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A SHORT AND CONVERGENT SYNTHESIS OF UNSATURATED MACRODILACTONES.

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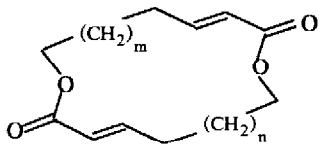
Abstract : A simple and versatile approach to macrodiolides **1**, using two consecutive Wittig reactions, is described.

Macrolide dilactone antibiotics are a very interesting class of natural products not only due to their structural features but also because of their useful biological properties [2,3]. The approach which is commonly used for the synthesis of the symmetrical derivatives involves the preparation of the monomeric linear acidalcohols followed by a, difficult, dimerization step [3,4]. For the unsymmetrical derivatives, new routes involving lactonisation procedures [3] or C-C bond formation by Wittig reactions [5] have recently been reported. The purpose of this note is to describe a new simple and versatile approach to unsaturated macrocyclic dilactones **1**, which are models for the natural products.



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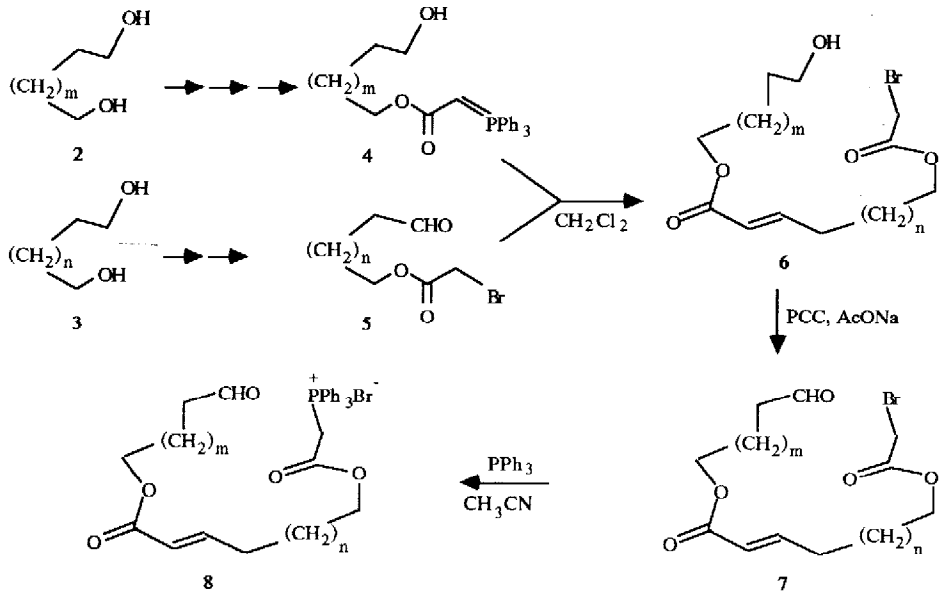
The synthesis of the key intermediates, the phosphonium salts **8**, starts from the commercially available ω-diols **2** and **3** and takes advantage of their selective functionnalization, as already described in the preceeding paper [6]. The phosphoranes **4** are easily prepared in three steps from **2** : reaction with bromoacetylbromide, and then Ph_3P in AcOEt and finally Na_2CO_3 (40-46 % overall yields). A first Wittig reaction of **4** with the aldehydes **5** (obtained in two steps from **3** [6]) in CH_2Cl_2 gives the olefins **6** as 9/1 mixtures of E and Z isomers easily separated by chromatography (68-82 % yields). The functionalized bromoesters **7** obtained after oxidation of **6** are readily transformed into the phosphonium salts **8** in 69-74 % overall yields from **6**. An intramolecular Wittig reaction, under the same high dilution conditions as before [6], completes the sequence to obtain **1** (69-78 % yields).



This short and versatile approach is very convenient for the synthesis of macrolide dilactones such as **1**. It complements the dimerization reaction described in the preceeding paper [6], giving easy access to the 14- and 16-membered derivatives. It also allows the preparation of unsymmetrical dilactones, such as the 15-membered cycle **1b**, by an appropriate choice of the starting glycols. Extension of this methodology to the synthesis of natural products is currently under study in our laboratory.

References and notes

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