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Synthesis of Monoterpenic Analogues of Puupehenone and Puupehedione

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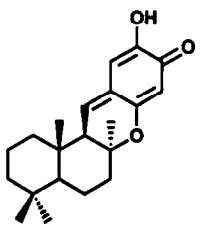
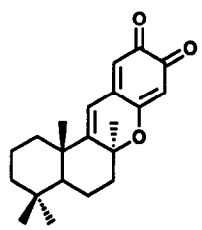
Abstract: Compounds **7-8**, monoterpenic analogues of the marine metabolites puupehenone (**1**) and puupehedione (**2**), were prepared from the easily available β-cyclocitral (**10**) and the aryllithium derived from **11** and **12**. **8** showed antitumoral activity 4 -10 times higher than that for the natural products.

The first enantiospecific synthesis of (+)-puupehenone (**1**), a marine metabolite which shows cytotoxic, antiviral and cholesteryl ester transfer protein (CETP) inhibitory properties,[1-4] was recently reported by the present authors.[5] Due to the interest of this and other related compounds, such as puupehedione (**2**), puupehediol (**3**), cyanopuupehenol (**4**) and 15-oxopuupehenol (**5**),[3] the preparation of the methylene derivative **6** has been recently described.[6]



1



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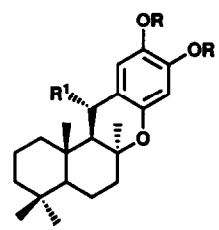
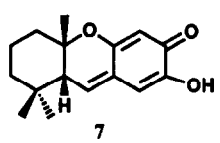


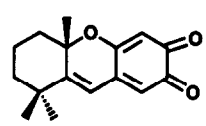
3 R, R¹: H **5** R: H, R¹: =O

4 R: H, R¹: CN **6** R, R: $-CH_2-$, R¹: =O

In order to study the structure-biological activity relationship for this class of compounds, the monoterpenic analogues **7-9** were prepared and the cytotoxic activities of **8** and **9** compared with those for diterpene compounds.



7



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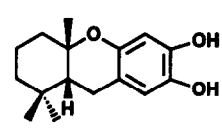

9

The synthetic strategy is based on the condensation of β-cyclocitral (**10**), as monoterpenic synthon, with the aryllithium derived from **11**[6,7] or **12**,[5] subsequent reduction when **12** was used, and the further acid-mediated cyclization. The final compound was obtained by using a suitable oxidizing agent.

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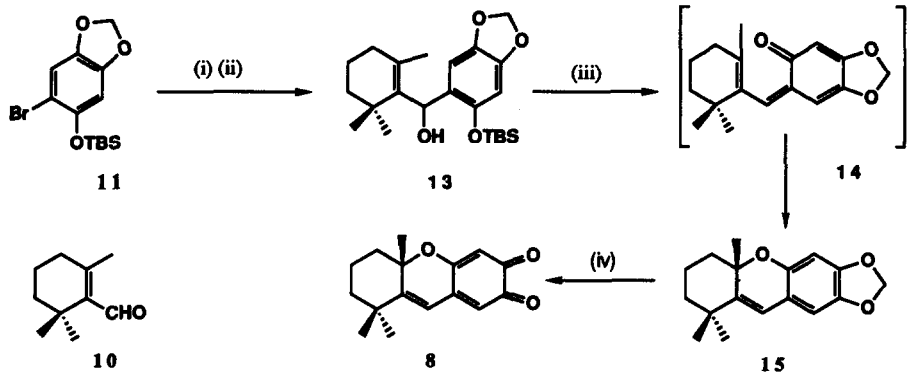
The condensation of β-cyclocitral (**10**) with the aryllithium derived from **11** yielded the allylic alcohol **13** (Scheme 1), which was converted into **15** through the relatively unstable **14** when it was refluxed with p-toluenesulphonic acid in benzene. The cyclization follows easily via an electrocyclic reaction. **15** was transformed into the puupehedione analogue **8**[9] in one step by a new procedure based on the oxidative opening of the methylenedioxy group by refluxing with a mixture of p-toluenesulphonic acid and DDQ in dioxane.[8]

Scheme 1



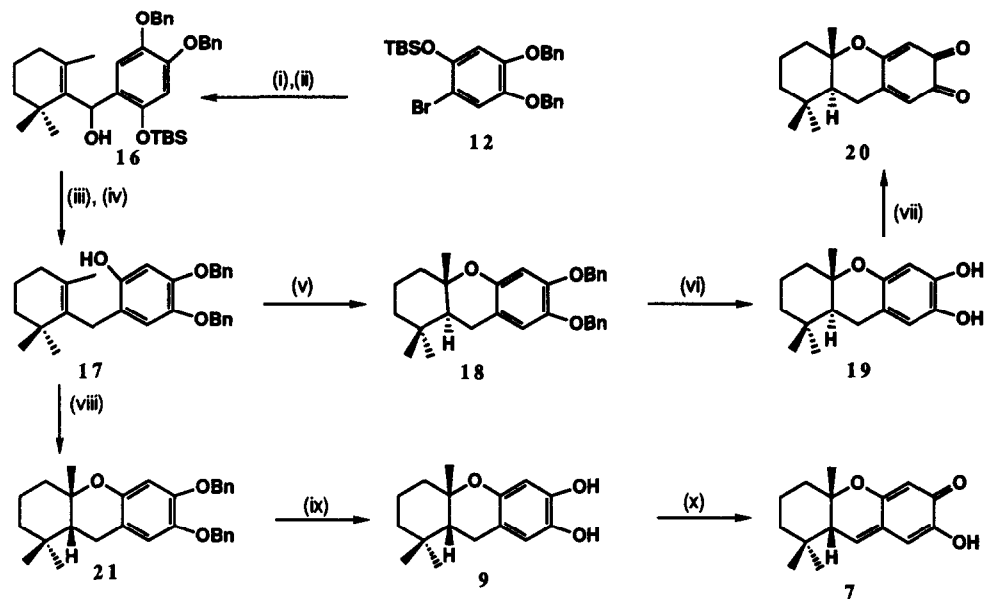
11 **13** **10** **8** **15**

(i) t-BuLi, Et_2O, -78°C, 45 min. (ii) **10**, Et_2O, 70 min. (iii) TsOH, Benzene, reflux, 30 min, 89% from **10**. (iv) DDQ, TsOH, Dioxane, reflux, 2h, 79%.

Addition of the anion derived from **12** to the aldehyde **10** yielded the product **16** (Scheme 2), which after cationic reduction of the benzylic alcohol and deprotection of the silylether gave **17**,[9] which was cyclized to **18** by treatment with $BF_3.OEt_2$ and then debenzylated to yield **19**.[9] Treatment of **19** with different oxidants produced the ortho-quinone **20** in high yields. This compound is attributed the *trans*-fused junction based on the coupling constants in the ^1H NMR.[9] Isomerization of this compound to the corresponding analogues of puupehenone was unsuccesful, under basic and acid conditions; in all cases the starting material was degraded or it remained unaltered.

The *cis*-fused compound **21** was obtained when **17** was cyclized by refluxing with p-toluenesulphonic acid in benzene. These results revealed that the *cis* -fused ring is formed under thermodynamic conditions and the *trans*-fused junction is obtained under kinetic control. **21** was transformed into the puupehediol analogues **9**[9] after debenzylation. The stereochemistry of **9** was established by comparison of its ^1H NMR data with those of **19**. Finally, **9** was oxidized to the puupehenone analogue **7**[9] by treating with PDC.[5] The isomerization to the enol form observed in this case may be attributed to the conformational flexibility of **9**, due to the *cis*-fused junction. The higher rigidity of **19**, due to its *trans*-fused ring structure, makes this process difficult and the ketone form is preferred.

Scheme 2



(i) t-BuLi, Et_2O, -78° C, 45 min. (ii) **10**, Et_2O, 1h. (iii) Et_3SiH, TFA, CH_2Cl_2, -78° C, 1h. (iv) TBAF, THF, rt, 10 min, 77% from **10**. (v) $BF_3.OEt_2$, CH_2Cl_2, rt, 30 min, 93%. (vi) $BF_3.OEt_2$, EtSH, rt, 1 h, 89%. (vii) CAN, CH_3CN, rt, 35 min, 80%. (viii) TsOH, Benzene, reflux, 45 min. (ix) $BF_3.OEt_2$, EtSH, rt, 1 h, 53% from **17**. (x) PDC, CH_2Cl_2, rt, 3 h, 60%.

The antitumoral activity of (±)-**8** and (±)-**9** was assayed against cells P-388, A-549, HT-29 and MEL-28 and compared with those from the diterpene series **2** and **3**.[2] As may be seen, (±)-**8** shows higher activity than **2**, whereas **9** shows a similar one.

Antitumoral Activity (IC_{50} μg/ml)

	P-388	A-549	HT-29	MEL-28
8	0.25	0.25	0.25	0.25
9	1	2.5	2.5	2.5
2	1	1-2	1-2	1-2
3	1	2.5	2.5	2.5

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References and notes:

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7. **11** was also prepared from sesamol by the same procedure for the synthesis of **12**.[5]
8. Illustrative experimental procedure for the oxidative rupture:

   To a stirred solution of 180 mg (o.66 mmol) of **15** in 10 ml of dry 1,4-dioxane was added 115 mg (0.66 mmol) of TsOH and 300 mg (1.32 mmol) of DDQ and the mixture was heated under reflux for 2h . After removal of the 1,4-dioxane in vacuo, the remaining solid was chromatographed on a silica gel column (Hexane-Diethyl Ether 1:1) to afford 134 mg (79%) of **8**.
9. Representative physical data are given below:

   7 : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.74 (d, J= 6.7 Hz, 1H), 6.21 (s, 1H), 5.86 (s, 1H), 2.30 (d, J= 6.7 Hz, 1H), 1.21 (s, 3H), 1.02 (s, 3H), 0.75 (s, 3H).

   8 : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.39 (s, 1H), 6.14 (s, 1H), 5.96 (s, 1H), 1.96 (d, J= 8.9 Hz, 2H), 1.59 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.8 (CH_2), 28.7 (CH_3), 29.8 (CH_3), 30.4 (CH_3) , 37.7 (C), 38.9 (CH_2), 82.9 (C), 108.2 (CH), 116.3 (CH), 121.9 (CH), 137.5 (C), 163.5 (C), 164.4 (C), 179.5 (C), 181.1 (C).

   9 : ^{1}H NMR (CD_3COCD_3, 400 MHz) δ 6.50 (s, 1H), 6.19 (s, 1H), 2.87 (dd, J= 17.3 and 7.4 Hz, 1H), 2.45 (d, J= 17.3 Hz, 1H), 1.13 (s, 3H), 0.92 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (CD_3COCD_3, 100 MHz) : δ 18.7 (CH_2), 21.8 (CH_3), 23.6 (CH_3), 27.0 (CH_3) , 32.5 (CH), 34.5 (C), 40.1 (CH_2), 42.2 (CH_2), 45.0 (CH), 75.1 (C), 104.5 (CH), 112.9 (CH), 115.5 (C), 139.4 (C), 144.6 (C), 148.1 (C).

   17 : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.20 (m, 20H), 6.65 (s, 1H), 6.44 (s, 1H), 5.08 (s, 2H), 5.07 (s, 2H), 5.01 (s, 1H), 3.23 (d, J= 17.9 Hz, 1H), 3.19 (d, J= 17.9 Hz, 1H), 1.96 (t, J= 6.2 Hz, 2H), 1.40 (s, 3H), 0.84 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 19.4 (CH_2), 20.4 (CH_3), 27.9 (CH_2), 28.4 ($2CH_3$) , 32.7 (CH), 35.0 (C), 39.8 (CH_2), 71.5 (CH_2), 72.6 (CH_2), 103.5 (CH), 117.9 (CH), 118.6 (C), 127.3 - 128.5 (10CH), 131.1 (C), 134.0 (C), 137.4 (C), 138.0 (C), 143.0 (C), 147.9 (C), 148.4 (C).

   19 : ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (bs, 1H), 7.18 (bs, 1H), 6.50 (s, 1H), 6.18 (s, 1H), 2.53 (dd, J= 16.0 and 5.4 Hz, 1H), 2.45 (dd, J= 16.0 and 12.9 Hz, 1H), 1.83 (da, J= 11.1 Hz, 1H), 1.14 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H).

   20 : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (bd, J= 2.7 Hz, 1H), 5.76 (s, 1H), 2.70 (dd, J= 18.8 and 5.0Hz, 1H), 2.60 (ddd, J= 18.8, 13.6 and 2.7 Hz, 1H), 1.98 (bd, J = 12.2 Hz, 1H), 1.76 (dd, J= 13.6 and 5.0 Hz, 1H), 1.34 (s, 3H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.6 (CH_2), 20.3 (CH_3), 21.2 (CH_3), 24.5 (CH_2), 31.4 (CH_3), 33.7 (C), 39.5 (CH_2), 40.7 (CH_2), 47.9 (CH), 82.2 (C), 108.1 (CH), 128.3 (CH), 145.3 (C), 165.4 (C), 178.9 (C), 180.5 (C).