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# **Electronic Supplementary Information:**

# Semi-syntheses of the 11-hydroxyrotenoids sumatrol and villosinol

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#### **1. General Methods**

All moisture sensitive reactions were carried out with anhydrous, freshly distilled solvents under nitrogen in glassware that was oven dried. Methanol was distilled from calcium hydride and THF was distilled from a mixture of calcium hydride and lithium aluminium hydride in the presence of triphenylmethane. (6aS,12aS,5'R)-Rotenone (**5**, 95% purity, obtained from Molekula Fine Chemicals as an off-white amorphous solid) was crystallised from ethanol three times to give colourless plates (m.p. 163 °C). All other reagents were used as obtained from commercial sources.

Analytical thin layer chromatography (TLC) was carried out on glass-backed silica gel 60  $F_{254}$ -coated plates with visualisation achieved by quenching the intrinsic UV fluorescence or by staining with ceric ammonium molybdate solution and heating. Retention factors ( $R_f$ ) are quoted to the nearest 0.05. Column chromatography was carried out using Sigma-Aldrich silica gel 60 (230-400 mesh), distilled solvents and positive pressure of nitrogen.

Proton magnetic resonance spectra were recorded using an internal deuterium lock at ambient probe temperature on Bruker Avance 400 or 500 (400 or 500 MHz spectrometers. Proton assignments are supported by <sup>1</sup>H-<sup>1</sup>H COSY spectra. Chemical shifts ( $\delta_{\rm H}$ ) are quoted in parts per million (ppm) to the nearest 0.01 ppm and are referenced to the residual non-deuterated solvent peak (CHCl<sub>3</sub>, 7.26 ppm). Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity (br, broad; s, singlet; d, doublet; t, triplet; sept, septet; m, multiplet; app, apparent; or as combinations or these (e.g. dd)), coupling constant(s) and assignment. Diastereotopic protons are assigned as H and H' where the ' indicates the higher field proton. Carbon magnetic resonance spectra were recorded using an internal deuterium lock at ambient probe temperature on Bruker Avance 400 or 500 (100.6 or 125.7 MHz) spectrometers with broadband proton spin decoupling. Carbon assignments are supported by DEPT editing, <sup>13</sup>C-<sup>1</sup>H HSQC and HMBC correlations. Chemical shifts ( $\delta_{\rm C}$ ) are quoted in ppm to the nearest 0.1 ppm and are referenced to the deuterated solvent peak (CDCl<sub>3</sub>, 77.16 ppm). Phosphorus magnetic resonance spectra were recorded using an internal deuterium lock at ambient probe temperature on a Bruker Avance 400 (162.0 MHz) spectrometer with broadband proton spin decoupling.

Optical rotations were recorded on an Anton-Paar MCP 100 polarimeter.  $[\alpha]_D^{20}$  values are reported in  $10^{-1}$  deg cm<sup>2</sup> g<sup>-1</sup> at 598 nm, concentration (*c*) is given in g(100 mL)<sup>-1</sup>. Melting points for crystalline compounds were obtained using a Büchi Melting Point B-545 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrometer with internal referencing as neat films. Absorption maxima are reported in wavenumbers (cm<sup>-1</sup>) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Low-resolution mass spectra (LRMS) were recorded using an LCMS system (Agilent series LC with an ESCi Multi-Mode Ionisation Waters ZQ spectrometer using MassLynx 4.1 software). Only molecular ions or major peaks are reported. High-resolution mass spectra (HRMS) were recorded using a Micromass Q-TOF in the Department of Chemistry, University of Cambridge, and reported mass values are within the error limits of ± 5 ppm.

The following atom numbering system conforms to established conventions (see, for example: L. Crombie and D. A. Whiting, *Phytochemistry*, 1998, **49**, 1479-1507) and is used consistently herein:



Figure S1: Representative numbering scheme for 11-hydroxyrotenoids, example shown for 11-O-acetyl villosinol (13).

#### 2. Synthetic Procedures for all Compounds

Preparation of (6a*S*,12a*S*,5'*R*)-rotenone oxime (**6**) using the method described by Harper<sup>1</sup>:

(6aS,12aS,5'R)-Rotenone (5, 4.0 g, 10.2 mmol), hydroxylamine hydrochloride (2.96 g, 40.6 mmol) and NaOAc (3.36 g, 40.6 mmol) were suspended in ethanol (200 mL) and the mixture was heated at reflux for 18 h. Water (120 mL) was then added and the mixture was allowed to cool to room temperature whereupon white crystals formed. The crystals were collected by filtration, washed with water and dried under vacuum. Recrystallisation from methanol gave (6aS, 12aS, 5'R)-rotenone oxime (6) as white needles (2.90 g, 70 %). Concentration of the mother liquor afforded a second crop of crystals (160 mg), bringing the total yield to 74 %. mp 233-235 °C (lit.<sup>1</sup> 237 °C);  $R_f$  0.20 (2:1 hexane-ethyl acetate);  $[\alpha]_D^{20}$  +268 (*c* 0.1, CHCl<sub>3</sub>); IR (neat): 3450w br, 2928w br, 1719w br, 1632m (C=N)<sup>oxime</sup>, 1609w, 1597m, 1499m, 1451m, 1330m, 1263m, 1190s, 1164m, 1080s, 1024m, 975m, 894m, 802m; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 7.95 (1H, s, C(12)NO<u>H</u>), 7.69 (1H, d, J 9.0 Hz, C(11)<u>H</u>), 6.63 (1H, s, C(1)<u>H</u>), 6.44 (1H, d, J 9.0 Hz, C(10)<u>H</u>), 6.43 (1H, s, C(4)H), 5.16 (1H, app t, J 8.8 Hz, C(5')H), 5.06 (1H, s, C(7')HH'), 4.90 (1H s, C(7')HH'), 4.88 (1H, d, J 3.2 Hz, C(12a)H), 4.61 (1H, dd, J 12.0, 2.8 Hz, C(6)HH'), 4.52 (1H, dd, J 2.8, 2.4 Hz, C(6a)H), 4.26 (1H, d, J 12.0 Hz, C(6)H<u>H</u>'), 3.81 (3H, s, C(3')<u>H</u><sub>3</sub>), 3.75 (3H, s, C(2')<u>H</u><sub>3</sub>), 3.29 (1H, dd, *J* 16.0, 10.0 Hz, C(4')<u>H</u>H'), 2.93 (1H, dd, / 16.0, 8.0 Hz, C(4')HH'), 1.76 (3H, s, C(8')H<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta_{C}$  163.4 (C(12)), 152.7 (<u>C</u>(9)), 151.8 (<u>C</u>(7a)), 149.5 (<u>C</u>(3)), 147.9 (<u>C</u>(4a)), 143.9 (<u>C</u>(2)), 143.7 (<u>C</u>(6')), 125.4 (<u>C</u>(11)H), 113.4 (<u>C</u>(8)), 112.3 (<u>C</u>(7')H<sub>2</sub>), 112.2 (<u>C</u>(1)H), 108.6 (<u>C</u>(1a)), 106.4 (<u>C</u>(11a)), 104.2 (<u>C</u>(10)H), 100.8 (<u>C</u>(4)H), 87.1 (C(5')H), 69.6 (C(6a)H), 67.0 (C(6)H<sub>2</sub>), 56.6 (C(2')H<sub>3</sub>), 56.0 (C(3')H<sub>3</sub>), 32.0 (C(4')H<sub>2</sub>), 31.8 (C(12a)H), 17.3 (<u>C(8')</u>H<sub>3</sub>); LRMS: *m/z* found 410.2, C<sub>23</sub>H<sub>24</sub>NO<sub>6</sub> [M+H]<sup>+</sup> requires 410.2; HRMS: *m/z* found 410.1591, C<sub>23</sub>H<sub>24</sub>NO<sub>6</sub> [M+H]<sup>+</sup> requires 410.1604.

Preparation of dimeric palladacycle 7:

 $Na_2PdCl_43H_2O$  (1.03 g, 2.93 mmol) was added to a solution of (6a*S*,12a*S*,5'*R*)-rotenone oxime (6, 1.20 g, 2.93 mmol) and NaOAc (0.29 g, 3.52 mmol) in acetic acid (80 mL). The mixture was stirred at room temperature for 4 days while a bright yellow precipitate slowly formed on the walls of the flask. The precipitate was collected by filtration, thoroughly washed with water (4 x 20 mL) and dried under vacuum for 2 days to afford dimeric palladacycle **7** as yellow powder (1.48 g, 92 %). This product was used without further purification.

Preparation of triphenylphosphine complex 8:

Triphenylphosphine (19.0 mg, 0.072 mmol) was added to a suspension of dimeric palladacycle 7 (40.0 mg, 0.036 mmol) in THF (8.0 mL) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 18 h before anhydrous hexane (8.0 mL) was added and a pale yellow precipitate was formed. The precipitate was collected by filtration, washed with anhydrous hexane (4 x 2 mL) and dried under vacuum overnight to afford triphenylphosphine complex  $\mathbf{8}$  as a pale yellow powder (52.0 mg, 88 %). Crystals suitable for analysis by X-ray crystallography were prepared by vapour diffusion of petroleum ether (b.p 30-40 °C) into a concentrated solution of triphenylphosphine complex 8 in THF at room temperature. A single large crystal was selected for analysis.  $R_f 0.25$  (2:1 hexane-ethyl acetate);  $[\alpha]_{D^{20}}$  +292 (c 0.04, CHCl<sub>3</sub>); IR (neat): 3113w br, 2934w br, 1603m (C=N)<sup>oxime</sup>, 1569m, 1513m, 1462m, 1436m, 1244m, 1215m, 1199m, 1098m, 841m, 745m; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 10.34 (1H, d, J<sub>H-P</sub> 3.2 Hz, C(12)NOH), 7.74-7.69 (6H, m, PPh<sub>3</sub> meta CH), 7.49-7.45 (3H, m, PPh<sub>3</sub> para CH), 7.41-7.37 (6H, m, PPh<sub>3</sub> *ortho* C<u>H</u>), 7.01 (1H, s, C(1)<u>H</u>), 6.44 (1H, s, C(4)<u>H</u>), 5.54 (1H, d, *J*<sub>H-P</sub> 7.0 Hz, C(10)<u>H</u>), 4.90 (1H, dd, *J* 9.6, 7.6 Hz, C(5')H), 4.77 (1H, s, C(7')HH'), 4.77 (1H, s, C(7')HH'), 4.68 (1H, d, J 3.6 Hz, C(12a)H), 4.63 (1H, dd, J 12.0, 2.8 Hz, C(6)HH'), 4.53 (1H, dd, J 2.8, 2.4 Hz, C(6a)H), 4.23 (1H, d, J 12.0 Hz, C(6)HH'), 3.83 (3H, s, C(3')H<sub>3</sub>), 3.82 (3H, s, C(2')H<sub>3</sub>), 3.11 (1H, dd, J 15.6, 10.0 Hz, C(4')HH'), 2.73 (1H, dd, J 15.6, 7.6 Hz, C(4')H<u>H</u>'), 1.58 (3H, s, C(8')<u>H</u><sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 162.0 (d, *J*<sub>C-P</sub> 7.0 Hz, <u>C(11)</u>), 161.3 (d, J<sub>C-P</sub> 2.2 Hz, C(12)), 154.7 (C(9)), 152.5 (C(7a)), 149.8 (C(3)), 147.7 (C(4a)), 144.2 (C(2)), 143.7 (C(6')), 135.4 (d, J<sub>C-P</sub> 12.2 Hz, PPh<sub>3</sub> meta <u>C</u>H), 131.3 (d, J<sub>C-P</sub> 2.2 Hz, PPh<sub>3</sub> para <u>C</u>H), 130.2 (d, J<sub>C-P</sub> 51.8 Hz, PPh<sub>3</sub> ipso <u>C</u>), 128.5 (d, J<sub>C-P</sub> 11.2 Hz, PPh<sub>3</sub> ortho <u>C</u>H), 117.8 (d, J<sub>C-P</sub> 1.8 Hz, <u>C</u>(11a)H), 114.2 (d, J<sub>C-P</sub> 8.2 Hz, <u>C</u>(10)H), 112.3 (C(1)H), 111.9 (C(7')H<sub>2</sub>), 109.1 (C(8)), 105.9 (C(1a)), 100.8 (C(4)H), 86.4 (C(5')H), 70.4 (C(6a)H), 66.3 (C(6)H<sub>2</sub>), 56.9 (C(3')H<sub>3</sub>), 56.0 (C(2')H<sub>3</sub>), 34.9 (C(12a)H), 31.4 (C(4')H<sub>2</sub>), 17.1 (C(8')H<sub>3</sub>); <sup>31</sup>P{<sup>1</sup>H} NMR (162.0 MHz, CDCl<sub>3</sub>): δ<sub>P</sub> 41.9; LRMS: *m/z* found 775.1, 776.2 and 778.1, C<sub>41</sub>H<sub>37</sub>NO<sub>6</sub>P<sup>105</sup>Pd [M-Cl]<sup>+</sup> requires 775.1 C<sub>41</sub>H<sub>37</sub>NO<sub>6</sub>P<sup>106</sup>Pd [M-Cl]<sup>+</sup> requires 776.1 and C<sub>41</sub>H<sub>37</sub>NO<sub>6</sub>P<sup>108</sup>Pd [M-Cl]<sup>+</sup> requires 778.1; HRMS: *m/z* found 775.1413, 776.1407 and 778.1399, C<sub>41</sub>H<sub>37</sub>NO<sub>6</sub>P<sup>105</sup>Pd [M-Cl]<sup>+</sup> requires 775.1409, C<sub>41</sub>H<sub>37</sub>NO<sub>6</sub>P<sup>106</sup>Pd [M-Cl]<sup>+</sup> requires 776.1393 and C<sub>41</sub>H<sub>37</sub>NO<sub>6</sub>P<sup>108</sup>Pd [M-Cl]<sup>+</sup> requires 778.1397.

Preparation of (6a*S*,12a*S*,5'*R*)-11-O-acetyl sumatrol oxime (**9**):

Pyridine (32 μL, 0.400 mmol) was added to a suspension of dimeric palladacyle 7 (200 mg, 0.182 mmol) in THF (10 mL) under an atmosphere of nitrogen. A homogeneous pale yellow solution formed rapidly and was stirred at room temperature for 10 min. The mixture was then cooled to 0 °C and a solution of Pb(OAc)<sub>4</sub> (177 mg, 0.400 mmol) in acetic acid (4.0 mL) was added dropwise over 2 min. The mixture was stirred at 0 °C for 2 hours before a solution of NaBH<sub>4</sub> (15.2 mg, 0.400 mmol) in saturated aqueous NaHCO<sub>3</sub> (4.0 mL) was added to quench the reaction and precipitate palladium black. The mixture was immediately filtered through a pad of Celite and the solid residue was washed with diethyl ether (40 mL). The filtrate was allowed to separate and the organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (3 x 40 mL), water (40 mL) and brine (40 mL), dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude yellow solid was purified by column chromatography (2:1 then 1:1 hexane-ethyl acetate) to afford (6a*S*,12a*S*,5'*R*)-11-O-acetyl sumatrol oxime (9) as a white amorphous solid (35.6 mg, 21 %). R<sub>f</sub> 0.10 (2:1 hexane-ethyl acetate); [α]<sub>D</sub><sup>20</sup> +210 (*c* 0.01, CHCl<sub>3</sub>); IR (neat): 3452w br, 2924w br, 1764m (C=O)ester, 1628m (C=N)oxime, 1596m, 1514m, 1483m, 1348m, 1197s, 1161m, 1082w, 1046m, 917m; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 6.45 (1H, s, C(1)<u>H</u>), 6.40 (1H, s, C(4)<u>H</u>), 6.18 (1H, s, C(10)<u>H</u>), 5.17 (1H, app t, J 8.8 Hz, C(5')H), 5.05 (1H, s, C(7')HH'), 5.00 (1H, d, J 3.2 Hz, C(12a)H), 4.91 (1H, s, C(7')HH'), 4.58 (1H, dd, J 11.6, 2.8 Hz, C(6)HH'), 4.56 (1H, dd, J 2.8, 2.4 Hz, C(6a)H), 4.25 (1H, d, J 11.6 Hz, C(6)HH'), 3.80 (3H, s, C(3')H<sub>3</sub>), 3.77 (3H, s, J C(2')H<sub>3</sub>), 3.25 (1H, dd, J 15.8, 9.8 Hz, C(4')HH'), 2.90 (1H, dd, J 15.8, 8.2 Hz,  $C(4')HH'_{1}$ , 2.32 (3H, s,  $C(10')H_{3}$ ), 1.75 (3H, s,  $C(8')H_{3}$ ). The oxime OH signal was not observed; <sup>13</sup>C NMR

(100.6 MHz, CDCl<sub>3</sub>):  $\delta_{C}$  169.7 (<u>C</u>(9')), 162.6 (<u>C</u>(9)), 152.9 (<u>C</u>(7a)), 151.3 (<u>C</u>(12)), 149.9 (<u>C</u>(11)), 149.5 (<u>C</u>(3)), 147.6 (<u>C</u>(4a)), 144.0 (<u>C</u>(2)), 143.3 (<u>C</u>(6')), 112.6 (<u>C</u>(7')H<sub>2</sub>), 111.7 (<u>C</u>(1)H), 111.6 (<u>C</u>(8)H), 106.0 (<u>C</u>(1a)), 101.9 (<u>C</u>(11a)), 100.7 (<u>C</u>(4)H), 99.8 (<u>C</u>(10)H), 87.7 (<u>C</u>(5')H), 69.2 (<u>C</u>(6a)H), 66.8 (<u>C</u>(6)H<sub>2</sub>), 56.4 (<u>C</u>(2')H<sub>3</sub>), 56.0 (<u>C</u>(3')H<sub>3</sub>), 31.9 (<u>C</u>(4')H<sub>2</sub>), 31.0 (<u>C</u>(12a)H), 21.5 (<u>C</u>(10')H<sub>3</sub>), 17.3 (<u>C</u>(8')H<sub>3</sub>); LRMS: *m/z* found 468.2, C<sub>25</sub>H<sub>26</sub>NO<sub>8</sub> [M+H]<sup>+</sup> requires 468.2; HRMS: *m/z* found 468.1655, C<sub>25</sub>H<sub>26</sub>NO<sub>8</sub> [M+H]<sup>+</sup> requires 468.1658.

Preparation of (6a*S*,12a*S*,5'*R*)-sumatrol oxime (**10**):

 $Na_2CO_3$  (18.2 mg, 0.171 mmol) was added to a solution of  $(6aS_12aS_5'R)$ -11-O-acetyl sumatrol oxime (9, 20 mg, 0.042 mmol) in methanol (8.0 mL) and the mixture was stirred vigorously at room temperature for 18 h. The mixture was filtered through a cotton wool-plugged Pasteur pipette and the filtrate was concentrated under reduced pressure. The crude pale yellow solid was purified by column chromatography (2:1 hexane-ethyl acetate) to afford (6aS, 12aS, 5'R)-sumatrol oxime (10) as a white amorphous solid (14.2 mg, 78 %).  $R_f$  0.20 (2:1 hexane-ethyl acetate);  $[\alpha]_D^{20}$  +180 (*c* 0.01, CHCl<sub>3</sub>); IR (neat): 3379w br, 2924w br, 1602m (C=N)<sup>oxime</sup>, 1513m, 1456m, 1346m, 1241m, 1214m, 1197s, 1146m, 1096s, 1071m, 1008m, 912m, 816m; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 6.63 (1H, s, C(1)<u>H</u>), 6.44 (1H, s, C(4)<u>H</u>), 6.08 (1H, s, C(10)<u>H</u>), 5.13 (1H, app t, J 8.8 Hz, C(5')<u>H</u>), 5.04 (1H, s, C(7')<u>H</u>H'), 4.89 (1H, s, C(7')H<u>H</u>'), 4.87 (1H, d, J 3.6 Hz, C(12a)H), 4.61 (1H, dd, J 12.0, 2.4 Hz, C(6)HH'), 4.51 (1H, app t, J 2.4 Hz, C(6a)H), 4.26 (1H, dd, J 12.0 Hz, C(6)HH'), 3.81 (3H, s, C(3')H<sub>3</sub>), 3.75 (3H, s, C(2')H<sub>3</sub>), 3.22 (1H, dd, J 15.2, 9.6 Hz, C(4')HH'), 2.85 (1H, dd, J 15.2, 7.6 Hz, C(4')HH'), 1.74 (3H, s, C(8')H<sub>3</sub>). The oxime and phenol OH signals were not observed; <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 164.4 (<u>C</u>(9)), 160.4 (<u>C</u>(11)), 156.6 (<u>C</u>(12)), 152.5 (<u>C</u>(7a)), 149.7 (<u>C</u>(3)), 147.8 (<u>C</u>(4a)), 143.9 (<u>C</u>(2)), 143.6 (<u>C</u>(6')), 112.3 (<u>C</u>(7')H<sub>2</sub>), 112.1 (<u>C</u>(1)H), 105.7 (<u>C(1a)</u>), 104.7 (<u>C(8)</u>), 100.9 (<u>C(4)</u>H), 95.4 (<u>C(11a)</u>), 92.1 (<u>C(10)</u>H), 87.5 (<u>C(5')</u>H), 69.2 (<u>C(6a)</u>H), 66.7 (C(6)H<sub>2</sub>), 56.7 (C(2')H<sub>3</sub>), 56.0 (C(3')H<sub>3</sub>), 32.1 (C(12a)H), 31.5 (C(4')H<sub>2</sub>), 17.3 (C(8')H<sub>3</sub>); LRMS: *m/z* found 426.2, C<sub>23</sub>H<sub>24</sub>NO<sub>7</sub> [M+H]<sup>+</sup> requires 426.2; HRMS: *m*/*z* found 426.1560, C<sub>23</sub>H<sub>24</sub>NO<sub>7</sub> [M+H]<sup>+</sup> requires 426.1553.

# Preparation of (6a*S*,12a*S*,5'*R*)-sumatrol (**1**):

A solution of TiCl<sub>3</sub> (240  $\mu$ L, 12 wt% in hydrochloric acid, approximately 0.19 mmol) was rapidly added to a solution of (6aS, 12aS, 5'R)-sumatrol oxime (10, 8.0 mg, 0.019 mmol) and NH<sub>4</sub>OAc (29 mg, 0.37 mmol) in THF (2.0 mL) and water (2.0 mL) under an atmosphere of nitrogen. The resulting grey suspension was stirred vigorously for 0.5 h before diethyl ether (8 mL) and water (8 mL) were added and the two phases were mixed vigorously for 0.5 h. The organic layer was separated, washed with saturated aqueous NaHCO<sub>3</sub> solution (3 x 8 mL), water (8 mL), and brine (8 mL), dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude pale yellow solid was purified by column chromatography (2:1 hexane-ethyl acetate) to afford (6aS, 12aS, 5'R)-sumatrol (1) as a white amorphous solid (3.1 mg, 40 %). R<sub>f</sub> 0.25 (2:1 hexane-ethyl acetate); [α]<sub>D</sub><sup>20</sup> -20 (*c* 0.01, CHCl<sub>3</sub>), lit.<sup>2</sup> [α]<sub>D</sub><sup>20</sup> -27.5 (*c* 0.2, CHCl<sub>3</sub>); IR (neat): 2924w br, 1649m (C=O)<sup>ketone</sup>, 1607m, 1515m, 1470m, 1455m, 1408m, 1381m, 1238m, 1217m, 1198s, 1153m, 1106m, 1069m, 1009m, 910m, 813m; <sup>1</sup>H NMR (500.1 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 12.42 (1H, s, C(11)0<u>H</u>), 6.87 (1H, s, C(1)<u>H</u>), 6.46 (1H, s, C(4)<u>H</u>), 6.02 (1H, s, C(10)<u>H</u>), 5.20 (1H, app t, J 8.5 Hz, C(5')<u>H</u>), 5.06 (1H, s, C(7')<u>H</u>H'), 4.93 (1H, s, C(7')H<u>H</u>'), 4.88 (1H, app t, J 3.5 Hz, C(6a)<u>H</u>), 4.59 (1H, dd, J 12.0, 3.0 Hz, C(6)<u>H</u>H'), 4.17 (1H, d, J 12.0 Hz, C(6)H<u>H</u>'), 3.85 (1H, d, J 4.5 Hz, C(12a)<u>H</u>), 3.82 (3H, s, C(3')<u>H</u><sub>3</sub>), 3.79 (3H, s, C(2')<u>H</u><sub>3</sub>), 3.23 (1H, dd, *J* 15.0, 9.5 Hz, C(4')<u>H</u>H'), 2.85 (1H, dd, *J* 15.0, 7.5 Hz, C(4')H<u>H</u>'), 1.75 (3H, s, C(8')<u>H</u><sub>3</sub>); <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>):  $\delta_{C}$  193.8 (<u>C</u>(12)), 169.5 (<u>C</u>(9)), 166.2 (<u>C</u>(11)), 156.4 (<u>C</u>(7a)), 149.8 (<u>C</u>(3)), 147.4 (<u>C</u>(4a)), 144.2 (<u>C</u>(2)), 143.1 (<u>C</u>(6')), 112.9 (<u>C</u>(7')H<sub>2</sub>), 110.4 (<u>C</u>(1)H), 104.8 (<u>C</u>(1a)), 104.3 (<u>C</u>(8)), 101.4 (<u>C</u>(11a)), 101.1 (<u>C</u>(4)H), 92.1 (<u>C</u>(10)H), 88.3 (<u>C</u>(5')H), 71.9 (<u>C</u>(6a)H), 66.2 (<u>C</u>(6)H<sub>2</sub>), 56.5 (<u>C</u>(2')H<sub>3</sub>), 56.0 (<u>C</u>(3')H<sub>3</sub>), 43.9 (<u>C</u>(12a)H), 30.7 (<u>C</u>(4')H<sub>2</sub>), 17.2 (<u>C</u>(8')H<sub>3</sub>); LRMS: m/z found 411.1, C<sub>23</sub>H<sub>23</sub>O<sub>7</sub> [M+H]<sup>+</sup> requires 411.1; HRMS: m/z found 411.1438, C<sub>23</sub>H<sub>23</sub>O<sub>7</sub> [M+H]<sup>+</sup> requires 411.1444. The observed NMR data were in good agreement with those reported previously.<sup>2,3</sup>

Preparation of (6a*R*,12a*R*,5'*R*)-11-0-acetyl villosinol (**13**):

A solution of K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (214 mg, 0.727 mmol) in water (4.0 mL) was added dropwise over a period of 2 min to a suspension of dimeric palladacycle 7 (200 mg, 0.182 mmol) in acetic acid (20 mL) at 60 °C. The dark homogenous solution formed was stirred at 60 °C for 0.5 h then cooled to room temperature and stirred for an additional 1.5 h. Water (20 mL) was added and the mixture was stirred vigorously for 0.5 h as a brown precipitate formed, which was collected by filtration, washed with water and dried under vacuum overnight. The crude precipitate was purified by column chromatography (2:1 hexane-ethyl acetate) to afford (6a*R*,12a*R*,5'*R*)-11-O-acetyl villosinol (13) as a white amorphous solid (20.3 mg, 12 %). R<sub>f</sub> 0.15 (2:1 hexane-ethyl acetate); [α]<sub>0</sub><sup>20</sup> +220 (*c* 0.01, CHCl<sub>3</sub>); IR (neat): 3448w br, 2925w br, 1766 (C=O)<sup>ester</sup>, 1672m (C=O)ketone, 1617m, 1509m, 1439m, 1348m, 1273m, 1197m, 1099m, 1015m, 911m, 816m; <sup>1</sup>H NMR (400.1 MHz,  $CDCl_3$ ):  $\delta_H$  6.46 (1H, s, C(1)H), 6.42 (1H, s, C(4)H), 6.21 (1H, s, C(10)H), 5.24 (1H, app t, J 8.8 Hz, C(5')<u>H</u>), 5.06 (1H, s, C(7')<u>H</u>H'), 4.94 (1H, s, C(7')H<u>H</u>'), 4.58 (1H, dd, *J* 11.6, 2.4 Hz, C(6)<u>H</u>H'), 4.56 (1H, app s, C(6a)<u>H</u>'), 4.47 (1H, d, J 11.6 Hz, C(6)H<u>H</u>'), 3.82 (3H, s, C(3')<u>H<sub>3</sub></u>), 3.78 (3H, s, C(2')<u>H<sub>3</sub></u>), 3.26 (1H, dd, J 15.6, 9.6 Hz, C(4')HH'), 2.91 (1H, dd, J 15.6, 8.0 Hz, C(4')HH'), 2.42 (3H, s, C(10')H<sub>3</sub>), 1.75 (3H, s, C(8')H<sub>3</sub>). The tertiary O<u>H</u> signal was not observed; <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 189.7 (<u>C</u>(12)), 169.5 (<u>C</u>(9')), 167.4 (C(9)), 157.5 (C(7a)), 153.0 (C(11)), 151.2 (C(3)), 148.2 (C(4a)), 144.1 (C(2)), 142.7 (C(6')), 113.2 (<u>C</u>(7')H<sub>2</sub>), 111.5 (<u>C</u>(8)), 109.5 (<u>C</u>(1)H), 108.7 (<u>C</u>(1a)), 104.9 (<u>C</u>(11a)), 101.0 (<u>C</u>(4)H), 100.5 (<u>C</u>(10)H), 88.7 (C(5')H), 75.6 (C(6a)H), 67.7 (C(12a)), 63.8 (C(6)H<sub>2</sub>), 56.3 (C(2')H<sub>3</sub>), 56.0 (C(3')H<sub>3</sub>), 31.2 (C(4')H<sub>2</sub>), 21.3 (C(10')H<sub>3</sub>), 17.2 (C(8')H<sub>3</sub>); LRMS: m/z found 451.1, C<sub>23</sub>H<sub>23</sub>O<sub>7</sub> [M-H<sub>2</sub>O+H]<sup>+</sup> requires 451.1; HRMS: m/zfound 468.1399, C<sub>25</sub>H<sub>25</sub>O<sub>9</sub> [M] requires 468.1420.

# Preparation of (6a*R*,12a*R*,5'*R*)-villosinol (2):

 $Na_2CO_3$  (7.2 mg, 0.068 mmol) was added to a solution of (6aR, 12aR, 5'R)-11-O-acetyl villosinol (13, 8.0 mg, 0.017 mmol) in methanol (4.0 mL) and the mixture was stirred vigorously at room temperature for 2 h. The mixture was filtered through a cotton wool-plugged Pasteur pipette and the filtrate was concentrated under reduced pressure. The crude pale yellow solid was purified by column chromatography (2:1 hexane-ethyl acetate) to afford (6aR,12aR,5'R)-villosinol (2) as a white amorphous solid (6.2 mg, 85 %). R<sub>f</sub> 0.20 (2:1 hexane-ethyl acetate); [α]<sub>D</sub><sup>20</sup> -44 (*c* 0.01, CH<sub>3</sub>OH), lit.<sup>4</sup> [α]<sub>D</sub><sup>20</sup> -60 (*c* 0.5, CH<sub>3</sub>OH); IR (neat): 3446w br, 2940w br, 1645m (C=O)ketone, 1615m, 1509m, 1466m, 1378m, 1226, 1200m, 1160m, 1102m, 1019m, 916m, 817m; <sup>1</sup>H NMR (500.1 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  11.82 (1H, s, C(11)OH), 6.71 (1H, s, C(1)H), 6.49 (1H, s, C(4)<u>H</u>), 6.04 (1H, s, C(10)<u>H</u>), 5.20 (1H, app t, J 8.5 Hz, C(5')<u>H</u>), 5.05 (1H, s, C(7')<u>H</u>H'), 4.93 (1H, s, C(7')<u>HH'</u>), 4.58 (1H, dd, J 12.0, 2.5 Hz, C(6)HH'), 4.55 (1H, dd, J 2.5, 1.0 Hz, C(6a)H), 4.47 (1H, dd, J 12.0, 1.0 Hz, C(6)HH'), 3.83 (3H, s, C(3')H<sub>3</sub>), 3.76 (3H, s, C(2')H<sub>3</sub>), 3.20 (1H, dd, / 15.5, 9.5 Hz, C(4')HH'), 2.84 (1H, dd, / 15.5, 7.5 Hz, C(4')HH'), 1.74 (3H, s, C(8')H<sub>3</sub>). The tertiary OH signal was not observed; <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>):  $\delta_{C}$  194.3 (<u>C</u>(12)), 170.3 (<u>C</u>(9)), 165.8 (<u>C</u>(11)), 156.1 (<u>C</u>(7a)), 151.4 (<u>C</u>(3)), 148.4 (<u>C</u>(4a)), 144.2 (<u>C</u>(2)), 142.9 (<u>C</u>(6')), 113.0 (<u>C</u>(7')), 109.4 (<u>C</u>(1)H), 108.8 (<u>C</u>(1a)), 104.9 (<u>C</u>(8)), 101.3 (<u>C</u>(4)H), 100.1 (C(11a)), 92.3 (C(10)H), 88.5 (C(5')H), 75.6 (C(6a)H), 67.0 (C(12a)), 63.8 (C(6)H<sub>2</sub>), 56.5 (C(2')H<sub>3</sub>), 56.1 ( $\underline{C}(3')H_3$ ), 30.6 ( $\underline{C}(4')H_2$ ), 17.2 ( $\underline{C}(8')H_3$ ); LRMS: m/z found 409.1,  $C_{23}H_{21}O_7$  [M-H<sub>2</sub>O+H]<sup>+</sup> requires 409.1; HRMS: m/z found 426.1309, C<sub>25</sub>H<sub>22</sub>O<sub>8</sub> [M] requires 426.1315. The observed NMR data were in good agreement with those reported previously.<sup>3</sup>

#### 3. X-ray crystallography

Crystals were transferred to a drop of inert perfluoropolyether oil and stuck on a MiTeGen mount using the same oil. The analysis was carried out under an Oxford Cryosystems open-flow N<sub>2</sub> cryostat operating at 180(2) K. Data were collected on a Nonius KappaCCD diffractometer, equipped with a Mo sealed-tube source ( $\lambda = 0.7107$  Å) using the COLLECT software.<sup>5</sup> Data were processed using HKL DENZO and SCALEPACK<sup>6</sup> and a multi-scan correction was applied using SORTAV.<sup>7</sup> The structure was solved using SHELXT<sup>8</sup> and refined using SHELXL.<sup>9</sup>

The majority of non-H atoms were refined routinely with anisotropic ADPs. Atoms C2' and C3' (methoxy groups) show moderately elongated ellipsoids, which were not restrained. Both O—C bonds were restrained to 1.44(1) Å to ensure a reasonable geometry. Atoms C7' and C8' also show distorted ellipsoids, possibly indicative of disorder in this region. Allowing these atoms to refine freely gave one C—C bond significantly shorter than the other, so C7' (CH<sub>2</sub>) and C8' (CH<sub>3</sub>) were assigned on this basis. The C6'—C7' and C6'—C8' bonds were then restrained to 1.35(1) and 1.50(1) Å, respectively, and ISOR restraints were applied to both C7' and C8'. A disordered model in this region did not give any significant benefit for the refinement and also introduced some unreasonable contacts between H atoms in neighbouring molecules. Hence, the ordered model was retained. The THF solvent molecule is quite clear, although relatively large displacement ellipsoids suggest the possibility of partial site occupancy (not modelled). ISOR restraints were applied to all non-H atoms.

The absolute structure is assigned confidently on the basis of the Flack parameter, determined from 2280 quotients using the method of Parsons *et al.*<sup>10</sup>



**Figure S2:** Molecular structure of **8**·THF showing the atom-labelling scheme. Displacement ellipsoids are shown at 50% probability. H atoms are omitted (except on O1). The solvent THF molecule is not shown.

Details of the crystallographic refinement for	8·THF
CCDC number	1859235

Empirical formula	$C_{41}H_{37}CINO_6PPd \cdot C_4H_8O$
Formula weight	884.64
Temperature / K	180(2)
Crystal system	monoclinic
Space group	$P2_{1}2_{1}2_{1}$
a / Å	9.1935(1)
<i>b /</i> Å	14.7832(2)
<i>c /</i> Å	30.8543(5)
α/°	90
β/°	90
γ/°	90
Volume / Å <sup>3</sup>	4193.39(10)
Ζ	4
$\rho_{calc}$ / g cm <sup>-3</sup>	1.401
$\mu / \text{mm}^{-1}$	0.595
F(000)	1824
Crystal size / mm <sup>3</sup>	0.16×0.07×0.05
Radiation	MoKα ( $\lambda$ = 0.7107 Å)
2θ range / °	7.07 to 54.96
Reflections collected	22512
Independent reflections	9142
R <sub>int</sub>	0.064
Goodness-of-fit on F <sup>2</sup>	1.08
Data/restraints/parameters	9142/50/509
<i>R</i> 1 [I>2σ(I)]	0.059
wR2 [all data]	0.115
Largest diff. peak/hole / eÅ <sup>-3</sup>	0.51/-0.60
Flack parameter	-0.02(2), 2280 quotients [(I+)-(I-)]/[(I+)+(I-)]

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# 5. <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR Spectra for all Compounds

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