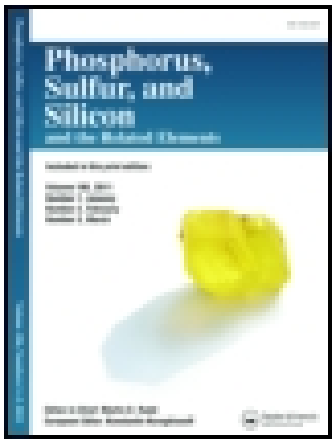

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PALLADIUM CATALYZED ADDITIONS TO ALLYLIC HYDROXY PHOSPHONATES: APPLICATIONS IN THE ENANTIOSELECTIVE SYNTHESIS OF ENTEROLACTONE AND TURMERONE

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Reaction of nonracemic allylic hydroxy phosphonates, prepared by the asymmetric phosphonylation of unsaturated aldehydes, with methyl chloroformate in pyridine yields the corresponding carbonates. The carbonates are excellent substrates for the palladium-catalyzed addition of nucleophiles. Addition of the nucleophile is highly regioselective, resulting in γ-substituted vinyl phosphonates. The reaction of the allylic carbonates with aryl stannanes and malonates has been investigated. Progress in the application of these reactions to the synthesis of turmerone and enterolactone is reported.

Keywords: Allylic carbonates; aryl stannanes; malonates; palladium; phosphonates

INTRODUCTION

The last 10 years have witnessed a rapid advance in methods for the enantioselective synthesis of hydroxy phosphonates, giving access to compounds with high enantiomeric purity.[1] It has been recognized that allylic hydroxy phosphonates are useful intermediates in the synthesis of many γ substituted phosphonates.[2,3] In particular, allylic hydroxy

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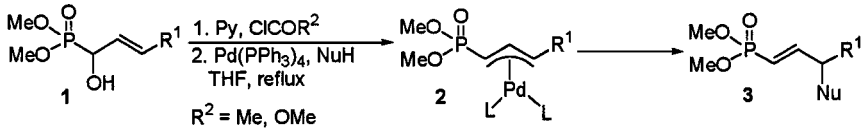
phosphonates display some of the rich chemistry associated with allylic alcohols. However, the steric and electronic influence of the phosphorus moiety may enhance the stereochemical and regiochemical outcome of the reactions. This effect is amply demonstrated in the palladium-catalyzed addition of nucleophiles to the corresponding acetate and carbonate derivatives. The acetate and carbonate derivatives of allylic hydroxy phosphonates **1** undergo palladium-catalyzed addition of various nucleophiles to give substituted vinyl phosphonates **3** in high yield (Scheme 1). The nucleophile often adds exclusively to the 3 position, with migration of the double bond into "conjugation" with phosphoryl group.[2] Our earlier success with the palladium catalyzed addition of amines to nonracemic allylic hydroxy phosphonate derivatives[3b] prompted the exploration of reactions with other nucleophiles, namely aryl stannanes and malonates.

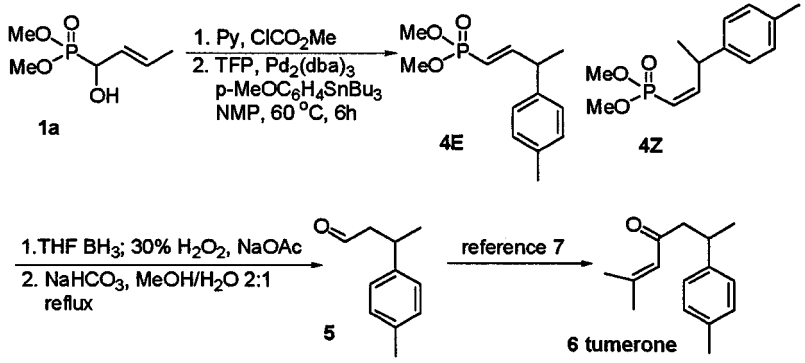


SCHEME 1

RESULTS AND DISCUSSION

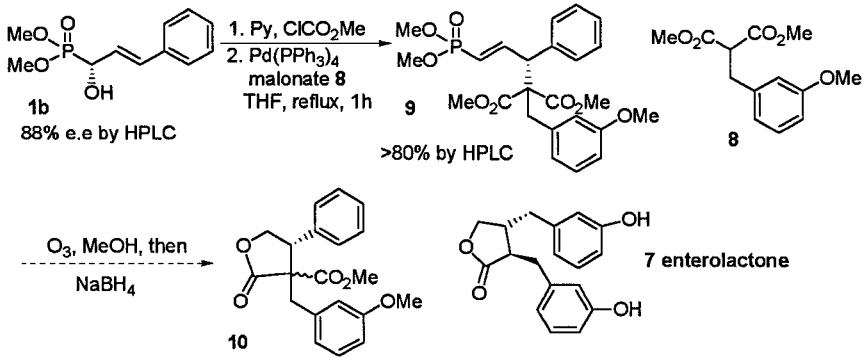
The (*R*) hydroxy phosphonate **1a** was prepared (Scheme 2) by a titanium alkoxide-catalyzed phosphonylation of crotonaldehyde in 65% e.e.[4] The alcohol was converted to the carbonate by reaction with methyl chloroformate in pyridine (80%). Reaction of the carbonate with *p*-tolyl tributylstannane in N-methyl pyrrolidinone (NMP) at 60°C in the presence of palladium (0) trifurylphosphine complex (formed in situ) gave the *E*-vinyl phosphonate **4E** (57%) and the *Z*-vinyl phosphonate **4Z** (9%). The use of trifurylphosphine was critical in this reaction.[5] Triphenylphosphine and triphenylarsine resulted in slow reactions and led to complex mixtures, predominating materials in which resulted from reduction of the allylic carbonate. The H-H and P-H coupling of the vinyl protons in the ^{1}H NMR spectra easily distinguish the *E* and *Z* isomers **4**. In particular, H-1 of the *Z*-vinyl phosphonate **4Z** exhibits a *trans* P-H coupling constant of 53 Hz, whereas the in *E*-vinyl phosphonate **4E**, H-1 shows a *cis* P-H coupling constant of 22 Hz. The mixture of *E*- and *Z*-vinyl phosphonates **4** (85:15) were subjected to hydroboration to give exclusively the α-hydroxy phosphonate as 1.5:1 mixture of diastereoisomers (80%).[6] Treatment of the hydroxy phosphonate with

sodium bicarbonate in refluxing methanol/water solution gave the (*R*) aldehyde **5** {78%, $[\alpha]_D - 15.2$ (c1, $CHCl_3$), 38% e.e.}. The stereochemical assignment was made by comparison with (S)-(+)-3-(*p*-tolyl)butanal {$[\alpha]_D + 39.6$ (c1, $CHCl_3$)} synthesized by Dulio et al.[7] The observed aldehyde stereochemistry (*R*) is consistent with the expected mechanism which involves inversion of configuration during π-allyl formation and retention during transmetallation and reductive elimination (i.e., overall retention). The erosion in the enantiomeric excess is probably due to formation of the *E*-vinyl phosphonate, which will have the opposite configuration at C3 (*S*) as the *Z*-vinyl phosphonate (*R*). Dulio also reported the conversion of the (*S*)-aldehyde **5** into *ar*-turmerone **6** by reaction with 2-methyl-2-propenyl Grignard, followed by MnO_2 oxidation of the resulting alcohol.



SCHEME 2

Hydroxy phosphonate **1b** was prepared (Scheme 3) by a titanium alkoxide-catalyzed phosphonylation[4] of cinnamaldehyde (88% e.e. after recrystallization) as a model substrate for enterolactone **7**.



SCHEME 3

The alcohol was converted to the carbonate by reaction with methyl chloroformate in pyridine (78%). Reaction of the carbonate with malonate **8** in refluxing THF in the presence of palladium (0) tetrakis-(triphenylphosphine) complex gave the *E*-vinyl phosphonate **9** (45% yield, >80% e.e. by HPLC). It is anticipated, based on results with the parent malonate, that ozonolysis of **9** and reduction of the ozonide with $NaBH_4$ will yield the lactone **10**. Decarboxylation of **10** will provide an analog of enterolactone.

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