A new and rapid route towards the regioselective synthesis of 2,3-disubstituted cyclopentenols was developed. The strategy is based on a selective metalation of a 2,3-dihalocyclopentenol. Columbetdione, recently isolated from the mushrooms *Tricholoma coulumbetta*, was synthesized using this novel approach.

1 Introduction

Cyclopentenones and cyclopentenols are important classes of widely distributed natural products occurring in animals, planta and even in different marine species. Among them 2,3-disubstituted cyclopentenones and cyclopentenols are well known for their broad spectrum of different biological activity [1]. Columbetdione 1 was recently isolated in our laboratory from the edible mushroom *Tricholoma coulumbetta* (Figure 1) [2].

The necessity to confirm our proposed structure for coulumbetdione lead us to develop a synthetic approach towards this compound that ultimately resulted, in a broader sense, in a new strategy for the synthesis of 2,3-disubstituted cyclopentenols.

The vast majority of the synthetic approaches towards 2,3-cyclopentenols or cyclopentenones are based on the construction of the five membered ring starting from acyclic precursors by means of traditional aldol chemistry [3] or more modern transition metal mediated transformations [4].

We foresaw a completely different approach based on the new bis-anionic synthon 3 corresponding to the 2,3-dihalocyclopentenol 2 depicted in Scheme 1. [5] We reasoned that a selective metalation of the carbon bearing iodo atom in the 2 position followed by reaction with a suitable electrophile would allow the selective introduction of a substituent. Further metalation of the bromine followed by treatment with a second electrophile would afford the desired 2,3-disubstituted cyclopentenol ring (Figure 1).

The high novelty of this work is the selective metalation of the C-I bond in the presence of the C-Br bond since similar selective metalations are known only in the field of aromatic or heteroaromatic compounds. On the other hand selective metalation of 1,2-dihalosubstituted 1,2-dicycloalkenes is known only for symmetrically substituted systems.

The rationale of the selective metalation of the C-I bond is the lower bond energy of the C-I bond on respect to the C-Br together with the electron withdrawing effect of the protected alcholic group stabilizing on a greater extent the negative charge in the 2 position.

2 Results

2,3-dihalocyclopentenol 2 was obtained in 4 steps starting from commercially available 1,3,cyclopentandiones [5].

The first experiment of selective metalation was performed adding 1.1 equivalent of Butyl-Lithium to a cold (-78°C) stirred solution of compound 2 in THF. When the reaction was quenched by the addition of a saturated solution of NH₄Cl, compound 5a was isolated in 88% yield. The structure of compound 5a was confirmed by means of spectroscopical studies showing that only the desired regioisomer 5a was obtained.
This preliminary experiment was useful to demonstrate the feasibility of our idea: therefore we extended our methodology to an array of different electrophile such as aldehydes, ketones as well as allyl and alkyl halide.

The results obtained with different aldehydes are shown in Figure 2. The yields are always good and the reactions are usually complete in 1 hour at -78°C. The reaction with a ketone (cyclopentanone, entry 5) was significantly slower and afforded the desired compound only in a modest yield.

After we established the possibility of the selective introduction of a substituent in the 2 position we investigated the metatation of the bromine in the 3-position. To this purpose treatment of compounds 5b-e with 3.3 equiv. of t-BuLi followed by addition of an electrophile afforded the desired 2,3-disubstituted compounds. The yields of the functionalizations at the 3-position are reported Figure 5. The yields are always good.

The reactions with different allyl and alkyl halides led to the desired products in modest to good yields (Figure 4). In particular the reaction with butyl iodide, entry 5, resulted to be quite difficult since it needed

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1.1 eq BuLi -78°C, THF, 12 min
1.2 eq electroph. from -78°C to -30°C, 4h

<table>
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<th>Entry</th>
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<tr>
<td>1</td>
<td>CH₃I</td>
<td>5e</td>
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"-78°C 1 hour  a 1.1 equiv. of a 0.25 M solution of Lithium 2 thiénylcyano-cuprate in THF was added before adding the electrophile b 6 eq HMPA were added before adding the electrophile
c

Fig. 3

Fig. 4

the presence of a cosolvent to afford the desired compound 5m. With some allyl halides transmetallation of the lithium species to organocopper species allowed to obtain the desired compound in better yields (Figure 4, entry 3 e 4).

3 Synthesis of columbetdione

Compound 6a, obtained from the double functionalization of compound 2, was an ideal intermediate towards the synthesis of columbetdione. Compound 6a was converted to columbetdione in two steps: the oxidation of the two secondary allylic hydroxyl groups to α, β-unsaturated ketones was followed by the deprotection of the OTBS ether on the cyclopentenol ring.
4 Conclusions

We have developed a rapid and flexible approach to 2,3-disubstituted cyclopentenols which are valuable intermediates in organic synthesis suitable for Claisen rearrangements, allylic couplings as well as simple hydrogenation of the double bond. Columbetedione was synthesized starting from an intermediate obtained using this new methodology.

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References