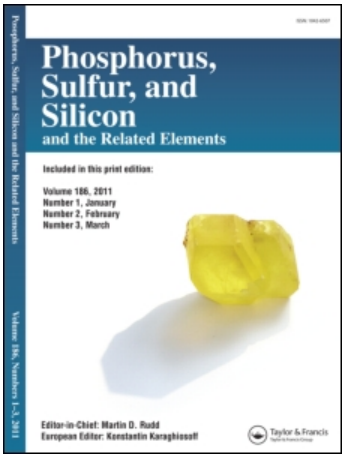

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Stereoselective Synthesis of Methoxy Substituted 2,3-Dibenzyl-γ-Butrolactones Using Organic Phosphonates as Intermediates

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STEREOSELECTIVE SYNTHESIS OF METHOXY SUBSTITUTED 2,3-DIBENZYL-γ-BUTYROLACTONES USING ORGANIC PHOSPHONATES AS INTERMEDIATES

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Abstract A stereoselective, short and convergent synthesis of methoxy substituted 2,3-dibenzyl-γ-butyrolactones was developed using organic phosphonates as key intermediates.

INTRODUCTION

There has been recently intense attention to the chemistry of butanolides lignans due to their antitumoral properties[1]. The natural ocurrence of lignans of the dibenzylbutyrolactone class,has been widely documented[2]. Several of the recently isolated alkoxy substituted dibenzylbutyrolactones lignans have been biologically tested as antitumorals[3], diuretics[4] and hormones inhibitor[5]. Many efforts have been directed towards the development of synthetic routes to these lignans[6]. Because of long synthetic sequences and low overall yields, further improvements in synthetic approaches to these natural products would be convenient.

RESULTS and DISCUSION

Our synthetic strategy for a stereoselective synthesis of a series of methoxy substituted 2,3-dibenzylbutyrolactones[7] was based on the following points: Early formation of the carbon skeleton of the target molecules using a Horner-Wadsworth-Emmons reaction (HWE)[8] as the key step for various methoxy-substituted 3-phenyl-2-diethylphosphinil ethyl propionates 2 with protected methoxy substituted 1-hydroxy-3-phenyl-

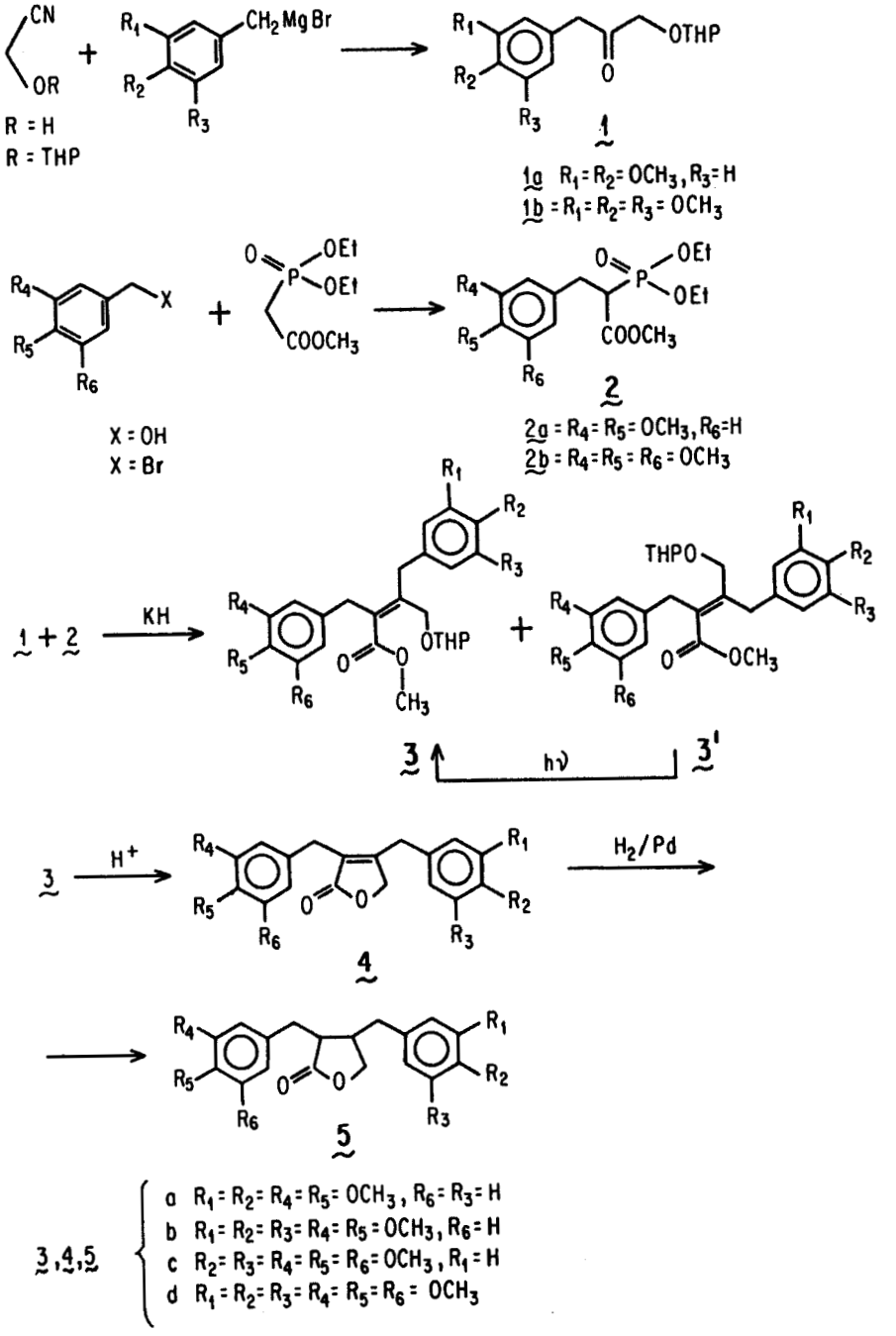
propanones 1. After the formation of the molecule's carbon skeleton, the protecting group, tetrahydrpyranyl (THP), was removed and lactonization was carried out. The resulting butenlactones 4 were hydrogenated in the last step to give the cis lignans 5. The development of the relative stereochemistry of the two chiral centers C-2 and C-3, of the targets molecules in the last stages, represents a practical improvement in methodology applied to the synthesis of lignan natural products.

From the cis lactones isomers, trans lactones may be obtained by epimerization of the C-2, according to literature methods[9].

We start our sequence with the protection of glyconitrile as tetrahydropyranyl ether, in 92% yield. Grignard reaction of the protected nitrile with a series of methoxy substituted arylmagnesium bromides in ether gave the ketones 1 in yields above 80%. Stoichiometric excess of the nitrile was necessary for this reaction to avoid the formation of the corresponding tertiary alcohols. Phosphonates 2 were prepared in yields above 90%, from dimethoxy and trimethoxy benzyl alcohols, by first converting them to the corresponding bromides with PBr_3[10], followed by alkylation with triethyl phosphonoacetate with potasium hydryde in glyme. HWE reaction between phosphonates 2 and the protected ketones 1 aforwed a 3:1 mixture of Z/E isomers of the olefins 3 in yields near 70%. The Z olefins 3 were deprotected with pyridine-p-toluensulphonate, and inmediately converted by treatment with base to the insaturated lactones 4 in approximately 90% yields. Catalytic hydrogenation of the insaturated lactones 4 with 5% Pd on Carbon gave the title compounds in near quantitative yields as a racemic mixture of the cis lactones 5.

The remaining E olefins 3', were photochemically isomerized to the corresponding Z olefins 3, by using a 100 watts Hanovia lamp in methanol for 30 min. After few recicling of the E olefin to the Z olefin all the olefins 3 were quantitatively converted to the insaturated lactones

SCHEME



4.

By a nonphenolic oxidative coupling[11], methoxy-substituted dibenzylbutyrolactones 5, may be converted to the corresponding dibenzyl octacyclodiene lactones. These last compounds are the basic moiety of powerfull antitumorals natural products such as stegans, steganacins and steganols.

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