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. © 1998 Elsevier Science Ltd. All rights reserved.

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

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.

The synthetic strategy is based on the condensation of β-cyclocitral (10), as monoterpenic synthon, with the aryllithium derived from 116,7 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.
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-toluene-sulphonic acid in benzene. The cyclization follows easily via an electrocyclic reaction. 15 was transformed into the puupehedione analogue 89 in one step by a new procedure based on the oxidative opening of the methylenedioxy group by refluxing with a mixture of p-toluene-sulphonic acid and DDQ in dioxane.

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 silyl ether gave 17, which was cyclized to 18 by treatment with BF₃·OEt₂ and then debenzylation to yield 19. 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. Isomerization of this compound to the corresponding analogues of puupehenone was unsuccessful, 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-toluene-sulphonic 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 99 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 79 by treating with PDC. 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.
The antitumoral activity of (f)-8 and (i)-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, (f)-8 shows higher activity than 2, whereas 9 shows a similar one.

Antitumoral Activity (IC_{50} \mu g/ml)

<table>
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<th></th>
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<th>A-549</th>
<th>HT-29</th>
<th>MEL-28</th>
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<td>0.25</td>
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References and notes:
11 was also prepared from sesamol by the same procedure for the synthesis of 12.5

Illustrative experimental procedure for the oxidative rupture:
To a stirred solution of 180 mg (0.66 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 2 h. 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.

Representative physical data are given below:

7: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 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) $\delta$ 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): $\delta$ 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$_3$COCD$_3$, 400 MHz) $\delta$ 6.50 (s, 1H), 6.19 (s, 1H), 2.87 (dd, $J$ = 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$_3$COCD$_3$, 100 MHz): $\delta$ 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) $\delta$ 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): $\delta$ 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) $\delta$ 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) $\delta$ 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): $\delta$ 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), 156.4 (C), 178.9 (C), 180.5 (C).