Synthesis, citotoxicity activity of new Cyclozonarone angular isomer

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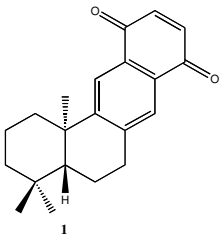
INTRODUCTION

Among the great variety of natural products, found in plants, algae and sea sponge, we can find compounds that have a quinonic/hydroquinonic moiety united to a terpenic skeleton. Natural (-)-cyclozonarone (**1**), is a drimanic benzoquinone derivative isolated from algae *Dintyopteris undulata* that posseses a powerful feeding-deterrant activity towards young abalones[1] furthermore shows anti-cancer activity.[2] The absolute configuration of **1** was establish through a six-step route, starting from natural (-) polygodial, leading us to the synthetic enantiomer (+)-cyclozonarone (**2**), that showed antileshmania activity.[3] Later, (-)-cyclozonarone was synthesized starting from (+)-albicanol.[4] Both routes of synthesis were based on the Diels-Alder reaction.



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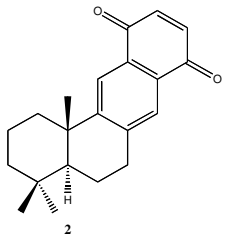

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RESULTS AND DISCUSSION

In this work, we described to the synthesis of an angular isomer of (+)-ciclozonarona. The compound **6** was synthesized using as synthetic strategy the Diels-Alder cycloaddition reaction between diene **5** and p-benzoquinone, in a sequence of six steps from confertifoline **3** (Scheme 1). Furthermore we reported herein the *in vitro* testing of **2** and **6** to include normal and tumor cell lines in order to determine the broadness of the activity. The antitumoral activities of compounds were assayed against two cells lines (DU-145 and PC-3) (Table 1).

Scheme 1. Reagents and conditions. (a) Ref 5; (b) vinylmagnesium bromide, THF; (c) $SOCl_2$; (d) p-benzoquinone, Bz, reflux.

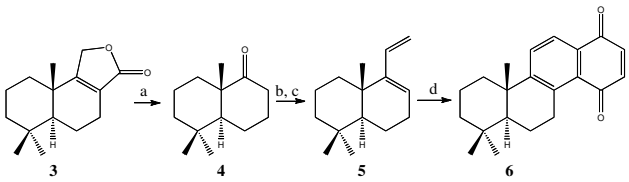

Table 1. Antitumoral activity, IC_{50} (μM)

Compound	DU-145	PC-3	DHF
2	20	25	37
6	42	45	65

CONCLUSION

In summary, we described here the synthesis of a new cyclozonarene isomer and anticancer evaluation of *ent*-cyclozonarone and its angular isomer. As compared with the tumor cell lines analyzed, we found ent-cyclozonarone had major antitumoral effect (Table 1). The comparison of the respective IC50 showed that normal cells were less sensitive to **2** and **6** compounds.

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