Synthesis and Antitumoral Activities of Marine ent-Chromazonarol and Related Compounds


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Abstract: Efficient syntheses of ent-isozonarol (6a), ent-isozonarone (7a) and ent-chromazonarol (8) from (-)-sclareol (12) are described. 6a and 7a show a significant antitumoral activity. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction:
Over the last few years the isolation of many marine metabolites showing a wide variety of biological activities has been reported. Among these, compounds of mixed biosynthesis which are constructed of sesquiterpene and poliphenolic moieties, such as puupehenone (1), wiedendiol-A (2), wiedendiol-B (3), avarol (4) and avarone (5), have attracted great interest because some of them inhibit reproduction of the HIV virus and cholesteryl ester transfer protein (CETP) or show immunomodulatory properties. Enantiospecific syntheses of 1-3 have recently been reported by the present authors.

In order to study the structure-biological activity relationship for this class of compounds more simple monoterpenic analogues were prepared. Some of these compounds showed antitumoral activity higher than natural products. Following this research, 6a, 7a and 8, enantiomers of natural antifungal isozonarol, antifeedant isozonarone and chromazonarol have been prepared. ent-Chromazonarol (8) has been isolated from sponge Disidea pallescens. The antitumoral activity of 6a, 7a and 8 were assayed against four cells and provided significant values.

Synthetic Chemistry:
The first step of the synthetic sequence involves the nucleophilic addition of the aryllithium derived from 11 to the drimanic acetoxyaldehyde 13, whose efficient synthesis from (-)-sclareol (12) has been previously

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reported by the present authors. The aromatic synthon 11 was prepared in high yield from hydroquinone (9) (Scheme 1).

\[ \text{HO} \quad \text{Br} \quad \text{HO} \quad \text{OTBS} \]

\[ \overset{\text{(i) } \text{Br}_2, \text{t-BuOMe, } -13^\circ \text{C, } 2 \text{ h (80%)}. \text{(ii) } \text{TBSCI, DMF, imidazole, rt, } 15 \text{ h (95%)}}{10} \rightarrow \text{Br} \quad \overset{\text{OTBS}}{11} \]

Condensation of 13 with the aryllithium derived from 11 afforded 14, which after dehydration with thionyl chloride and pyridine yielded a mixture of regioisomers 15a-b (ratio 1:2). Treatment with tetrabutyl ammonium fluoride and further reduction with sodium borohydride gave ent-isozonarol (6a), via en-dienones 16a-b, as the only product. Even if 16a-b have not been isolated, similar compounds have been previously obtained. The exo-endo isomerization may be attributed to the acidic conditions of the deprotection with tetrabutylammonium fluoride. Significant amounts of exo isomer beside ent-isozonarol were obtained when deprotection was carried out in the presence of base. 6a-b was reached in a 5:1 ratio when pyridine was used.
whereas a 2:1 proportion was obtained with triethylamine. The low yield achieved during the deprotection-reduction steps may be due to the instability of the orthoquinomethylene groups of 16a-b (Scheme 2).

![Scheme 2](image-url)

An alternative route which avoids the intermediates 16a-b is depicted in Scheme 3. Phenols 17a-b were obtained when the saponification of the acetate group of 15a-b was attempted by treating with potassium hydroxyde in methanol. The selective deprotection of the silyl ether group ortho to the terpenic moiety was favoured by the formation of the intramolecular hydrogen bond. Further reduction with sodium borohydride afforded 20a as the only product, with 17b being recovered unaltered. Treatment of 20a with tetrabutylammonium fluoride gave *ent*-isoazonarol (6a) in a high yield. Oxidation of 6a with Jones reagent yielded *ent*-isoazonarone (7a). 6a and 7a showed identical spectroscopic properties and optical rotations opposite to those reported for the natural compounds. 15

Treatment of the mixture of regioisomers 6a-b with boron trifluoride-etherate yielded *ent*-chromazonarol (8) with complete diastereoselectivity. 8 showed identical physical properties to those reported for the natural compound. 17
Biological activity:

Antitumoral activities of 6a, 7a and 8 were assayed against cells P-388, A-549, HT-29 and MEL-28. Two of these compounds showed significant activity. ent-Isozonarone (7a) exhibited selectivity against the cell P-388 whereas ent-Isozonarol (6a) showed high activity against all four cells.

### Antitumoral Activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>P-388 (µM)</th>
<th>A-549</th>
<th>HT-29</th>
<th>MEL-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>0.16</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>7a</td>
<td>0.80</td>
<td>3.20</td>
<td>3.20</td>
<td>3.20</td>
</tr>
<tr>
<td>8</td>
<td>15.91</td>
<td>15.91</td>
<td>15.91</td>
<td>15.91</td>
</tr>
</tbody>
</table>

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References and notes: