First Total Synthesis of Artekeiskeanol A, C and Altissimacoumarin D

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Abstract The total syntheses of artekeiskeanol A and C, and altissimacoumarin D have been achieved. The syntheses commenced from commercially available starting materials, 2,4-dihydroxybenzaldehyde and geraniol. The key steps involve Wittig and Riley oxidation reactions.

Keywords geronyl, scopoletin, isofraxidin, altissimacoumarin, artekeiskeanol

Coumarins are privileged core units in many bioactive molecules and they are responsible for scavenging of reactive oxygen species (ROS). Scopoletin [6-methoxy-7-hydroxycoumarin], is obtained from the stem extracts of Erycibe obtusifolia Benth, a traditional medicine of China with multiple bioactivities. Isofraxidin [7-hydroxy-6,8-dimethoxy-2H-chromen-2-one], isolated mainly from Acanseopanax senticosus, exhibits antitumor activity on human hepatoma cell lines HuH-7 and HepG2. Altissimacoumarin D [(E)-7-[(3,7-dimethylocta-2,6-dien-1-yl)oxy]-6,8-dimethoxy-2H-chromen-2-one], isolated from the Chinese medicinal plant, Ailanthus altissima, exhibits significant St1 activation and its structure was confirmed by Oh et al.

Artekeiskeanols A–D (Figure 1) were isolated by Kwak et al. from Artemisia keiskeana Miq (Compositae), which is used as a Korean traditional medicine for amenorrhea, gynaecopathy, bruising and rheumatic diseases. Their structures were reported by Schmitz et al. and their antigen-stimulant RBL-2H3 mast cell activation through inhibition of Akt, JNK and P38 cells was reported by Honga et al. As part of our research program on the synthesis of biologically active natural and synthetic molecules, we herein report the first total syntheses of artekeiskeanol A and C, and also the structurally related altissimacoumarin D.

As shown in the retrosynthetic analysis (Scheme 1), the natural coumarins scopoletin (6) and isofraxidin (10), were identified as key intermediates for the sequential synthesis of artekeiskeanol A (1), C (2) and altissimacoumarin D (3). Artekeiskeanol A and C could be obtained from compound...
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The synthesis of artekeiskeanol C (2) also started from 2,4-dihydroxybenzaldehyde, this time with an excess of bromine in methanol at room temperature to give, 3,5-dibromo-2,4-dihydroxybenzaldehyde (8) in quantitative yield. The dibromo compound 8 was subjected to nucleophilic substitution with NaOMe in the presence CuCl in DMF at reflux for 8 h to furnish, 2,4-dihydroxy-3,5-dimethoxybenzaldehyde (9) in 75% yield. Compound 9 was subjected to Wittig olefination with ethyl (triphenylphosphoranylidene) acetate, in N,N-diethylaniline at reflux to afford, 7-hydroxy-6,8-dimethoxy-2H-chromen-2-one (10) in 72% yield, corresponding to isofraxidin.

Isofraxidin, on reaction with geranyl bromide and K$_2$CO$_3$ in DMF at room temperature, afforded (E)-7-[(3,7-dimethylocta-2,6-dien-1-yl)oxy]-6,8-dimethoxy-2H-chromen-2-one (3) in 80% yield, which corresponds to the natural product altissimacoumarin D, with spectroscopic data consistent with those reported. Again, we adopted the Riley protocol for oxidation of compound 3, with SeO$_2$ and TBHP in CH$_2$Cl$_2$ at 0 °C to afford, 7-[(2E,6E)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl]oxy]-6,8-dimethoxy-2H-chromen-2-one (2), in good yield (Scheme 3), to furnish artekeiskeanol C. The spectroscopic data of the synthetic material was consistent with those reported for the natural product (Table 2).  

(7) and compound (3), respectively, via Riley oxidation. Intermediates (3) and (7) could be synthesized by reaction between geranyl bromide (11) with isofraxidin (10) or scopoletin (6). Isofraxidin and scopoletin may be synthesized from commercially available 2,4-dihydroxybenzaldehyde (Scheme 1).  

Regioselective bromination$^9$ of 2,4-dihydroxybenzaldehyde was carried out using bromine in an equimolar ratio with the substrate in methanol at room temperature to afford 5-bromo-2,4-dihydroxybenzaldehyde (4) in excellent yields. The monobromo compound 4 was then subjected to nucleophilic substitution with NaOMe in the presence of CuCl at reflux in DMF to furnish, 2,4-dihydroxy-5-methoxybenzaldehyde (5) in good yield. The resultant product 5 was subjected to Wittig olefination with ethyl (triphenylphosphoranylidene) acetate, in N,N-diethylaniline at reflux to give the intermediate 7-hydroxy-6-methoxy-2H-chromen-2-one (6) (scopoletin) in 70% yield.  

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In summary, we have executed the first total synthesis of artekeiskeanol A and C in five steps with overall yields of 21% and 27%, respectively. The key reactions involved in this synthetic approach are a regioselective bromination reaction, Wittig olefination, followed by cyclization and Riley oxidation. All air- and moisture-sensitive reactions were carried out under a nitrogen or argon atmosphere. Oven-dried glass apparatus was used to perform all reactions. Freshly distilled anhydrous solvents were used for air- and moisture-sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out by column chromatography using silica gel (60–120 mesh). \(^1\mathrm{H}\) and \(^{13}\mathrm{C}\) NMR spectra were recorded in CDCl\(_3\) with 400 and 500 MHz spectrometers, respectively, using TMS as internal standard. IR spec-
tra were recorded with a Perkin–Elmer FT-IR 240-c Spectrophotometer using KBr / Thin Film optics. Mass spectra were recorded with a Finnigan MAT 1020 mass spectrometer operating at 70 eV. High-resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

5-Bromo-2,4-dihydroxybenzaldehyde (4)

To a stirred solution of 2,4-dihydroxybenzaldehyde (0.5 g, 3.62 mmol) in EtOH (10 mL) was added dropwise bromine (0.1 mL, 3.26 mmol) at r.t. and the mixture was stirred for 1 h. After the completion of the reaction (monitored by TLC), the reaction was quenched with saturated aqueous sodium thiosulfate, the mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. The solvent was evaporated under reduced pressure to give 4.

Yield: 0.63 g (80%); off-white solid; mp 147–150 °C.

IR (neat): 3360, 2920, 1715, 1465, 780, 575 cm⁻¹.

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta = 11.24 \) (s, 1 H), 9.69 (s, 1 H), 7.65 (s, 1 H), 6.62 (s, 1 H), 6.17 (brs, 1 H).

\(^1\)C NMR (100 MHz, CDCl₃): \( \delta = 194.2, 160.3, 159.5, 134.3, 115.5, 108.3, 98.7.\)

HRMS: \( m/z \ [M – H]^+ \) calcd for C₈H₅O₃Br: 214.9333; found: 214.9338.

2,4-Dihydroxy-5-methoxybenzaldehyde (5)

To a stirred solution of sodium methoxide (1.2 g, 23.3 mmol) in DMF was added bromo compound 4 (0.5 g, 2.3 mmol) followed by CuCl (23 mg, 0.23 mmol). The reaction mixture was heated to reflux for 8 h with vigorous stirring. After the completion of the reaction (monitored by TLC), solvent was removed under vacuum, cold water was added, and the mixture stirred for 20 min, neutralized with HCl then stirred for another 20 min and extracted with CHCl₃ (2 × 10 mL). The separated organic layers were washed with brine, dried with Na₂SO₄, filtered and the solvent was evaporated under reduced pressure to give 5.

Yield: 0.28 g (73%); white solid; mp 120–123 °C.

IR (neat): 3355, 2900, 1730, 1135, 1015, 780, 553 cm⁻¹.

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta = 11.32 \) (s, 1 H), 9.67 (s, 1 H), 6.89 (s, 1 H), 6.53 (s, 1 H), 6.41 (s, 1 H), 3.92 (s, 3 H).

Table 2 \(^1\)H and \(^1\)C NMR Data for the Natural Product Artekeiskeanol C and Synthetic Compounds (\(^1\)H NMR 400 MHz and \(^1\)C NMR 100 MHz, in CDCl₃)

<table>
<thead>
<tr>
<th>(^1)H/(^1)C Position</th>
<th>Artekeiskeanol C, Natural product</th>
<th>Synthetic product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1)H NMR (ppm) ((J), Hz)</td>
<td>(^1)C NMR (ppm)</td>
<td>(^1)H NMR (ppm) ((J), Hz)</td>
</tr>
<tr>
<td>2</td>
<td>160.6</td>
<td>160.5</td>
</tr>
<tr>
<td>3</td>
<td>6.30 (d, 9.5)</td>
<td>115.1</td>
</tr>
<tr>
<td>4</td>
<td>7.58 (d, 9.5)</td>
<td>143.5</td>
</tr>
<tr>
<td>4*</td>
<td></td>
<td>114.4</td>
</tr>
<tr>
<td>5</td>
<td>6.63 (s)</td>
<td>103.5</td>
</tr>
<tr>
<td>6</td>
<td>150.6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>144.7</td>
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<td>8</td>
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<tr>
<td>8*</td>
<td></td>
<td>142.9</td>
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<tr>
<td>1’</td>
<td>4.63 (d, 7.5)</td>
<td>70.1</td>
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<tr>
<td>2’</td>
<td>5.52 (tdd, 6.4, 2.3, 1.3)</td>
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</tr>
<tr>
<td>3’</td>
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<td>142.1</td>
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<tr>
<td>4’</td>
<td>2.04 (t, 7.5)</td>
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<td>5’</td>
<td>2.11 (q, 7.0)</td>
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<td>6’</td>
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<tr>
<td>7’</td>
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<td>8’</td>
<td>3.94 (s)</td>
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<tr>
<td>9’</td>
<td>1.61 (s)</td>
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<tr>
<td>OCH₃-6</td>
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<tr>
<td>OCH₃-8</td>
<td>3.99 (s)</td>
<td>61.7</td>
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</table>

Artekeiskeanol C (2)
To a stirred solution of 5 (0.2 g, 1.11 mmol) in N,N-diethylaniline (10 mL) was added ethyl (triphenylphosphoranylidene) acetate (0.49 g, 1.42 mmol) and the resulting mixture was heated to reflux for 12 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The resulting brown oily residue was purified by column chromatography, eluting with EtOAc–hexane (4:6) mixture to afford 6.

Yield: 0.16 g (70%); yellow solid; mp 202–205 °C.

IR (neat): 3345, 3040, 2956, 1421, 1616, 1276, 1145, 758 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.61 (d, J = 9.5 Hz, 1 H), 6.85 (s, 1 H), 6.83 (s, 1 H), 6.28 (d, J = 9.5 Hz, 1 H), 5.48 (dd, J = 6.4, 2.3, 1.2 Hz, 2 H), 5.37 (dd, J = 6.9, 2.6, 1.4 Hz, 1 H), 4.69 (d, J = 6.4 Hz, 2 H), 3.97 (s, 2 H), 3.91 (s, 3 H), 2.20 (m, 2 H), 2.10 (m, 2 H), 1.78 (s, 3 H), 1.66 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 161.5, 152.1, 149.9, 146.6, 143.3, 141.5, 135.4, 125.0, 118.8, 113.3, 111.3, 108.0, 101.2, 68.8, 66.3, 56.3, 39.0, 25.5, 16.8, 13.7.

HRMS: m/z [M + H]+ calcld for C20H23O5: 343.1540; found: 343.1551.

3,5-Dibromo-2,4-dihydroxybenzaldehyde (8)
To a stirred solution of 2,4-dihydroxybenzaldehyde (0.50 g, 3.6 mmol) in EtOH (10 mL) was added bromine (0.22 mL, 9.1 mmol) dropwise at r.t. and the mixture was stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated aqueous sodium thiosulfate and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and the solvent was evaporated under reduced pressure to give 8.

Yield: 1.00 g (98%); white solid; mp 197–200 °C.

IR ( neat): 3263, 3052, 2923, 1467, 785, 555 cm–1.

1H NMR (400 MHz, CDCl3): δ = 11.98 (s, 1 H), 9.68 (s, 1 H), 7.70 (s, 1 H), 6.64 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = 193.4, 159.6, 156.2, 136.0, 116.2, 100.0, 98.9.


(2E)-7-[3-(3,7-Dimethyl-2,6-dien-1-yl)oxy]-6-methoxy-2H-chromen-2-one (7)
To a stirred solution of geranyl bromide (84 mg, 0.39 mmol) in DMF (5 mL) was added K₂CO₃ (71 mg, 0.52 mmol), KI (cat) and a solution of 4,5-dimethoxy-2-phenylpyridine (50 mg, 0.26 mmol) in DMF (5 mL). The resulting mixture was stirred for 2 h at r.t. After completion of reaction (monitored by TLC) the mixture was diluted with EtOAc (10 mL), quenched with cold water and further extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and the solvent was evaporated under reduced pressure to give 7.

Yield: 70 mg (82%); amorphous solid.

IR ( neat): 3365, 2875, 1710, 1562, 1120, 1070, 828, 580 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.62 (d, J = 7.6 Hz, 1 H), 6.92 (s, 1 H), 6.85 (s, 1 H), 6.27 (d, J = 7.6 Hz, 1 H), 6.18 (s, 1 H), 3.96 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 161.5, 152.1, 149.9, 146.6, 143.3, 113.4, 111.5, 107.5, 103.2, 56.4.

HRMS: m/z [M + H]+ calcld for C₁₃H₁₄O₃: 217.0928; found: 217.0924.

(50 mg, 0.26 mmol) in DMF (5 mL). The resulting mixture was stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated aqueous sodium thiosulfate and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and the solvent was evaporated under reduced pressure to give 8.

Yield: 0.24 g (72%); mp 146–148 °C.

1H NMR (400 MHz, CDCl3): δ = 11.10 (s, 1 H), 9.78 (s, 1 H), 7.70 (s, 1 H), 6.64 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = 193.4, 159.6, 156.2, 136.0, 116.2, 100.0, 98.9.

HRMS: m/z [M -- H]– calcld for C₁₃H₁₄O₃: 217.0928; found: 217.0924.

2,4-Dihydroxy-3,5-dimethoxybenzaldehyde (9)
To stirred solution of sodium methoxide (1.64 g, 30.5 mmol) in DMF (20 mL) was added dibromo compound 8 (0.9 g, 3.05 mmol) and CuCl (30 mg, 0.3 mmol), and the reaction mixture was heated to reflux for 8 h, with vigorous stirring. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum, ice was added, and the mixture was stirred for 20 min. The mixture was then neutralized with HCl, stirred for another 20 min and extracted with CHCl₃ (2 × 15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and the solvent was evaporated under reduced pressure to give 9.

Yield: 0.45 g (75%); white solid; mp 87–89 °C.

IR ( neat): 3379, 2924, 1735, 1645, 1324, 1137, 1088, 745, 553 cm–1.

1H NMR (400 MHz, CDCl3): δ = 11.31 (s, 1 H), 7.97 (s, 1 H), 6.75 (s, 1 H), 6.42 (bs, 1 H), 4.01 (s, 3 H), 3.91 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 194.5, 151.6, 146.9, 141.2, 134.5, 112.9, 108.9, 60.9, 56.6.

HRMS: m/z [M + H]+ calcld for C₁₉H₂₁O₂: 297.7542; found: 297.7551.

7-Hydroxy-6,8-dimethoxy-2H-chromen-2-one (10)
The above procedure for 6 was followed for the preparation of 10 (0.3 g, 0.30 mmol).

Yield: 0.24 g (72%); mp 146–148 °C.

IR ( neat): 3352, 2924, 1702, 1459, 1310, 1118, 1080, 590 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.60 (d, J = 9.5 Hz, 1 H), 6.66 (s, 1 H), 6.28 (d, J = 9.5 Hz, 1 H), 6.22 (s, 1 H), 4.09 (s, 3 H), 3.94 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = 160.6, 144.6, 143.8, 143.0, 142.5, 134.4, 113.4, 111.2, 103.2, 61.6, 56.5.

HRMS: m/z [M + H]+ calcld for C₁₁H₁₈O₃: 223.1376; found: 223.1370.
To a stirred solution of geranyl bromide (73 mg, 0.33 mmol) in DMF (5 mL) was added K₂CO₃ (62 mg, 0.45 mmol), KI (cat) and a solution of isofaxiridin (10; 50 mg, 0.23 mmol) in DMF (5 mL). The resulting mixture was stirred for 2 h at rt. After completion of reaction was confirmed by TLC, the mixture was diluted with EtOAc (10 mL) and quenched with cold water and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with EtOAc–hexane (3:7) mixture to give 7.

Yield: 64 mg (80%); amorphous solid.

IR (neat): 3345, 3054, 2986, 1721, 1616, 1275, 1148, 758 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.61 (d, J = 9.4 Hz, 1 H), 6.66 (s, 1 H), 6.33 (d, J = 9.5 Hz, 1 H), 5.56 (td, J = 7.2, 1.2 Hz, 1 H), 5.07 (m, 1 H), 4.68 (d, J = 7.2 Hz, 2 H), 4.03 (s, 3 H), 3.89 (s, 3 H), 2.06 (m, 4 H), 1.70 (s, 3 H), 1.66 (s, 3 H), 1.59 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 160.5, 150.6, 144.8, 143.5, 142.9, 142.5, 141.7, 131.7, 123.8, 119.5, 115.1, 114.4, 103.5, 70.2, 61.7, 56.2, 39.6, 26.3, 25.6, 17.6, 16.3.

HRMS: m/z [M + H⁺] calc for C₁₂H₁₆O₅Na: 359.1737; found: 359.1747.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610873.

References
(12) Geranyl bromide (11) was prepared as per reported procedure, see: Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. J. Am. Chem. Soc. 1990, 112, 5276.