Supporting Information

for

First Enantiospecific Synthesis of the Antitumor Marine Sponge Metabolite (-)-15-Oxopuupehenol from (-)-Sclareol

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Synthesis of *1,2-di-O-benzyl-4-O-diethylcarbamylbenzenetriol*(**17a**)

Diethyl carbamyl chloride (6.64g, 47.48 mmol) and DMAP (100 mg) were added to a solution of **16a** (13.2g, 43.16 mmol) in dry pyridine (20 ml) and the mixture was stirred at reflux under argon atmosphere for 18 h. Then it washed into ice and extracted with ether (3 x 50 ml), the organic phase was washed with 2N HCl (3 x 30 ml) and brine (2 x 20 ml). After drying and evaporating the solvent, the crude was chromatographed on silica gel (H-E 7:3) affording 16.4g of **17a** (89%) as a colourless oil.

Physical properties:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48-7.28 (m, 10H), 6.92 (d, J= 8.7 Hz, 1H), 6.83 (d, J= 2.7 Hz, 1H), 6.67 (dd, J= 8.7, 2.7 Hz, 1H), 5.13 (s, 2H), 5.12 (s, 2H), 3.40 (m, 4H), 1,22 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.4 (C), 149.5 (C), 146.1 (C), 145.8 (C), 137.3 (C), 136.9 (C), 128.5 (4 x CH), 128.2 (2 x CH), 127.4 (4 x CH), 115.8 (CH), 113.9 (CH), 109.1 (CH), 72.0 (CH_2), 71.2 (CH_2), 42.2 (CH_2), 41.8 (CH_2), 14.2 (CH_3), 13.4 (CH_3).

IR (film): 1714, 1601, 1506, 1415, 1263, 1214, 1163, 978 cm^{-1}.

MS-EI *m/z* (relative intensity) : 387 (15), 314 (38), 306 (11), 288(5), 227(4), 215 (18), 181 (28), 139 (42), 91 (100).

HRMS (FAB) *m/z*: calcd for $C_{25}H_{27}NO_4Na$ 428.1838, found 428.1839.

Synthesis of *4,5-di-O-benzyl-2-bromo-1-O-diethylcarbamylbenzenetriol* (**18a**)

N-Bromosuccinimide (7.39g, 40.74 mmol) and silica gel (2.0g) were added to a solution of **17a** (15g, 37.0 mmol) in CCl_4 (80 ml) and the mixture was stirred at room temperature for 1h. After filtration of precipitate, washing with small portions of ether, the solvent was evaporated, yielding a crude which was filtered through silica gel, to give 16,67g of **18a** (93%) as a colourless oil.

Physical properties:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.30 (m, 10H), 7.15 (s, 1H), 6.92 (s,1H), 5.10 (s, 2H), 5.08 (s, 2H), 3.48 (q, J= 7.1Hz, 2H) 3.41 (q, J= 7.1Hz, 2H), 1.30 (t, J= 7.1Hz, 3H), 1.23 (t, J= 7.1Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2 (C), 148.8 (C), 146.8 (C), 142.9 (C), 136.6 (C), 136.4 (C), 128.4 (4 x CH), 127.9 (2 x CH), 127.3 (4 x CH), 118.8 (CH), 110.6 (CH), 106.6 (C), 71.9 (CH_2), 71.3 (CH_2), 42.3 (CH_2), 41.9 (CH_2), 14.2 (CH_3), 13.3 (CH_3).

IR (film): 1724, 1594, 1503, 1315, 1268, 1025, 861 cm^{-1}.

MS-EI *m/z* (relative intensity): 485 (M^+,1), 404 (100), 372 (12), 330 (27), 222 (10), 191 (9), 181 (13), 139 (32), 91 (50).

HRMS (FAB) *m/z*: calcd for $C_{25}H_{26}NO_4NaBr$ 506.0943, found 506.0936.

Synthesis of *O-diethylcarbamylsesamol* (**17b**)

Diethyl carbamyl chloride (5 g, 40 mmol) and DMAP (100 mg) were added to a solution of sesamol (**16b**) (5 g, 36.23 mmol) in dry pyridine (15 ml) and the mixture was stirred at reflux under argon atmosphere for 18 h. Following the same procedure described for **16a** 7.9 g of **17b** (92%) was obtained.

Physical properties:

^{1}H NMR ($CDCl_3$, 400 MHz):δ, 6.70 (d, J= 8.3 Hz, 1H), 6.61 (d, J= 2.4 Hz, 1H), 6.51 (dd, J= 8.3, 2.4 Hz, 1H), 5.90 (s, 2H), 3.35 (m, 4H), 1,17 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5 (C), 147.9 (C), 146.0 (C), 144.9 (C), 114.2 (CH), 107.8 (CH), 104.3 (CH), 101.3 (CH_2), 42.3 (CH_2), 41.9 (CH_2), 14.3 (CH_3), 13.4 (CH_3).

IR (film): 1714, 1634, 1506, 1472, 1274, 1174, 1037, 964 cm^{-1}.

MS-EI *m/z* (relative intensity) :166 (22), 137(100), 121 (5), 109 (39), 97(15), 83(12).

HRMS (FAB) *m/z*: calcd for $C_{12}H_{15}NO_4Na$ 260.0899, found 260.0907.

Synthesis of *4,5-methylendioxy-2-bromo-1-O-diethylcarbamyloxybenzene* (**18b**)

N-Bromosuccinimide (7.39g, 40.74 mmol) and silica gel (2.0g) were added to a solution of **17b** (6g, 25.31 mmol) in CCl_4 (35 ml) and the mixture was stirred at room temperature for 1h. Following the same procedure described for **17a** 7.2 g of **18b** (90%) was obtained.

Physical properties:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.92 (s, 1H), 6.67 (s, 1H), 5.89 (s, 2H), 3.40 (q, J= 6.9 Hz, 2H), 3.31 (q, J= 7.0Hz, 2H), 1.24 (t, J= 6.9Hz, 3H), 1.15 (t, J= 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.0 (C), 147.3 (C), 145.5 (C), 142.9 (C), 111.5 (CH), 106.6 (C), 105.2 (CH), 102.0 (CH_2), 42.2 (CH_2), 41.8 (CH_2), 14.0 (CH_3), 13.1 (CH_3).

IR (film): 1729, 1613, 1503, 1315, 1269, 1036, 863 cm^{-1}.

MS-EI *m/z* (relative intensity) : 316 (M^+,2), 236 (50), 163 (3), 137 (100), 121 (3), 105 (8), 91 (2), 73 (35).

HRMS (FAB) *m/z*: calcd for $C_{12}H_{14}BrNO_4Na$ 338.0004, found 338.0011.

Synthesis of *9,11-drimen-8α- ol* (**12**)

Potassium *t*-butoxyde (2g, 17.8 mmol) and dimethylsulfoxyde (30 ml) was added to a solution of **11** (2g, 5.1 mmol) in *t*-butyl methyl ether (20 ml) and the mixture was stirred at room temperature for 1h. Then, water (15 ml) was added and the reaction mixture was stirred for 5h at this temperature. Ether (30 ml) was added and the suspension was washed with brine (8 x 20 ml). The organic phase was dried, filtered and evaporated to give 0.96 g of **12** (85%) as yellow oil. $[\alpha]_D^{25}$= -9.8 (*c*= 0.02M, $CHCl_3$).

Synthesis of *8α,11-drimanodiol* (**13**)

To a solution of **12** (0.5g, 2.25 mmol) in THF (8 ml) was added at 0ºC borane-tetrahedrofuran complex 1M solution in THF (3 ml), and the resulting colourless solution was slowly warmed to room temperature and stirred for 2h. Then, ethanol (5 ml), 3M NaOH (5 ml) and 30% H_2O_2 (4 ml) were slowly added at 0ºC and the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated and the mixture was diluted with AcOEt (20 ml), washed with water, brine, dried and evaporated to give 0.51g of **13** (94%) as a white solid. $[\alpha]_D^{25}$= +2.1 (*c*= 0.15M, $CHCl_3$).

Synthesis of *drimenol* (**14**)

To a solution of triphenylphosphine (TPP) (3.3g, mmol) in dry benzene (6 ml) was added at room temperature diethyl azodicarboxylate (DEAD) (2.3g, mmol) under argon atmosphere. After stirring for 15 min, **13** (1.5g, 6.25 mmol) in benzene (5 ml) was added and the mixture was further stirred for 1h at room temperature. The solvent was evaporated and the crude was chromatographed on silica gel (H-E, 8:2) to afford 1.28g of drimenol (**14**) (92%) as a white solid. $[\alpha]_D^{25}$= -14.8 (*c*= 0.23M, $CHCl_3$).

Synthesis of *drimenal* (**15**)

To a stirred solution of drimenol (**14**) (3g, 13.5 mmol) in dichloromethane (70 ml) was added PCC (3.5g, 16.2 mmol) and the mixture was stirred at room temperature under argon atmosphere for 1h. Then it was filtered through a short silica gel column (eluted with ether) and the solvent was evaporated under reduced pressure affording 2.11g of drimenal (**15**) (71%) as a colourless oil. This product was used inmediately in the next reaction. $[\alpha]_D^{25}$= +22.5 (*c*= 0.16M, $CHCl_3$).

Synthesis of *3,4-di-benzyloxy-6-(7'-drimen-11'-yliden)-2,4-cyclohexadienone* (**19a**)

A 1.7 M solution of tert-butyllithium in pentane (12 ml) was added at -80ºC to a solution of **18a** (7.5g, 18.5 mmol) in diethyl ether (35 ml), under argon atmosphere. After stirring for 30 min at this temperature, **15** (2g, 9.1 mmol) was added and the mixture was further stirred for 35 min at -80ºC. Water (10 ml) was added and the mixture was diluted with ether (80 ml) and the organic phase was washed with brine, dried and concentrated to give a crude which was chromatographed on silica gel column (H-E, 7:3) to give 4.1g of **19a** (87%) as a yellow oil.

Physical properties:

$[\alpha]_D^{25}$= +48.1 (c= 0.24M, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51-7.31 (m, 10H) ,7.05 (d, J=12.2 Hz, 1H), 6.17 (s, 1H), 5.84 (s, 1H), 5.57 (bs, 1H), 5.15 (d, J=12.6 Hz, 1H), 5.07 (s, 2H), 5.02 (d, J=12.6 Hz, 1H), 2.86 (d, J=12.2 Hz, 1H), 2.01 (m, 2H), 1.42 (s, 3H), 0.92 (s, 3H), 0.89 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.7 (C-1'), 18.7 (C-2'), 42.3 (C-3'), 33.2 (C-4'), 49.9 (C-5'), 23.7 (C-6'), 123.0 (C-7'), 136.4 (C-8')*, 54.5 (C-9'), 38.6 (C-10'), 148.8 (C-11'), 22.1 (C-12'), 33.4 (C-13'), 22.5 (C-14'), 15.1 (C-15'), 135.2 (C-1)*, 184,0 (C-2), 103.1C-3), 164.1 (C-4), 146.8 (C-5), 105.4 (C-6).70.3 (CH_2), 70.7 (CH_2), 128.3 (4 x CH), 128.1 (2 x CH), 127.6 (4 x CH), 131.(CH), 133.8 (CH).

* Interchangeable signals

IR (film): 3065, 2925, 1647, 1613, 1431, 1360, 894, 833 cm^{-1}.

MS-EI *m/z* (relative intensity) : 509 (M^++1, 27), 418 (10), 319 (17), 229 (14), 191 (11), 189 (8), 137 (12), 119 (16), 107 (64), 91 (100), 79 (38), 57 (42), 43 (93).

HRMS (FAB) *m/z*: calcd for $C_{35}H_{40}O_3Na$ 531.2874, found 531.2874.

Synthesis of *6-(7'-drimen-11'-yliden)-3,4-methylendioxy-2,4-cyclohexadienone* (**19b**)

A 1.7 M solution of tert-butyllithium in pentane (5.7 ml) was added at -80ºC to a solution of **18b** (2.87g, 9.08 mmol) in diethyl ether (18 ml), under argon atmosphere. After stirring for 30 min at this temperature, **15** (1g, 4.54 mmol) was added and the

mixture was further stirred for 30 min at -80ºC. Following the same procedure described for **18a** 1.28 g of **19b** (83%) was obtained as a yellow oil after chromatography on silica gel column (H-E, 6:4). $[\alpha]_D$= +44.2 (c= 0.013M, $CHCl_3$).

Synthesis of *4,5-di-benzyloxy-2-(7'-drimen-11'-yl)-4,5-phenol* (**20a**)

0.7 g of a slurry of commercial aqueous Raney-nickel (Fluka, cat. nº 83440)* was added to a solution of **19a** (0.2g, 0.39 mmol) in THF (10 ml) and the mixture was further vigorously stirred at room temperature for 30 min. The mixture was diluted with ether (20 ml) and filtered through silica gel, and the solvent was evaporated to yield 195 mg of **20a** (98%) as colourless oil.

* The Raney nickel was weighed as an aqueous slurry after removing four fifth of water.

Physical properties:

$[\alpha]_D^{25}$= -4.4 (c= 0.02M, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.25 (m, 10H), 6.74 (s, 1H), 6.38 (s, 1H), 5.35 (m, 1H), 5.07 (s, 2H), 5.05 (s, 2H), 4.45 (s, 1H), 2.49 (dd, J= 15.3, 2.8 Hz, 1H), 2.42 (dd, J= 15.3, 8.8 Hz, 1H), 2.16 (s, 1H), 1.83 (bd, J=14.4Hz, 1H), 1.39 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.6 (C-1'), 19.2 (C-2'), 42.3 (C-3'), 33.1 (C-4'), 50.3 (C-5'), 23.8 (C-6'), 122.4 (C-7'), 135.4 (C-8')*, 54.3 (C-9'), 36.9 (C-10'), 25.9 (C-11'), 22.0 (C-12')*, 33.4 (C-13'), 22.3 (C-14')*, 13.9 (C-15'), 121.6 (C-1)*, 142.5 (C-2), 103.7C-3), 147,7 (C-4)#, 147.9 (C-5)#, 107.5 (C-6) 71.4 (CH_2), 73.2 (CH_2), 128.5 (4 x CH), 127.8 (2 x CH), 127.3 (4 x CH), 137.3.(C), 137.8 (C).

*,# Interchangeable signals

IR (film): 3388, 3062, 3030, 1611, 1513, 1452, 1188, 1112, 1080, 912, 735 cm^{-1}

MS-EI *m/z* (relative intensity) : 510 (M^+,49), 420 (15), 319 (100), 229 (50), 191 (35), 139 (19), 107 (30), 91 (83).

HRMS (FAB) *m/z*: calcd for $C_{35}H_{42}O_3Na$ 533.3032, found 533.3026.

Synthesis of *2-(7'-drimen-11'-yl))-4,5-methylendioxyphenol* (**20b**)

0.6 g of a slurry of commercial aqueous Raney-nickel (Fluka, cat. nº 83440) was added to a solution of **19b** (100 mg, 0.29 mmol) in THF (6 ml) and the mixture was further vigorously stirred at room temperature for 30 min. Following the same procedure described for **19a** 95 mg of **20b** (96%) was obtained as a colourless oil. $[\alpha]_D^{25}$= +7.5 (*c*= 0.02M, $CHCl_3$).

Synthesis of 8-epi-*19,20-di-O-benzyl-puupehenol* (**21a**)

Camphorsulfonic acid (110 mg, 0.475 mmol) was added to a solution of **20a** (100 mg, 0.19 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 1h 50 min and refluxed for 6h Then it was diluted with ether (20 ml) and washed with sat. NaHCO3 (3 x 10 ml) and brine. The organic phase was dried and the solvent was evaporated to yield 95 mg of **21a** and its 8-epimer (ratio 9:1) (95%). $[\alpha]_D^{25}$= +9.8 (c= 0.013M, $CHCl_3$)

Synthesis of 8-epi-*19,20-di-O-methylen-puupehenol* (**21b**)

Camphorsulfonic acid (108 mg, 0.468 mmol) was added to a solution of **20b** (80 mg, 0.234 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 45 min and refluxed for 14h. Following the same procedure described for **20a** 71 mg of **21b** and its 8-epimer (ratio 4:1) (89%) was obtained as a yellow oil. $[\alpha]_D^{25}$= +15.3 (*c*= 0.02M, $CHCl_3$).

Synthesis of *19,20-di-O-benzyl-6-ene-puupehenol* (**22**)

$PdCl_2$ (83 mg, 0.276 mmol) and $Pd(OAc)_2$ (10 mg, 0.04 mmol) were added to a solution of **20a** (141 mg, 0.276 mmol) in methanol-water (9.9:0.1 ml). The mixture was stirred at 40ºC for 48 h and the solvent was evaporated to give a crude which was dissolved in dichloromethane (5 ml) and filtered on silica gel to afford 127 mg of **22** (91%) as a white solid.

Physical properties:

$[\alpha]_D^{25}$= -2.2 (c= 0.018M, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.24 (m, 10H), 6.63 (s, 1H), 6.39 (s, 1H), 5.86 (d, J=10.3 Hz, 1H), 5.77 (dd, J=10.3 Hz, J=2.9 Hz, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 2.82 (dd, J=17.9, Hz J=8.4 Hz 1H), 2.76 (d, J=17.9 Hz, 2H), 1.17 (s, 3H), 0.93 (s, 3H), 0.84 (s, 3H), 0.76 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.7 (C), 148.2 (C), 142.4 (C), 138.0 (C), 137.4 (C) , 131.4 (CH), 129.1 (CH), 128.5 (2 x CH), 128.4 (CH), 127.7 (2 x CH), 127.4 (2 x CH), 116.8 (CH), 113.1 (C), 103.7 (CH), 73.5 (C), 73.0 (CH_2), 71.0 (CH_2), 55.2 (CH), 48.8 (CH), 41.2 (CH_2), 37.7 (CH_2), 37.4 (C), 33.0 (C), 32.8 (CH_3), 31.0 (CH), 27.3 (CH_3), 21.7 (CH_3), 20.4 (CH_2), 18.5 (CH_2), 13.7 (CH_3). 138.0 (C), 137.4 (C).

IR (film): 1731, 1574, 1455, 1376, 1260, 1173, 1128, 1025 cm^{-1}.

MS-EI *m/z* (relative intensity) : 485 (1), 417 (1), 404 (2), 229 (1), 139 (2), 91 (100), 72 (11).

HRMS (FAB) *m/z*: cald for $C_{35}H_{40}O_3Na$ 531.2875, found 531.2874.

Synthesis of *puupehenol* (**23**)

A solution of **22** (0.5 g, 0,98 mmol) in dry MeOH (15 ml), was stirred with 10% Pd-C (100 mg) at room temperature for 48 h under hydrogen atmosphere. Filtration and concentration yielded 320 mg of **23** (99%) as a colourless oil.

Physical properties:

$[\alpha]_D^{25}$= -4.3 (c= 0.01M, $CHCl_3$)

^{1}H NMR (CD_3COCD_3, 400 MHz): δ 6.39 (s, 1H), 6.09 (s, 1H), 2.65 (dd, J=17.5, 8.0 Hz, 1H), 2.48 (d, J=17.5 Hz, 1H), 0.99 (s, 3H), 0.76 (s, 3H), 0.68 (s, 3H), 0.59 (s, 3H).

^{13}C NMR (CD_3COCD_3, 100 MHz): δ 40.6 (C-1), 18.97 (C-2), 41.3 (C-3), 33.7 (C-4), 50.3 (C-5), 19.1 (C-6), 42.6 (C-7), 75.3 (C-8), 55.8 (C-9), 39.0 (C-10), 34.0 (C-11), 22.2 (C-12), 27.3 (C-13), 14.7 (C-14), 22.6 (C-15), 113.6 (C-16), 139.4 (C-17), 104.7 (C-18), 148.4 (C-19), 144.6 (C-20), 115.2 (C-21).

IR (film): 3386, 1580, 1519, 1455, 1280, 1256, 1082 cm^{-1}

MS-EI *m/z* (relative intensity) : 331 (M^++1, 28), 315 (10), 191 (18), 177 (11), 139 (33), 57 (65), 43 (100).

HRMS (FAB) *m/z*: calcd for $C_{21}H_{30}O_3Na$ 353.2092, found 353.2093.

Synthesis of (+)- *puupehenone (**1a**)*

To a stirred solution of puupehenol (**23**) (90 mg, 0.27 mmol) in tetrahydrofuran (5 ml) was added water (0.1 ml) and Ag_2O (93 mg, 0.40 mmol) and the mixture was stirred at room temperature under argon atmosphere for 1h 30 min. Then the solvent was evaporated under reduced pressure and the residue was filtered through a florisil column (eluted with acetone) affording 83 mg of (+)- *puupehenone (***1a**) (94%) as a yellow oil. $[\alpha]_D^{25}$= +249.5(*c*= 0.02M, CCl_4) [Lit.[2b] $[\alpha]_D^{25}$= +297.0 (*c*= 0.44, CCl_4)].

Synthesis of 18-*cyanopuupehenone (**27**)*

To a stirred solution of puupehenol (**23**) (130 mg, 0.39 mmol) in tetrahydrofuran (5 ml) was added water (0.1 ml), NaCN (80 mg, 1.63 mmol) and Ag_2O (0.3 mg, 1.29 mmol) and the mixture was stirred at room temperature under argon atmosphere for 45min. Then the solvent was evaporated under reduced pressure and the residue was filtered through florisil column (eluted with ether) affording 83 mg of *18-cyano-puupehenone* (**27**) (94%) as a yellow oil.

Physical properties:

$[\alpha]_D^{25}$= +102.5 (*c*= 0.03M, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (bs, 1H), 6.54 (d, J= 7.1 Hz, 1H), 5.95 (s, 1H), 2.20 (m, 1H), 2.02 (d, J=7.1 Hz J=8.0 Hz 1H), 1.85 (m, 1H), 1.21 (s, 3H), 0.93 (s, 6H), 0.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.1 (C-1), 18.5 (C-2), 41.7 (C-3), 33.4 (C-4), 53.9 (C-5), 18.2 (C-6), 39.2 (C-7), 778.8 (C-8), 55.0 (C-9), 41.3 (C-10), 33.8 (C-11), 22.0 (C-12), 28.1 (C-13), 14.7 (C-14), 141.8 (C-15), 127.3 (C-16), 163.7 (C-17), 77.3 (C-18), 181.3 (C-19), 144.8 (C-20), 105.7 (C-21), 108.6 (C-22).

IR (film): 3331, 2165, 1600, 1368, 1194, 1162, 1017 cm^{-1}.

MS-EI *m/z* (relative intensity): 353 (M^+, 1), 328 (2), 313 (1), 202 (5), 177(16), 163 (2), 136 (5), 119 (7), 109 (11), 95(9).

HRMS (FAB) *m/z*: calcd for $C_{22}H_{27}NO_3Na$ 376.1888, found 376.1879.

Synthesis of (+)- 15-*cyano puupehenone (**7**)*

To a stirred solution of puupehenol (**23**) (110 mg, 0.33 mmol) in tetrahydrofuran (5 ml) was added water (0.1 ml) and Ag_2O (308 mg, 1.33 mmol) and the mixture was stirred at room temperature under argon atmosphere for 1h 40 min. Then it was added NaCN (44 mg, 0.9 mmol) and the mixture was further stirred at room temperature for 1h. Following the same procedure described for **27**, 100 mg of (+)-*15-cyanopuupehenone* (**7**) (86%) was obtained as a yellow oil. $[\alpha]_D^{25}$= +149.7 (*c*= 0.01M, MeOH) [Lit.[2b] $[\alpha]_D^{25}$= +168.0 (*c*= 0.08, MeOH)].

Synthesis of (+)- *puupehedione (**2a**)*

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.5g, 2.20 mmol) was added to a solution of puupehenol (**23**) (150 mg, 0.45 mmol) in 1,4-dioxane (8 ml) and the

mixture refluxed for 2h. Then the solvent was evaporated under reduced pressure and the residue was diluted with ether (20 ml) and washed with sat. NaHCO3 (3 x 10 ml) and brine. The organic phase was dried and the solvent was evaporated to yield a crude which after chromatography on silica gel (H:E 1:1) afforded 104 mg of **2a** (71%) as a red solid. $[\alpha]_D^{25}$= +180.5 (*c*= 0.01M, MeOH) [Lit.[2b] $[\alpha]_D^{25}$= +208.0 (*c*= 0.09M, MeOH)].

Synthesis of *puupehenoldiacetate* (**24**)

Acetic anhydride (3 ml) and DMAP (30 mg) were added to a solution of **23** (100 mg, 0.3 mmol) in pyridine (5 ml) and the mixture was stirred at room temperature for 4h. The reaction mixture was poured into ice (5g) and diluted with ether (30 ml). The organic layer was washed with 2N HCl, sat. $NaHCO_3$ and brine, dried and evaporated to give 120 mg of **24** (95%) as a colourless oil.

Physical properties:

$[\alpha]_D^{25}$= -36.7 (c= 0.02M, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (s, 1H), 6.54 (s, 1H), 2.87 (dd, J=18 Hz, J=7.9 Hz 2H), 2.7 (d, J=18 Hz, 1H), 2.22 (s, 6H), 1.11 (s, 3H), 0.82 (s, 3H), 0.79 (s, 3H), 0.69 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.7 (C), 168.1 (C), 152.6 (C), 140.3 (C), 134.9 (C), 122.3 (CH), 120.7 (C), 111.6 (CH), 76.0 (C), 55.3 (CH), 49.3 (CH), 41.9 (CH_2), 40.6 (CH_2), 40.0 (CH_2), 38.4 (C), 33.7 (CH_3), 33.2 (C), 27.4 (CH_3), 27.0 (CH_3), 22.4 (CH_2), 21.9 (CH_3), 20.6 (CH_3), 18.4 (CH_2), 18.2 (CH_2), 14.4 (CH_3).

IR (film): 1772, 1501, 1423, 1369, 1212, 1103, 1012, 926 cm^{-1}.

MS-EI *m/z* (relative intensity) : 415 (M^++1, 2), 372 (50), 330 (100), 191 (45), 177 (20), 139 (84), 121 (22), 107 (31), 95 (31), 84 (41), 69 (41).

HRMS (FAB) *m/z*: calcd for $C_{25}H_{34}O_5Na$ 437.2304, found 437.2302.

Synthesis of *19,20- diacetate-15-oxopuupehenol* (**25**)

To a solution of **24** (100 mg, 0.24 mmol) in benzene (5 ml) sodium chromate (340 mg, 0.74 mmol), sodium acetate (254 mg, 3.1 mmol), acetic anhydride (1 ml), and glacial acetic acid (1 ml) were added, and the mixture was stirred at 70ºC for 5h. The reaction mixture was poured into ice (2g) and extracted with ether (3x 10 ml). The combined organic phases were washed with sat. $NaHCO_3$ and brine. The ethereal phase was dried, filtered and evaporated to give 99 mg of **25** (96%) as a white solid.

Physical properties:

$[\alpha]_D^{25}$= -16.8 (c= 0.03M, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59(bs, 1H), 6.78 (s, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 2.13 (s,1H), 1.92 (s, 1H), 1.22 (s, 3H), 0.15 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.1 (C), 168.3 (C), 167.3 (C), 158.3 (C), 147.9 (C), 136.1 (C), 123.9 (C), 120.3 (CH), 112.9 (CH), 81.2 (C), 64.5 (CH), 54.3 (CH), 41.7 (CH_2), 40.0 (CH_2), 39.9 (CH_2), 38.6 (C), 33.5 (C), 27.0 (CH_3), 26.7 (CH_3), 22.0 (CH_3), 20.8 (CH_3), 20.5 (CH_3), 18.4 (CH_2), 18.1 (CH_2), 15.4 (CH_3).

IR (film): 3358, 1770, 1670, 1612, 1509, 1457, 1369, 1262, 1202, 1018 cm^{-1}

MS-EI *m/z* (relative intensity): 428 (M^+, 1), 404 (51), 386 (18), 344 (19), 330 (22), 277(15), 235 (17), 193 (58), 153 (32), 139 (28), 136 (4), 72 (100).

HRMS (FAB) *m/z*: calcd for $C_{25}H_{32}O_6Na$ 451.2097, found 451.2106.

Synthesis of *15-oxopuupehenol* (**4a**)

To a solution of **25** (150 mg, 0.35 mmol) in DMF (9 ml), a solution of sat. $NaHCO_3$ (2 ml) was added and the mixture was stirred at 60ºC for 8h. sat. NH_4Cl (3 ml) was added, and the mixture was extracted with ether (2 x15 ml) the combined organic phases were washed with water, brine, dried, filtered and evaporated to afford a crude, which after being chromatographed on florisil column (ether) gave 81 mg of 15-oxo-puupehenol (**4a**) (67%) as a white solid and 15 mg of *20- acetyloxy-15-oxopuupehenol*

(**26**) (11%) as a white solid. **4a** $[\alpha]_D^{25}$= -94.3 (*c*= 0.01M, MeOH) [Lit.[4] $[\alpha]_D^{25}$= -106.0 (*c*= 0.52, MeOH)].

Physical properties of **26**:

$[\alpha]_D^{25}$= -21.1 (c= 0.04M, MeOH)

^{1}H NMR (CD_3COCD_3, 400 MHz): δ 9.45 (bs, 1H), 7.40 (s, 1H), 6.44 (s, 1H), 2.22 (s, 3H), 1.92 (s, 1H)), 1.20 (s, 3H), 0.90 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.8 (C-1), 19.0 (C-2), 42.3 (C-3), 33.9 (C-4), 54.5 (C-5), 18.2 (C-6), 40.3 (C-7), 81.3 (C-8), 64.6 (C-9), 38.9 (C-10), 34.0 (C-11), 22.3 (C-12), 26.7 (C-13), 15.6 (C-14), 192.3 (C-15), 115.8 (C-16), 156.6 (C-17), 105.3 (C-18), 160.0 (C-19), 132.0 (C-20), 120.6 (C-21), 169.4 (C-O<u>CO</u>CH_3), 20.6 (C-OCO<u>CH_3</u>)

IR (film): 3313, 2947, 1740, 1664, 1592, 1464, 1389, 1294, 1165 cm^{-1}.

MS-EI *m/z* (relative intensity): 386 (M^+, 13), 344 (44), 330 (12), 277(8), 235 (21), 193 (100), 153 (26), 139 (19), 136 (15),

HRMS (FAB) *m/z*: calcd for $C_{33}H_{30}O_5Na$ 409.1991, found 409.1995.