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Note

Synthesis of Atromentin and Its *O*-Alkylated Natural Products

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The structure of a long-known natural pigment, atromentin, was established by a total synthesis based on double Suzuki-Miyaura coupling and by a single-crystal X-ray analysis of the synthetic sample thereby obtained. A similar strategy including ceric ammonium nitrate (CAN) oxidation was applied to prepare 2-*O*-methoxyatromentin and thelephantin I.

Key words: terphenyl; atromentin; single-crystal X-ray analysis; Suzuki-Miyaura coupling

Our search for new bioactive compounds from edible Chinese mushrooms had led us to isolate atromentin (**1**)[1] from the dry fruiting bodies of *Thelephora vialis*. However, we found some discrepancies with the reported spectral data for **1**; for example, two different sets of ^{1}H-NMR data for **1** were reported in the literature,[2,3] and neither set of the data matched that for our natural sample.* The ^{13}C-NMR data also offered no reliable evidence for the structure, because two intense resonances of the 2,5-dihydroxy-cyclohexa-2,5-diene-1,4-dione moiety were not observed by broadening with slow exchange on the NMR time-scale. Confirmation by using a synthetic method was therefore needed. Described here are a total synthesis of **1** and its natural congeners (2-*O*-methylatromentin (**2**)[2,4] and thelephantin I (**3**)[5]) and a single-crystal X-ray analysis of **1**. The synthesis began with Suzuki-Miyaura coupling[6] of **4**[7] and **5** with $Pd(OAc)_2$ and Ph_3P in the presence of Na_2CO_3 in aqueous propanol at 100 °C to give **6**. The use of K_3PO_4in aqueous THF at 70 °C instead of that base afforded corresponding TBS ether **7**. Acidic hydrolysis of **6** and subsequent O_2 oxidation provided **1** whose spectral data were identical with those of our natural sample. A single-crystal X-ray analysis of 1 was then performed in order to unambiguously establish the structure. The ORTEP drawing in Fig. 2 show that the structure was consistent with the one depicted in Fig. 1. The bond distances of the cyclohexadiene-1,4-dione moiety indicate that **1** was not tautomerized in the solid state. It was furthermore revealed that the hydroxyl groups formed intramolecular hydrogen bonds with the neighbouring carbonyl groups. To prepare of **2** and **3**, **7** was selectively oxidized with CAN, affording **8**. After reduction, the resulting hydroquinone was treated with methyl iodide-K_2CO_3 to furnish **9**. Benzoylation of this afforded **10**, and the substitution pattern in **10** was confirmed by a NOESY experiment. Treating **9** with HCl and subsequent oxidation gave **2**, whose ^{1}H-NMR data matched those reported in ref. 4, but not those in ref. 3. A similar method was applied to transform **10** into **3**. The ^{1}H- and ^{13}C-NMR data for **3** were consistent with those in the literature.[5]

In summary, we developed a simple method for preparing of **1** and its *O*-alkylated natural products **2** and **3**. The structure of **1** was unambiguously established by a single-crystal X-ray analysis. A bioassay of **2** and **3** is now underway.

Experimental

General procedure. IR spectra were recorded with a Jasco VALOR-III spectrophotometer by the ATR method. Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained with a Jeol JNM-A400 (400 MHz), JNM-ECA600 (600 MHz) or Varian NMR System 500 (500 MHz) spectrometer as solutions in $CDCl_3$, unless otherwise noted. X-Ray diffraction data were obtained with a Rigaku AFC-8 diffractomter. Mass spectra were recorded with a Jeol JMS-HX/HX 110A or JMS-T100LC mass spectrometer.

Atromentin (1). A mixture of **4** (515 mg, 1.08 mmol) and **5** (691 mg, 2.74 mmol) in 1-propanol (8.0 ml) was treated with palladium acetate (12.1 mg, 0.05 mmol), triphenylphosphine (42.5 mg, 0.16 mmol), 2 M sodium carbonate (1.6 ml, 3.24 mmol) and water (1.0 ml), and then heated at 100 °C while stirring for 4 h, before being cooled and diluted with water. The usual work-up followed by chromatography on silica gel (*n*-hexane-ethyl acetate = 10:1 → 5:1) gave **6** (486 mg, 89%) as a colourless solid, mp 186.5–188.0 °C (*n*-hexane-ethyl acetate); IR υ_{max} (ZnSe) cm^{-1}: 3328, 2951, 1523, 1421, 1377, 1266, 1204, 1148, 996, 932, 904; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.40 (2H, s), 7.30 (4H, d, J = 8.3 Hz), 6.92 (4H, d, J = 8.3 Hz), 4.79 (8H, s), 2.93 (12H, s); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 157.4, 145.2, 133.5, 131.7, 126.1, 115.3, 99.4, 56.8. *Anal.* Found: C, 62.16; H, 6.00%. Calcd for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02%. A solution of **6** (108 mg, 0.22 mmol) in a 5% HCl solution in methanol (4.0 ml) was stirred at rt for 19 h, before being concentrated to give a solid which was suspended in methanol. The mixture was stirred at rt for 24 h under an O_2 atmosphere and then concentrated to give a dark brown solid which was recrystallized from acetonitrile to give **1** (51 mg, 73%) as a purple solid, mp >300 °C (CH_3CN); IR υ_{max} (ZnSe) cm^{-1}: 3294, 1610, 1596, 1315, 1246, 1179, 996; ^{1}H-NMR (500 MHz, methanol-d_4) δ: 7.32 (4H, d, J = 8.5 Hz), 6.79 (4H, d, J = 8.5 Hz); ^{13}C-NMR (150 MHz, DMSO-

* The physical, UV and MS data in references 2 and 3 seem to indicate that the compound isolated by Liu *et al.* was **1**. The reason for the discrepancy in NMR data is unclear.

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Abbreviations: MOM, methoxymethyl; TBS, *t*-butyldimethylsilyl; $Pd(OAc)_2$, palladium acetate; Ph_3P, triphenylphosphine; K_3PO_4, potassium phosphate; CAN, ceric ammonium nitrate

d_6, 80 °C) δ: 167.5, 156.5, 131.3, 120.8, 115.2, 114.2; HRMS (ESI) m/z: calcd. for $C_{18}H_{12}O_6Na$ $[M + Na]^+$, 347.0532; found, 347.0544.

4′,4″-Di-O-t-*butyldimethylsilyl-3,6-di*-O-*methoxymethylatromentin (**8**).* To a stirred solution of **4** (500 mg, 1.1 mmol), **5** (609 mg, 2.4 mmol), Ph_3P (86.6 mg, 0.34 mmol), and K_3PO_4 (700 mg, 3.3 mmol) in THF-water (40:3, 8.6 ml) was added $Pd(OAc)_2$ (24.6 mg, 0.10 mmol) and the mixture was heated under reflux while stirring for 19 h. The treatment just described gave **7** (647 mg, 84%) as a solid, mp 116–116.5 °C (*n*-hexane-ethyl acetate); IR υ_{max} (ZnSe) cm^{-1}: 2929, 2893, 2857, 1518, 1430, 1376, 1254, 1154, 1047, 993, 911; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33 (4H, d, $J = 8.5$ Hz), 6.90 (4H, d, $J = 8.5$ Hz), 4.81 (8H, s), 2.89 (12H, s), 0.99 (18H, s), 0.18 (12H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 154.8, 144.2, 132.5, 131.1, 127.3, 119.6, 98.9, 56.8, 25.7, 18.3, −4.4; HRMS (ESI) m/z: calcd. for $C_{38}H_{58}O_{10}NaSi_2$ $[M + Na]^+$, 753.3466; found, 753.3486. To a stirred solution of **7** (704 mg, 0.96 mmol) in acetonitrile (40 ml) and water (0.6 ml) was added CAN (2.11 g, 3.85 mmol) at 0 °C. The mixture was stirred for 1 h and then diluted with water. The usual work-up followed by chromatography on silica gel (*n*-hexane-ethyl acetate = 100:1 → 25:1) gave **8** (529 mg, 86%) as an orange solid; IR υ_{max} (ZnSe) cm^{-1}: 2927, 1602, 1508, 1250, 1002, 994, 909; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.30 (4H, d, $J = 8.5$ Hz), 6.89 (4H, d, $J = 8.5$ Hz), 5.11 (4H, s), 3.04 (6H, s), 0.99 (18H, s), 0.22 (12H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 183.6, 156.2, 152.0, 132.1, 130.7, 122.3, 119.6, 98.5, 57.1, 25.6, 18.2, −4.4; HRMS (EI) m/z: calcd. for $C_{34}H_{48}O_6Si_2$ $[M]^+$, 640.2888; found, 640.2916.

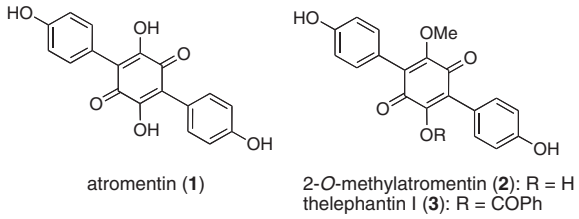
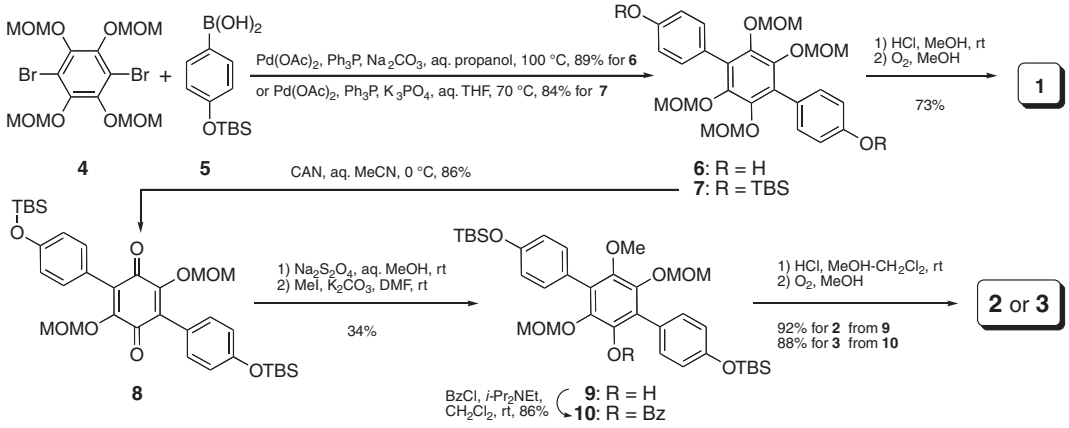


Fig. 1. Structures of Natural *p*-Terphenyls.

3-O-*Methylatromentin (**2**).* To a stirred solution of **8** (139 mg, 0.22 mmol) in THF-water (10:1, 11.0 ml) was added sodium dithionite (152 mg, 0.87 mmol) at rt in portions, and the resulting mixture was stirred for 15 min. The usual work-up gave a solid which was dissolved in DMF (5.0 ml), and to the solution were added potassium carbonate (33.4 mg, 0.24 mmol) and methyl iodide (24 µl, 0.43 mmol) at 0 °C. The resulting mixture was stirred at 0 °C → rt for 10 h and then diluted with water. The usual work-up followed by chromatography on silica gel (*n*-hexane-ethyl acetate = 50:1) gave **8** (27.6 mg) and **9** (35.8 mg, 34% based on **8** consumed); IR υ_{max} (ZnSe) cm^{-1}: 3394, 2927, 1604, 1518, 1248, 1022, 951, 911; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.37 (2H, d, $J = 8.5$ Hz), 7.29 (2H, d, $J = 8.6$ Hz), 6.93 (2H, d, $J = 8.5$ Hz), 6.91 (4H, d, $J = 8.6$ Hz), 6.36 (1H, s), 4.87 (2H, s), 4.66 (2H, s), 3.49 (3H, s), 3.30 (3H, s), 2.96 (3H, s), 1.01 (9H, s), 1.00 (9H, s), 0.24 (6H, s), 0.22 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 155.0, 154.9, 144.9, 143.8, 143.1, 138.9, 132.0, 131.5, 128.8, 126.4, 126.2, 123.0, 119.75, 119.66, 99.5, 98.9, 60.7, 57.2, 56.7, 25.68, 25.66, 18.2, −4.38, −4.39; HRMS (EI) m/z: calcd. for $C_{35}H_{52}O_8Si_2$ $[M]^+$, 656.3201; found, 656.3222. Treatment of **9** (15.0 mg, 23 µmol) as described for the preparation of **1** yielded **2** (7.1 mg, 92%) as an orange solid; IR υ_{max} (ZnSe) cm^{-1}: 3469, 2930, 1635, 1592, 1514, 1211, 1025; ^{1}H-NMR (500 MHz, methanol-d_4) δ: 7.29 (2H, d, $J = 8.6$ Hz), 7.20 (2H, d, $J = 8.5$ Hz), 6.83 (2H, d, $J = 8.6$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 3.76 (3H, s); ^{13}C-NMR (1250 MHz, methanol-d_4) δ: 185.2, 185.0, 158.9, 158.2, 156.9, 153.2, 133.2, 126.4, 122.8, 122.3, 119.1, 115.7, 115.4, 62.0; HRMS (EI) m/z: calcd. for $C_{19}H_{14}O_6$ $[M]^+$, 338.0790; found, 338.0805.

*Thelephantin I (**3**).* To a stirred solution of **9** (15.0 mg, 23 µmol) and *N*,*N*-diisopropylethylamine (0.02 ml, 0.11 mmol) in dichloromethane (0.5 ml) was added benzoyl chloride (5 µl, 43 µmol) at 0 °C, and the resulting mixture was stirred at 0 °C → rt for 22 h. The usual work-up followed by chromatography on silica gel gave **10** (15.0 mg, 86%) as an amorphous solid; IR υ_{max} (ZnSe) cm^{-1}: 2857, 1748, 1517, 1386, 1248, 1057, 909; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.95 (2H, dd, $J = 7.5$, 1.2 Hz), 7.53 (1H, t, $J = 7.5$ Hz), 7.40–7.35 (4H, m), 7.30 (2H, d, $J = 8.6$ Hz), 6.91 (2H, d, $J = 8.6$ Hz), 6.79 (2H, d, $J = 8.6$ Hz), 4.91 (2H, br), 4.63 (2H, br), 3.55 (3H, s), 2.97 (3H, s), 2.95 (3H, s), 1.00 (9H, s), 0.90 (9H, s), 0.21 (6H, s), 0.06 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 164.2, 155.0, 154.9, 149.1, 144.7, 143.6, 138.2, 133.3, 131.9, 131.5,



Scheme 1. Synthesis of Atromentin (**1**) and Its Related Compounds **2** and **3**.

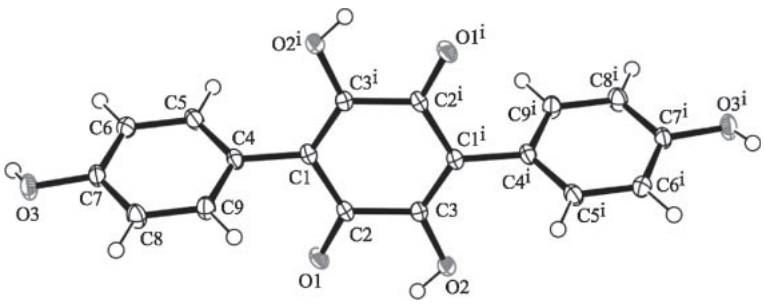


Fig. 2. ORTEP Drawing of **1**.

130.2, 130.1, 130.0, 129.0, 128.3, 126.2, 126.1, 119.72, 119.67, 99.0, 98.9, 60.5, 56.8, 56.7, 25.7, 25.6, 18.24, 18.19, −4.4, −4.6; HRMS (EI) m/z: calcd. for $C_{42}H_5O_9Si_2$ $[M]^+$, 760.3463; found, 760.3470. Treatment of **10** (14.0 mg, 18 μmol) as described for the preparation of **1** yielded **3** (7.3 mg, 90%) as a solid; IR υ_{max} (ZnSe) cm^{-1}: 3343, 2922, 1735, 1654, 1604, 1510, 1235, 1100, 1171, 1100; ^{1}H-NMR (500 MHz, methanol-d_4) δ: 8.03 (2H, dd, $J = 8.0$, 1.2 Hz), 7.68 (1H, tt, $J = 7.4$, 1.2 Hz), 7.52 (2H, dd, $J = 8.0$, 7.4 Hz), 7.28 (2H, d, $J = 8.8$ Hz), 7.23 (2H, d, $J = 8.8$ Hz), 6.83 (2H, d, $J = 8.8$ Hz), 6.79 (2H, d, $J = 8.8$ Hz), 3.84 (3H, s); ^{13}C-NMR (125 MHz, methanol-d_4) δ: 184.3, 182.2, 165.7, 160.0, 159.3, 156.3, 148.3, 135.4, 134.8, 133.3, 132.9, 131.3, 129.9, 129.4, 129.2, 122.0, 120.8, 115.9, 115.7, 61.8; HRMS (EI) m/z: calcd. for $C_{26}H_{19}O_7$ $[M + H]^+$, 443.1130; found 443.1109.

Acknowledgments

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