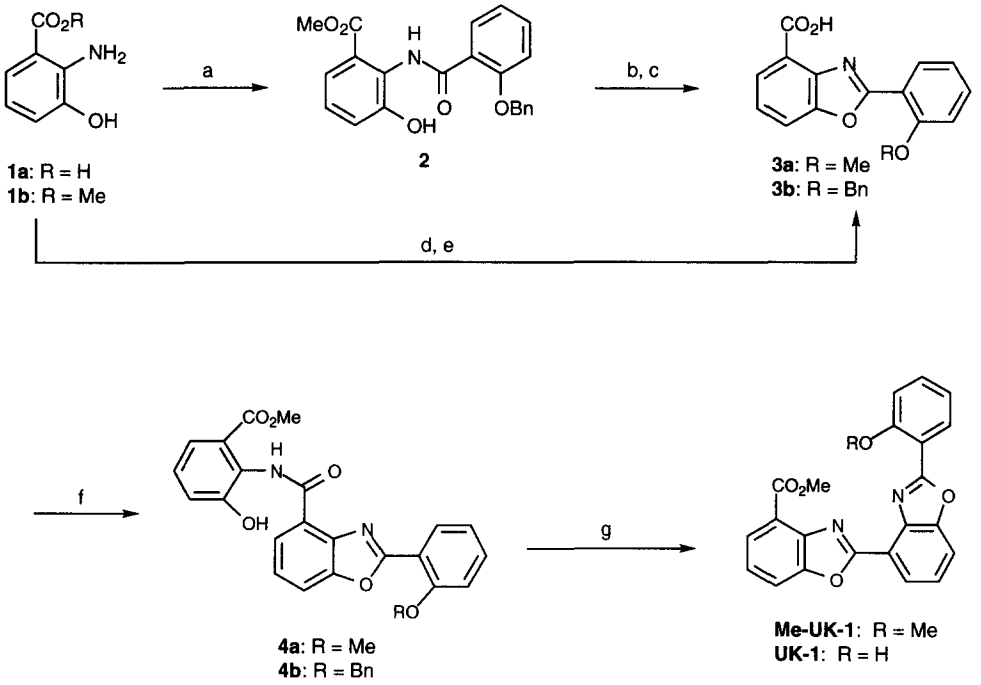
UK-1, an antitumor metabolite produced by *Streptomyces* sp. 517-02, was first isolated and characterized in 1993 by Taniguchi and co-workers.[1,2] UK-1 is a structurally unique bis(benzoxazole) in which the 2-position of one benzoxazole is joined to the 4-position of a second benzoxazole ring.[3] UK-1 shows moderate cytotoxic activity against B16, HeLa and P338 cells, but does not inhibit the growth of Gram-positive or Gram-negative bacteria, yeast, or fungi.[1] The structure of UK-1 was assigned based on IR, UV, NMR spectroscopy and chemical derivatization.[2] However, no total synthesis of UK-1 has previously been reported. We set out to synthesize UK-1 in order to confirm the assigned structure and to provide the basis for the production of analogs of this biologically interesting natural product.



UK-1

Our first approach to the synthesis of UK-1 relied on the sequential construction of the benzoxazole rings followed by deprotection of the phenol hydroxyl group. Because the methyl ether of UK-1 (Me-UK-1) had been synthesized from UK-1 as part of the structural characterization studies, we chose a methyl ether as the phenol protecting group. Me-UK-1 was particularly attractive as a penultimate target, since it would also serve as additional proof of structure as well as provide an analog for our biological studies. The condensation of 3-

hydroxyanthranilic acid (**1a**) with *o*-anisoyl chloride, followed by direct treatment of the condensation products with *para*-toluenesulfonic acid (TsOH) under reflux in xylenes gave the benzoxazole-4-carboxylic acid **3a** in 83% yield (Scheme 1).[4] Condensation of the acid **3a** with methyl 3-hydroxyanthranilate[5] (**1b**) gave the amide **4a**.[6] Treatment of the amide **4a** with TsOH afforded Me-UK-1, identical in all respects to that synthesized from UK-1,[2] in nearly quantitative yield.[7]



Scheme 1. (a) 2-benzyloxybenzoyl chloride, benzene, pyridine, 1h; 79% (b) 230 °C, 1h; 66% (c) 5M NaOH, H_2O/THF, 60 °C, 1h; 83% (d) *o*-anisoyl chloride, pyridine, benzene, 1h (e) TsOH, xylenes, 140 °C, 2h; 83% (from **1a**) (f) $(COCl)_2$, CH_2Cl_2, 1h, then **1b**, CH_2Cl_2, pyridine, 1h ; **4a**, 59%; **4b**, 45% (g) TsOH, xylenes, 140 °C, 1h; **UK-1**, 99%; **Me-UK-1**, 96%.

Attempts to cleave the methyl ether functionality of Me-UK-1 were unsuccessful. The use of standard cleavage conditions (BBr_3, NaI/DMF, TMSI) gave mixtures of products due to competitive cleavage of one or both of the benzoxazole rings. Faced with the inability to affect the deprotection of Me-UK-1, we turned to the benzyl protecting group for the phenol hydroxyl group. Our first approach to the synthesis of the benzyl ether of UK-1 followed the same reaction sequence used to synthesize Me-UK-1. The condensation of 3-hydroxyanthranilic acid (**1a**) with 2-benzyloxybenzoyl chloride[8] followed by treatment with TsOH gave only trace amounts of the desired acid **3b**. This reaction was complicated by the unexpected cleavage of the benzyl ether moiety during the TsOH cyclodehydration step.

The inability to synthesize the prerequisite acid **3b** via a TsOH-catalyzed cyclocondensation forced us to look at other methods of benzoxazole synthesis. One of the most common methods involves the thermal cyclodehydration of acylated 2-aminophenols.[9] The reaction of the ester **1b**[5] with 2-benzyloxybenzoyl chloride[8] gave the monoacylated 2-aminophenol **2**.[6] Heating amide **2** to 230 °C under argon afforded the benzoxazole ester, which was hydrolyzed with aqueous NaOH to give the acid **3b** in good yield.[10] Condensation of the acid **3b** with methyl 3-hydroxyanthranilate (**1b**) afforded in the amide **4b**.[6] We found that treatment of **4b** with TsOH affects both the cyclocondensation and the deprotection of the benzyl ether to afford UK-1 directly in nearly quantitative yield.[7] The IR, ^{1}H NMR, ^{13}C NMR, MS, and UV/VIS spectra of synthetic UK-1 are identical with the reported data.[2]

In conclusion, we have developed an efficient route for the synthesis of UK-1 and Me-UK-1. By straightforward modifications of this route, analogs of UK-1 can be prepared. Work directed towards the synthesis of these analogs and the detailed study of the mode of action of UK-1 are now in progress.[11]

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2. Shibata, K.; Kashiwada, M.; Ueki, M.; Taniguchi, M. *J. Antibiotics* **1993**, *46*, 1095-1100.
3. Previously reported synthetic, cytotoxic bis(benzoxazoles) have the 2-position of one benzoxazole ring joined to the 5-position of the second ring: Bathini, Y.; Rao, K.E.; Shea, R.G.; Lown, J.W. *Chem. Res. Toxicol.* **1990**, *3*, 268-280.
4. Synthesis of **3a**: A suspension of **1a** (300 mg, 1.96 mmol) in benzene (10 mL) and pyridine (0.56 mL) was treated with *o*-anisoyl chloride (0.88 mL, 5.9 mmol). The resulting mixture was heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (30 mL), and washed with 1% HCl (2X) and sat. aq. NaCl. The residue, upon drying (Na_2SO_4) and evaporation of the solvent, was dissolved in xylenes (20 mL) and treated with TsOH (800 mg, 4.2 mmol). The resulting mixture was heated under reflux for 3 hours. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (20 mL), and washed with water (3X) and sat. aq. NaCl. The residue, upon drying (Na_2SO_4) and evaporation of the solvent, was recrystallized from EtOAc to give the acid **3a** as a tan solid (420 mg, 80%): m.p. 185-187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.12-7.18 (m, 2H), 7.51 (t, J=7.9 Hz, 1H), 7.60 (dt, J=8.3, 1.8 Hz, 1H), 7.83 (d, J=7.7 Hz, 1H), 8.15 (d, J=7.9 Hz, 1H), 8.21 (dd, J=7.6, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.01, 112.25, 114.06, 115.28, 119.89, 120.82, 125.32, 126.90, 131.48, 134.34, 140.97, 149.80, 159.09, 163.10, 164.84; IR ($CHCl_3$) 1746 cm^{-1}; MS (CI) *m/z* 270 (MH^+), 252; HRMS (CI) *m/z* calcd for $C_{15}H_{12}NO_4$: 270.0766, found 270.0767.
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6. Synthesis of **4a**: A solution of the acid **3a** (200 mg, 0.75 mmol) in CH_2Cl_2 (10.0 mL) and DMF (0.030 mL) was treated with oxalyl chloride (1.0 mL, 5.4 mmol). The resulting solution was stirred for 1 hour at room temperature. Evaporation of the solvent under vacuum afforded the acid chloride as a yellow solid. A solution of this acid chloride in CH_2Cl_2 (3.0 mL) was added to a solution of **1b** (124 mg, 0.75 mmol) in CH_2Cl_2 (2.0 mL) and pyridine (0.50 mL). After being stirred at room temperature for 30 min, the reaction mixture was diluted with CH_2Cl_2 and washed with 1% HCl, sat. aq. $NaHCO_3$, and sat. aq. NaCl. The residue, upon drying (Na_2SO_4) and evaporation of the solvent, was subjected to flash chromatography on silica gel (25% EtOAc/hexanes) to give the amide **4a** as a faint yellow solid (224 mg, 75%). An analytical sample was prepared by recrystallization from EtOAc/hexanes to give light yellow

plates: m.p. 165-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.90 (s, 3H), 7.08-7.13 (m, 2H), 7.28 (t, J=7.9 Hz, 1H), 7.37 (dd, J=8.3, 1.9 Hz, 1H), 7.47-7.57 (m, 2H), 7.70 (dd, J=7.9, 2.0 Hz, 1H), 7.83 (dd, 8.3, J=1.2 Hz, 1H), 8.27 (d, J=7.9 Hz, 1H), 8.44 (dd, J=8.4, 2.0 Hz, 1H), 8.83 (br s, 1H), 12.63 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.32, 55.98, 112.12, 114.91, 115.15, 120.80, 122.42, 123.00, 123.64, 124.67, 125.69, 126.34, 126.59, 127.67, 132.27, 133.76, 139.91, 150.83, 151.24, 158.82, 163.52, 164.42, 167.19; IR ($CHCl_3$) 1726, 1649 cm^{-1}; MS (CI) *m/z* 419 (MH^+); HRMS (CI) *m/z* calcd for $C_{23}H_{19}N_2O_6$: 419.1243, found 419.1232. The following were similarly prepared:

2: Recrystallization from ether gave light yellow plates (330 mg, 79%): m.p. 104-106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.48 (s, 2H), 7.02-7.12 (m, 2H), 7.18-7.37 (m, 5H), 7.41-7.48 (m, 3H), 7.60 (dd, J=7.7, 1.4 Hz, 1H), 8.26 (dd, J=7.8, 1.6 Hz, 1H), 9.35 (br s, 1H), 12.33 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.18, 70.78, 113.34, 120.92, 121.28, 121.57, 122.96, 125.68, 126.03, 126.92, 128.00, 128.20, 128.59, 132.69, 133.92, 136.22, 150.75, 157.02, 165.50, 167.56; IR ($CHCl_3$) 3268, 1716, 1639 cm^{-1}; MS (CI) *m/z* 378 (MH^+), 346, 211; HRMS (CI) *m/z* calcd for $C_{22}H_{20}NO_5$: 378.1341, found 378.1342.

4b: (59%). An analytical sample was prepared by recrystallization from EtOAc/hexanes to give light yellow plates: m.p. 155-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 5.26 (s, 2H), 7.13-7.38 (m, 8H), 7.47-7.53 (m, 4H), 7.63 (dd, J=7.8, 1.3 Hz, 1H), 7.78 (d, J=8.2 Hz, 1H), 8.29 (d, J=7.8 Hz, 1H), 8.48 (dd, J=7.7, 1.3 Hz, 1H), 12.58 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.22, 70.69, 113.74, 114.69, 115.71, 121.15, 122.47, 122.96, 123.60, 124.71, 125.58, 126.32, 126.49, 126.67, 127.66, 127.84, 128.33, 132.25, 133.67, 136.25, 139.87, 150.84, 151.19, 157.86, 163.43, 164.37, 167.08; IR ($CHCl_3$) 1727, 1647 cm^{-1}; MS (CI) *m/z* 495 (MH^+); HRMS (CI) *m/z* calcd for $C_{29}H_{23}N_2O_6$: 495.1556, found 495.1547.

7. Synthesis of **UK-1**: A mixture of amide **4b** (65 mg, 0.13 mmol) and TsOH (60 mg, 0.32 mmol) in toluene (1.5 mL) was heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, and washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl. The residue, upon drying (Na_2SO_4) and evaporation of the solvent, was subjected to flash chromatography on silica gel (30% EtOAc/hexanes) to give UK-1 as a yellow solid (50 mg, 99%). The spectral data of an analytical sample, prepared by recrystallization from EtOAc, are identical with those reported by Yamamura *et al.*[2] **Me-UK-1** was prepared in a similar manner (32 mg, 96%).
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9. Dunwell, D.W.; Evans, D.; Hicks, T.A.; Cashin, C.H.; Kitchen, A. *J. Med. Chem.* **1975**, *18*, 53-58.
10. Synthesis of **3b**: The amide **2** (243 mg, 0.64 mmol) was heated to 230 °C for 1 hour under an atmosphere of argon. The resulting mixture was allowed to cool to room temperature and subjected to flash chromatography on silica gel (20% EtOAc/hexanes) to give the benzoxazole ester as a pale yellow solid (152 mg, 66%). A solution of the ester (132 mg, 0.37 mmol) in THF (3.0 mL) was treated with 5M NaOH (1.0 mL) at 60 °C for 2 hours. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, and made acidic by the addition of conc. HCl. The layers were separated, and the organic layer was washed with sat. aq. NaCl, dried (Na_2SO_4), and evaporated to give the acid as a tan solid (105 mg, 83%). An analytical sample was prepared by recrystallization from EtOAc/hexanes: m.p. 103-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 2H), 7.06-7.13 (m, 2H), 7.33-7.54 (m, 7H), 7.71 (d, J=8.0 Hz, 1H), 8.08 (d, J=7.8 Hz, 1H), 8.14 (dd, J=7.8, 1.1 Hz, 1H), 10.7 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.63, 113.42, 114.20, 115.00, 119.73, 120.93, 125.14, 126.74, 127.00, 128.04, 128.59, 131.38, 134.15, 135.83, 140.84, 149.55, 157.92, 162.84, 164.84; IR ($CHCl_3$) 3214, 1748 cm^{-1}; MS (CI) *m/z* 346 (MH^+); HRMS (CI) *m/z* calcd for $C_{21}H_{16}NO_4$: 346.1079, found 346.1076.

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