Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2325–2328

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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

Alejandro F. Barrero,* Enrique J. Alvarez-Manzaneda, M. Mar Herrador, Rachid Chahboun and P. Galera

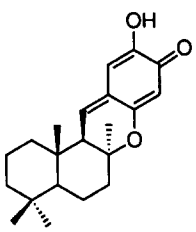
Insitituto de Biotecnologia. Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada (Spain)

Received 17 May 1999; accepted 5 July 1999

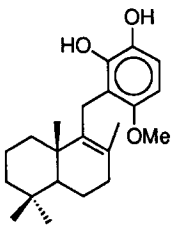
Abstract: Efficient syntheses of *ent*-isozonarol (**6a**), *ent*-isozonarone (**7a**) and *ent*-chromazonarol (**8**) from (-)-sclareol (**12**) are described. **6a** and **7a** show a significative antitumoral activity.

Introduction:

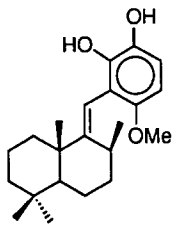
Over the last few years the isolation of many marine metabolites showing a wide variety of biological activities has been reported.[1] Among these, compounds of mixed biosynthesis which are constructed of sesquiterpene and poliphenolic moieties, such as puupehenone (**1**),[2] wiedendiol-A (**2**),[3] wiedendiol-B (**3**),[3] avarol (**4**) and avarone (**5**),[4-6] have attracted great interest because some of them inhibit reproduction of the HIV virus[7] and cholesteryl ester transfer protein (CETP)[3] or show inmunomodulatory properties. [2,8-9] Enantiospecific syntheses of **1-3** have recently been reported by the present authors.[10-12]



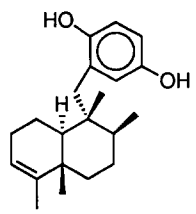
1



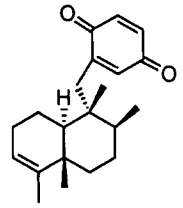
2



3



4



5

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.[13] Following this research, **6a**, **7a** and **8**, enantiomers of natural antifungal isozonarol, antifeedant isozonarone and chromazonarol have been prepared.[14-16] *ent*-Chromazonarol (**8**) has been isolated from sponge *Disidea pallescens*. [16,17] The antitumoral activity of **6a**, **7a** and **8** were assayed against four cells and provided significant values.

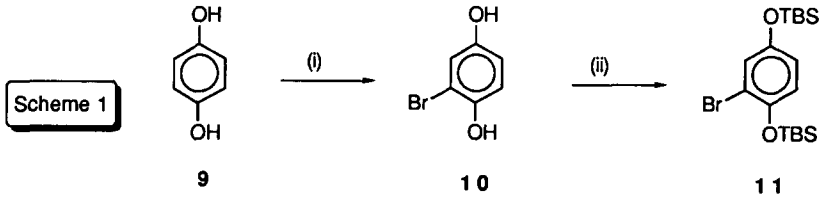
Synthetic Chemistry:

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

* E-mail: afbarre@goliat.ugr.es. FAX: 34 58 24 33 18.

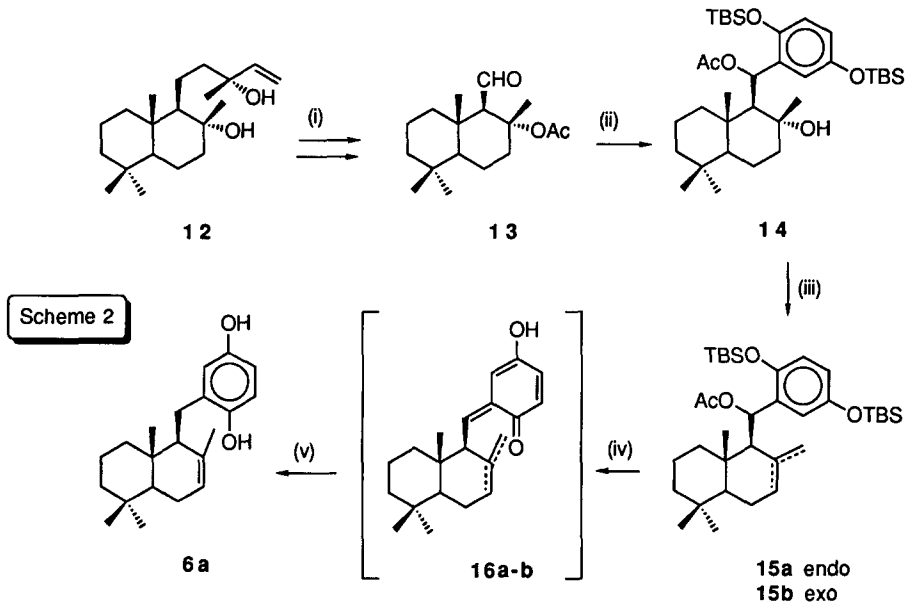
0960-894X/99/$ - see front matter
PII: S0960-894X(99)00382-0

reported by the present authors.[18] The aromatic synthon **11** was prepared in high yield from hydroquinone (**9**) (Scheme 1).



(i) Br_2, t-BuOMe, -13°C, 2 h (80 %). (ii) TBSCl, DMF, imidazole, rt, 15 h (95 %).

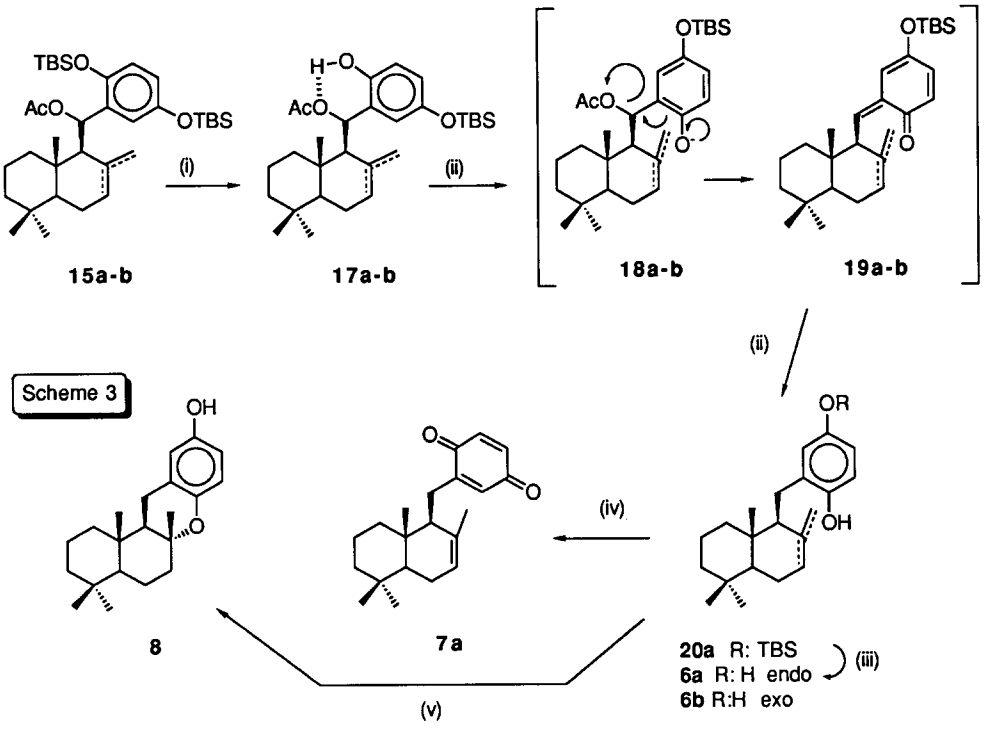
Condensation of **13** with the aryllithium derived from **11** afforded **14**, which after dehydration with thionyl chloride and pyridine yielded a mixture of regioisomers **15a-b** (ratio 1:2). Treatment with tetrabutyl ammonium fluoride and further reduction with sodium borohydride gave *ent*-isozonarol (**6a**), via en-dienones **16a-b**, as the only product. Even if **16a-b** have not been isolated, similar compounds have been previously



(i) Ref. 18. (ii) **11**, t-BuLi, OEt_2, -78 °C, 1 h 30 min (91 %). (iii) Cl_2SO, Py, -14 °C, 20 min (97 %). (iv) TBAF, EtOH, rt, 5 min. (v) $NaBH_4$, EtOH, rt, 25 min (40 %).

obtained.[10] 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).



(i) 2N KOH-MeOH, rt, 10 min (85 %). (ii) $NaBH_4$, EtOH, reflux, 15 h (47 % of **20a**; **17b** recovered). (iii) TBAF, THF, rt, 15 min (90 %). (iv) Jones, acetone, 0 °C, 5 min (93 %). (v) $BF_3.OEt_2$,CH_2Cl_2, -14 °C, 5 min (90 %).

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*-isozonarol (**6a**) in a high yield. Oxidation of **6a** with Jones reagent yielded *ent*-isozonarone (**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

IC_{50} (μM)

Compound	P-388	A-549	HT-29	MEL-28
6a	0.16	0.79	0.79	0.79
7a	0.80	3.20	3.20	3.20
8	15.91	15.91	15.91	15.91

Acknowledgments: We thank Dr. D. Gravalos, BIOMAR S.A. (C. de la Calera 3, Tres Cantos, 28760 Madrid, Spain) for the antitumoral screening.

References and notes:

1. Faulkner, D.J., *Nat. Prod. Rep.* **1998**, 113-158.
2. Navi, B.N.; Perzanowski, H.P.; Ross, R.A.; Erdman, T.R.; Scheuer, P.J., *Pure & Appl. Chem.* **1979**, *51*, 1893-1900.
3. Coval, S.J.; Conover, M.A.; Mierzwa, R.; King, A.; Puar, M.S.; Phife, D.W.; Pai, J.K.; Burrier, R.E.; Ahn, H.-S.; Boykow, G.C.; Patel, M.; Pomponi, S.A. *Bioorg. Med. Chem. Letters* **1995**, *5*, 605-610.
4. Minale, L.; Riccio, R.; Sodano, G., *Tetrahedron Lett.* **1974**, 3401-3401.
5. Locke, E.P.; Hecht, S.M., *Chem. Commun.* **1996**, 2717-2718.
6. An. J.; Wiemer, D.F., *J. Org. Chem.* **1996**, *61*, 8775-8779.
7. Sarin, P.S., Sun, D.; Thorton, A.; Muller, W.E.G., *J. Nat. Cancer Inst.* **1987**, *78*, 663-665.
8. Hamann, M.T.; Scheuer, P.J.; Kelly-Borges, M., *J. Org. Chem.* **1993**, *58*, 6565-6569.
9. Nasu, S.S.; Yeung, B.K.S.; Hamann, M.T.; Scheuer, P.J.; Kelly-Borges, M.; Goins, K., *J. Org. Chem.* **1995**, *60*, 7290-7292.
10. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R., *Tetrahedron Lett.* **1997**, *38*, 2325-2328.
11. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R., *Tetrahedron Lett.* **1997**, *38*, 8101-8104.
12. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R., *Tetrahedron* **1998**, *54*, 5635-5650.
13. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Herrador, M. Mar; Valdivia, M.V.; Chahboun, R., *Tetrahedron Lett.* **1998**, *39*, 2425-2428.
14. Kurata, K.; Taniguchi, K.; Suzuki, M, *Phytochem.* **1996**, *41*, 749-752.
15. Fenical, W.; Sims, J.J.; Squatrito, D.; Wing, R.M.; Radlick, P., *J. Org. Chem.* **1973**, *38*, 2383-2386.
16. Cimino, G.; De Stefano, S.; Fenical, W.; Minale, L.; Sims, J.J., *Experientia*, **1975**, *31*, 1250-1254.
17. Cimino, G.; De Stefano, S.; Minale, L., *Experientia*, **1975**, *31*, 1117-1118.
18. Barrero, A. F.; Alvarez-Manzaneda, E. ; Altarejos, J.; Salido, S.; Ramos, J. M.; Simmonds, M.S.J.; Blaney, W.M. . *Tetrahedron* **1995**, *51*, 7435-7450.