Total Synthesis of (±)-(1β,6α,9β,10α)-9-Chloro-10-hydroxy-8-(methoxycarbonyl)-4-methylene-2,5-dioxabicyclo[4.4.0]dec-7-en-3-one, the First Chloride-Containing Chorismate Metabolite from Fungi

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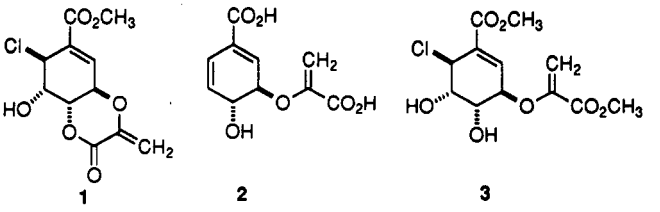
During a meeting of The Agricultural Chemical Society of Japan in 1989, two independent research groups at the University of Osaka Prefecture and Fujisawa Pharmaceutical Co. reported the isolation of a chlorine-containing metabolite from different fungi.[1] Direct comparison in both laboratories established the two samples to be identical. The structure and absolute stereochemistry of the metabolite 1 was established by spectroscopic and X-ray crystallographic studies.[1] In consideration of the structure of 1, it would appear to be derived from chorismic acid (2), the last common intermediate in the biosynthesis of aromatic amino acids via the shikimate pathway.[2] The absolute stereochemistry of 1 corresponds to that of chorismate and shikimate. Reaction of 1 with $NaOCH_3$ gave diester 3.[1]

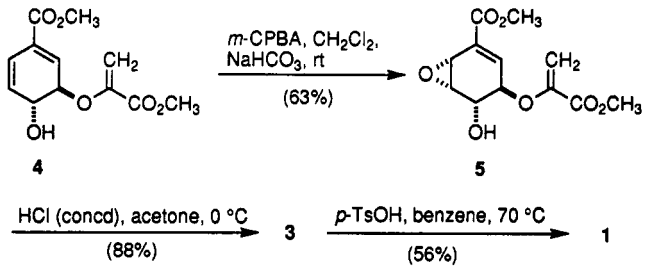
We rationalized that 1 should be available by lactonization of 3 (Chart I) which would be prepared from dimethyl chorismate (4); a convenient synthesis of 4 is available from procedures developed in our laboratory.[3,4] Described below is the total synthesis of racemic 1 by this route.

Epoxidation of 4 with *m*-CPBA gave exclusively the hydroxyl-directed cis-epoxidation product 5 in 63% yield. Assignment of stereochemistry is based on the corresponding epoxidation of 2 which provided only the hydroxyl-directed cis-epoxidation product.[5] Opening of the epoxide with concentrated HCl in acetone went smoothly to give 3 in 88% yield. The ^1H and ^{13}C NMR spectral data of 3 were identical with the corresponding spectral data reported for 3.[1] The coupling constant between the C-3 and C-4 protons of 3 is 8.0 Hz. This indicates a pseudoequatorial conformation for the two substituents on C-3 and C-4, which sets the molecule in the proper orientation to undergo lactonization. Formation of the target molecule (±)-1 was achieved in 56% yield by acid-catalyzed lactonization of 3 in refluxing benzene. The ^1H NMR and ^{13}C NMR spectra of (±)-1 were identical with the corresponding spectra provided by Professor Nakayama.

Chart I



Scheme I



Experimental Section

General.[6] **Methyl (1β,4β,5α,6β)-4-[[1-(Methoxycarbonyl)ethenyl]oxy]-5-hydroxy-7-oxabicyclo[4.1.0]hept-2-ene-2-carboxylate (5).** To (±)-4 (301 mg, 1.18 mmol) in CH_2Cl_2 (25 mL) was added $NaHCO_3$ (248 mg, 2.98 mmol, 2.5 equiv) followed by *m*-CPBA (383 mg, 1.78 mmol, 1.5 equiv). The reaction was continued at room temperature for 2 h. It was washed with 10% Na_2CO_3 and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/petroleum ether 1:3) to give 5 (200 mg, 63%) as a colorless oil: IR (neat) 3445, 1733, 1622 cm^{-1}; ^1H NMR (300 MHz) δ 6.97 (1 H, t, J = 2.1 Hz), 5.60 (1 H, d, J = 3.0 Hz), 4.85 (1 H, d, J = 3.0 Hz), 4.66 (1 H, dd, J = 8.3, 1.5 Hz), 4.30 (1 H, dbrs, J = 8.2 Hz), 4.13 (1 H, dd, J = 4.2, 2.1 Hz), 3.88 (3 H, s), 3.87 (3 H, s), 3.76 (1 H, d, J = 4.3 Hz); ^{13}C (75 MHz) δ 164.8, 163.8, 149.6, 139.4, 129.7, 99.3, 77.6, 70.6, 53.7, 52.8, 52.4, 48.6; MS *m/z* (rel inten) 270 (M^+, 0.5), 252 (3.2), 221 (11), 169 (28), 151 (13), 137 (90), 109 (100), 95 (30); HRMS calcd for $C_{12}H_{14}O_7$: 270.0740, found: 270.0737. Anal. Calcd for $C_{12}H_{14}O_7$: C, 53.34; H, 5.22. Found: C, 53.20; H, 4.80.

Methyl (3β,4α,5α,6β)-3-[[1-(Methoxycarbonyl)ethenyl]oxy]-4,5-dihydroxy-6-chloro-1-cyclohexene-1-carboxylate (3). To epoxide 5 (40 mg, 14.8 mmol) in acetone (1 mL) at 0 °C was added concd HCl (15 mL, 1.2 equiv, 12 M). The reaction was continued at 0 °C for 20 min. Solvent was removed, and the crude product was purified by flash column chromatography (ethyl acetate/petroleum ether 1:1) to give 3 (40 mg, 88%) as a sticky white solid: IR (neat) 3427, 1718, 1624 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 6.99 (1 H, d, J = 2.6 Hz), 5.56 (1 H, d, J = 2.7 Hz), 5.11 (2 H, overlapped), 5.02 (1 H, dd, J = 8.0, 2.1 Hz), 4.98 (1 H, d, J = 2.5 Hz), 4.80 (1 H, dd, J = 5.8, 1.3 Hz, hydroxyl proton), 4.37, (2 H, overlapped), 3.87 (3 H, s), 3.85 (3 H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.5, 164.0, 151.4, 137.8, 131.2, 97.7, 77.2, 75.1, 68.7, 55.5, 52.6, 52.5; MS *m/z* (rel inten) 306 (M^+, 0.38), 271 (5.7), 253 (20), 205 (30), 169 (38), 137 (100), 109 (99); HRMS calcd for $C_{12}H_{15}O_7{}^{35}Cl$: 306.0506, found: 306.0503. Anal. Calcd for $C_{12}H_{15}O_7Cl$: C, 46.99; H, 4.93. Found: C, 47.17; H, 5.24.

(±)-(1β,6α,9β,10α)-9-Chloro-10-hydroxyl-8-(methoxycarbonyl)-4-methylene-2,5-dioxabicyclo[4.4.0]dec-7-ene-3-one (1). Compound 3 (40 mg, 0.13 mmol) was dissolved in dry benzene (8 mL). *p*-TsOH (5 mg, 0.2 equiv) was added, and the reaction was brought to 70 °C for 1.5 h. The mixture was cooled and concentrated under reduced pressure. The crude product was

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(2) For reviews see: (a) Weiss, U.; Edwards, J. M. *The Biosynthesis of Aromatic Compounds*; Wiley: New York, 1980. (b) Haslam, E. *The Shikimate Pathway*; Halstead Press, Wiley: New York, 1974. (c) Ganem, B. Tetrahedron **1978**, *34*, 3353–3383.

(3) (a) McGowan, D. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 7036–7041. (b) Hoare, J. H.; Policastro, P. P.; Berchtold, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6264–6267.

(4) Synthesis of (±)-2 was accomplished by preparation of the epoxide intermediate for addition of PhSe-utilizing the procedure reported for the synthesis of (−)-2: Pawlak, J.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765–1771.

(5) Ife, R. J.; Ball, L. F.; Lowe, P.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1776–1783.

(6) For general procedures, see: Delany, J. J., III; Padykula, R. E.; Berchtold, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 1394–1397.

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purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1:3) to give 1 (20 mg, 56%) as a white solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 6.96 (1H, d, J = 2.1 Hz), 5.52 (1H, d, J = 1.6 Hz), 5.07 (1H, d, J = 1.6 Hz), 5.04 (1H, dd, J = 8.8, 2.2 Hz), 4.94 (1H, d, J = 2.8 Hz), 4.92 (1H, dd, J = 9.1, 2.2 Hz), 4.51 (1H, m), 3.82 (3H, s); ^{13}C (75 MHz, acetone-d_6) δ 164.9, 160.3, 148.6, 135.8, 132.0, 103.8, 75.6, 71.6, 71.2, 54.7, 52.9. As was observed for naturally-occurring 1, (±)-1 does not have a clear melting point; it gradually decomposed upon heating.

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