

# SYNTHESIS OF $\alpha$ -AMBRINOL, ONE OF MAIN ODOR COMPONENTS OF AMBERGRIS



IX SIMPOSIO  
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J. L. López-Martínez, I. Torres-García, M. Bonilla-Martínez,  
M. Muñoz-Dorado, I. Rodríguez-García, M. Álvarez-Corral

Organic Chemistry, Faculty of Experimental Sciences, ceiA3, University of Almería  
E04120 Almería (Spain); pepaloma91@hotmail.com



## INTRODUCTION

Ambergris, a bile secretion produced by the sperm whale, has been used for centuries in the perfume industry for its olfactory characteristics. Although uncontrolled hunting of sperm whale has been banned, the species is listed as vulnerable by the International Union for Conservation of Nature. Debris can be found in the sand on the coast or floating in the sea, which raises the purchase price of this substance between 50,000 and 80,000 euros per kilo.



Figure 1. Ambergris.

Therefore, the study of the chemical composition of this substance is of great interest. One of the main compounds that give it its odor is (-)- $\alpha$ -ambrinol, a degradation product of ambrein which is a major component of ambergris.<sup>1</sup>  $\alpha$ -Ambrinol can also be found in small amounts in several plant extracts, like those of *Bellardia trixago* L.,<sup>2</sup> *Cistus ladaniferus* L.,<sup>3</sup> etc.

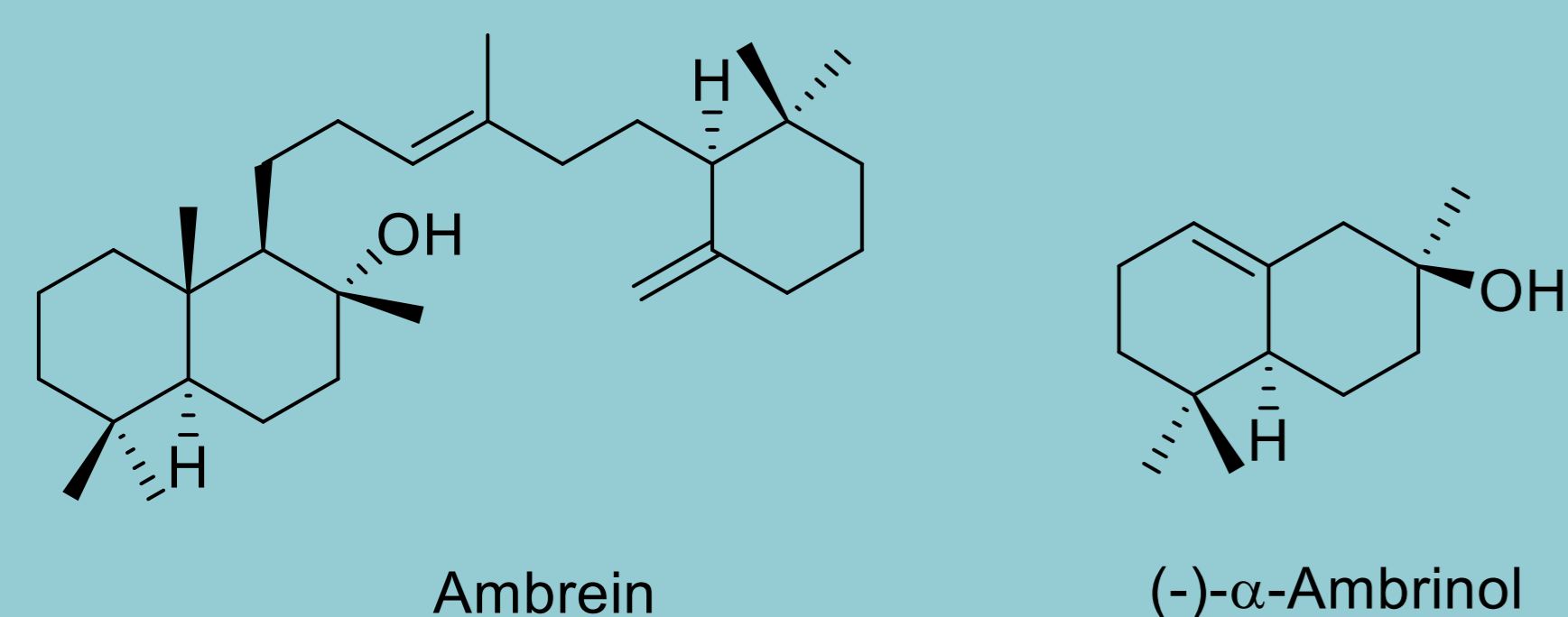
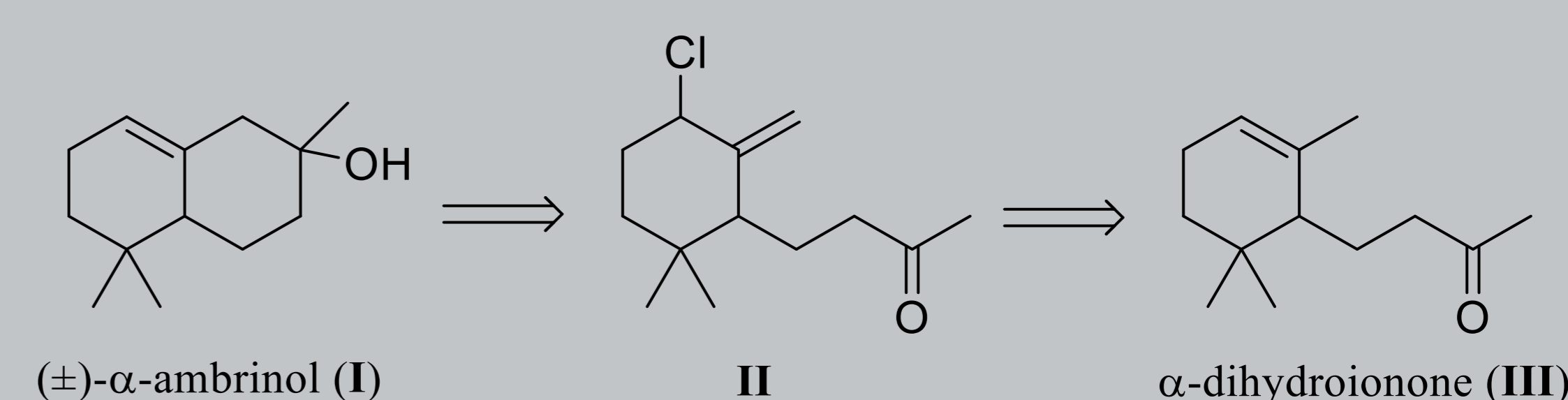


Figure 2. Structure of ambrein and (-)- $\alpha$ -ambrinol.

## PROPOSED SYNTHESIS

Although several syntheses have been described for this compound, both racemic and chiral, they are either long or start from inaccessible substances. Here we describe a new, two steps synthesis of ( $\pm$ )- $\alpha$ -ambrinol (I), using as raw material  $\alpha$ -dihydroionone (III), an inexpensive commercial compound.



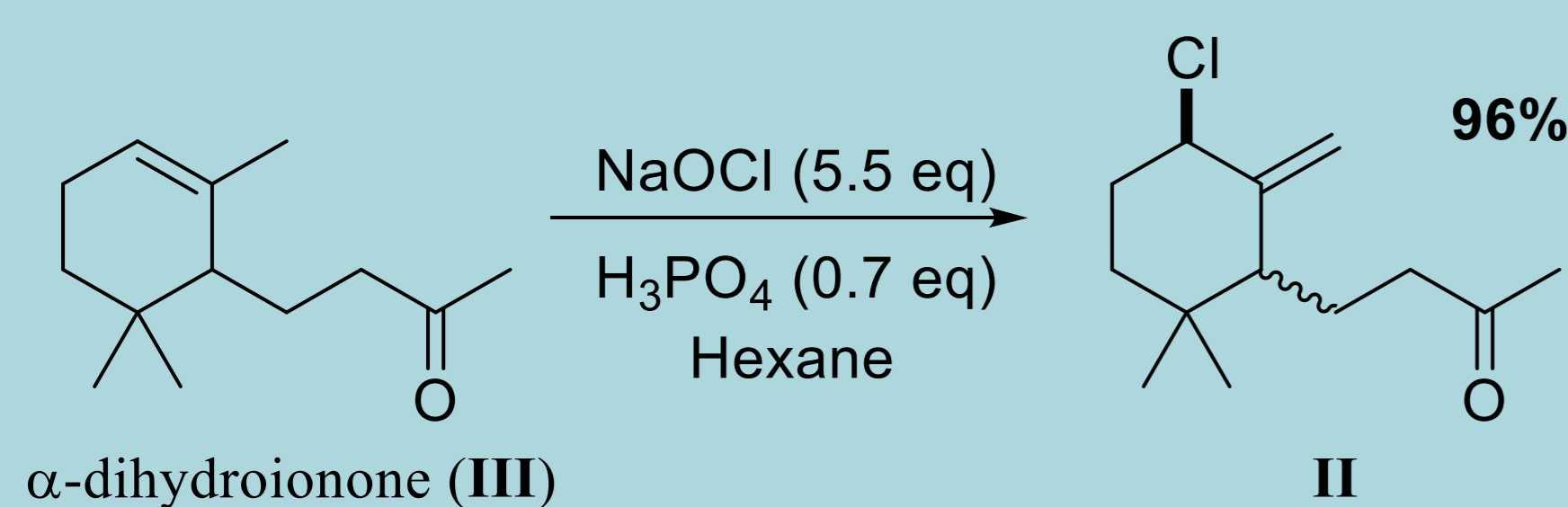
Scheme 1. Retrosynthetic scheme proposed for the preparation of  $\alpha$ -ambrinol.

The key step in the synthesis is the intramolecular cyclization between the allyl chloride and the ketone present in II, through a Barbier-type reaction induced by  $\text{CpTiCl}_2$ . This Ti(III) system can be prepared *in situ* by  $\text{CpTiCl}_3$  reduction with Mn, following our own protocol.<sup>4</sup>

## SYNTHESIS OF $\alpha$ -AMBRINOL

### 1. Synthesis of II

The first step is the preparation of the intermediate II that has an allyl chloride with an exocyclic double bond. This can be easily achieved if  $\alpha$ -dihydroionone (III) is treated with a mixture of sodium hypochlorite and phosphoric acid.<sup>5</sup> The reaction is so clean that compound II is obtained almost quantitatively and can be used in the next step without purification.



### 2. Barbier-type intramolecular cyclization

Under argon atmosphere,  $\text{CpTiCl}_3$  (0.1 eq) and Mn (2 eq) are dissolved in THF.

TMSBr (3 eq) addition

A solution of II in THF is dropwise added.

Chemical shifts identical with those described for this compound in literature.<sup>6</sup>

H13 (1,25 ppm)

H11, H12

H1 (5,48 ppm)

1 13 12 2

( $\pm$ )- $\alpha$ -ambrinol (I) 48% + IV 19%

The reaction is diastereoselective, affording  $\alpha$ -ambrinol (I) and its epimer IV in a 70:30 ratio.

## CONCLUSIONS

In conclusion, the new strategy here described allows for the preparation of the natural product ( $\pm$ )- $\alpha$ -ambrinol (I) in only 2 steps, improving significantly other longer strategies previously published.

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