Expanding the structural diversity of biologically active spirocyclohexadienones from Morita-Baylis-Hillman (MBH) adducts

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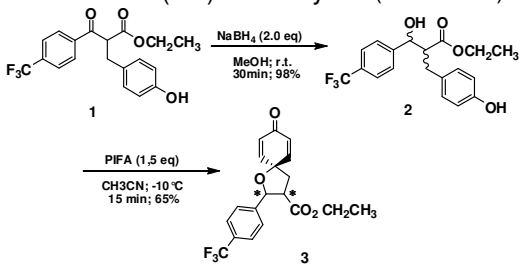
INTRODUCTION

Recently we have developed a new strategy for the synthesis of spirocyclohexadienones.[1,2]
Due to the antibacterial and antiproliferative activities showed by these compounds it was necessary to obtain a set of them with great structural diversity in order to establish a broad biological profile of these compounds. In this comunication we describe some modifications in our original sequence which allowed the preparation of new spirocyclohexadienones.

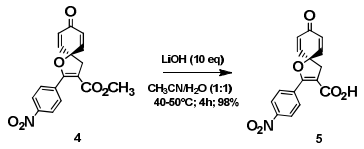
RESULTS AND DISCUSSION

Searching to establish a SAR profile, we need to prepare saturated spirocyclohexadienone, represented by compound **3**. So, Heck adduct **1** was reduced in the presence of $NaBH_4$ to give a mixture of diastereisomeric alcohols in 98% yield. The mixture was treated with PIFA at low temperature to afford **3** as a mixture of non separable diastereoisomers (1:3) in 65% yield (Scheme 1).



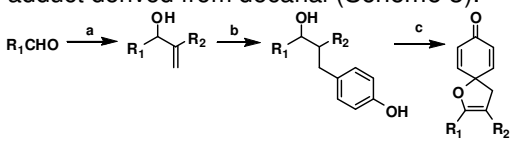
Scheme 1. Synthetic steps to obtain the spiro **3**.

The previously synthezised spirocyclohexadienones were tested against some microorganisms. These compounds have showed the biological profile of some spirocyclohexadienones was the spirocyclohexadienone a good anti-bacterial activity, however only against Gram-(+) strains. Searching to broaden the action of these spirocompounds, **5** was prepared by base hydrolysis of **4** (LiOH - 10 eq) under mild conditions, to gave acid **5** in 98% (Scheme 2).



Scheme 2. Synthesis of spiroacid derivative **5**.

Starting from MBH adducts prepared with acrylonitrile, spirocompounds as **6** were also obtained (Figure 1).
Spirocompounds having aromatic rings substituted by electrodonating have showed a remarkable anti-bacterial profile. Based on that experimental observation spiro compound **7** has been prepared (Figure 1).
Gimnastatin I[4] is a natural compounds isolated from a japonese sponge. This compound has a very good antiproliferative profile. Based on the structural similarity, we synthesized spiro compound **8**, from the MBH adduct derived from decanal (Scheme 3).



Reagentes e condições: a. alceno ativado, DABCO, r.t., 168h; b. Iodofenol (1,2 eq.), Et_3N (2,8 eq.), catalisador de Nàjera (0,5 mol%). DMF, 110°C, 3h; c. PIFA (1,5 eq.), CH3CN, -10°C, 15 min.

Compound	R_1	R_2	Yield (%)
6	acrylonitrile	3-OMePh-	35
7	Ethyl acrylate	3,4,5-triOMePh-	40
8	Methyl acrylate	$CH_3(CH_2)_8$-	16

Scheme 3 Synthetic steps to obtain the spiros **6, 7, and 8.**

CONCLUSION

A set of biologically active spirocyclohexadienones has been synthesized using a direct approach

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