

## Intramolecular Wittig Reactions With Lactones Utilising Triphenylphosphine and Dimethyl Acetylenedicarboxylate

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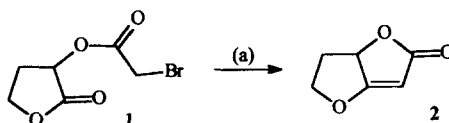
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**Abstract:** The intramolecular Wittig olefination of  $\gamma$ -butyrolactones has been effected in high yield using a combination of triphenylphosphine and dimethyl acetylenedicarboxylate.  
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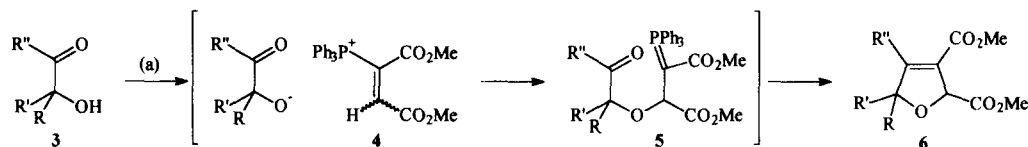
**Keywords:** Furans, lactones, Wittig reaction.

We have been interested for some time in the intramolecular Wittig reaction of stabilised phosphoranes with lactones and its applications in synthesis.<sup>1</sup> We have previously reported<sup>1</sup> that phosphoranes derived from the bromoacetylated lactones **1** cyclise to give the bicyclic tetronates **2** in good yields (Scheme 1).



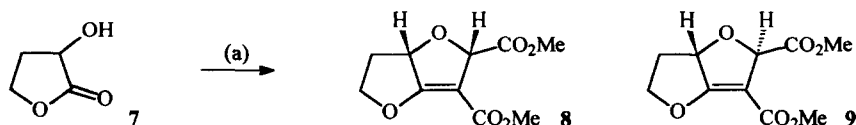
Scheme 1: (a)  $\text{PPh}_3/\text{MeCN}$  then  $\text{DBU}/\text{MeCN}/\text{reflux}$ .

We were intrigued by a report by Yavari *et al.*<sup>2</sup> who described the reaction of  $\alpha$ -hydroxyketones **3** with triphenylphosphine (TPP) and dimethyl acetylenedicarboxylate (DMAD) leading to the formation of the dihydrofurans **6** via the vinyl phosphonium intermediate **4** and the phosphorane **5** (Scheme 2).

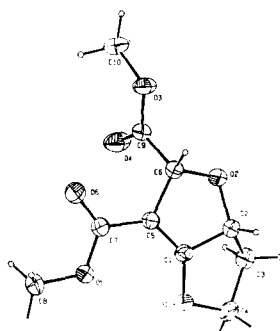
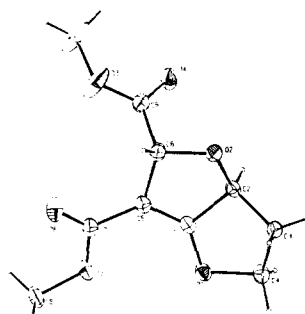


Scheme 2: (a)  $\text{PPh}_3/\text{DMAD}/\text{DCM}$ .

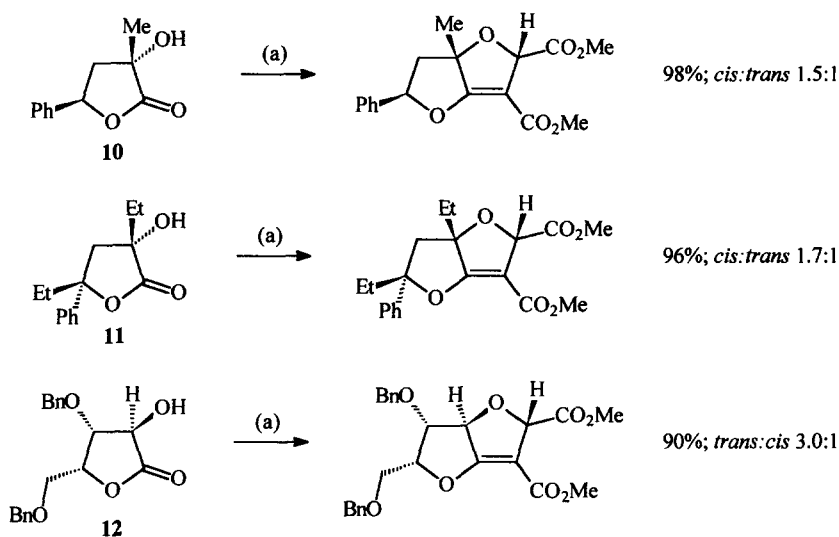
To the best of our knowledge this combination of reagents has not been applied to the annulation of  $\alpha$ -hydroxylactones and we were thus keen to investigate this possibility. We thus took  $\alpha$ -hydroxy- $\gamma$ -butyrolactone **7** and treated it with TPP/DMAD under reflux in THF for 20 hours. Despite the fact that the cyclisation step was sluggish we were pleased to observe the formation of two products **8** and **9** in a 2 : 1 ratio and 55% yield. These compounds were separable by chromatography and crystallisation and shown by X-ray crystallography to be the *cis*- (fig 1) and *trans*- (fig 2) fused dihydrofurans respectively. Repetition of this reaction in dioxane at reflux for 3 hours led to an improved yield of 84%. (Scheme 3)



Scheme 3: (a)  $\text{PPh}_3/\text{DMAD}$  in  $\text{THF}/0^\circ\text{C}$ , 1 hr, then reflux 24hrs, 55% (2 : 1) or dioxane reflux 3hrs 84% (2 : 1).

Figure 1: *cis*-fused dihydrofuran **8**Figure 2: *trans*-fused dihydrofuran **9**

The reaction was then applied to a range of  $\gamma$ -butyrolactones **10-12** with results comparable to those reported above (Scheme 4; major products shown). The more sterically congested lactones **10<sup>3</sup>** and **11<sup>1c</sup>** were converted to the corresponding bicyclic systems in very high yields, whilst reaction of the lactone **12<sup>1b</sup>** was effected with only a small amount of epimerisation (ca 5%) being observed at the labile C-4 position.<sup>1b</sup> The relative stereochemistry of the products were determined by nOe measurements,<sup>4</sup> however as yet we have no clear rationale to explain the selectivity observed in the reaction.

Scheme 4: (a)  $\text{PPh}_3/\text{DMAD}$  in dioxane/ $0^\circ\text{C}$ , 1 hr then reflux 3hrs.

This process appears to be general for the annulation of butyrolactones under very mild conditions and in high yield. We are currently seeking to apply this methodology to other  $\alpha$ -substituted lactones which should lead to fused dihydrothiophenes and pyrroles. In addition the array of functionality formed in this process offers several possibilities for further chemical transformations, including Michael and enolate based processes.

#### References

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