

# SELECTIVE TRANSFORMATIONS OF CARBONYL FUNCTIONS IN THE PRESENCE OF $\alpha,\beta$ -UNSATURATED KETONES: CONCISE ASYMMETRIC TOTAL SYNTHESIS OF DECYTOSPOLIDES A AND B

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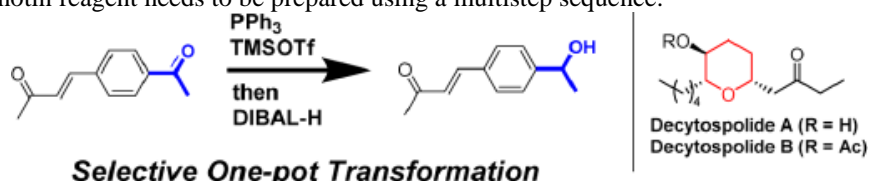
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## ABSTRACT

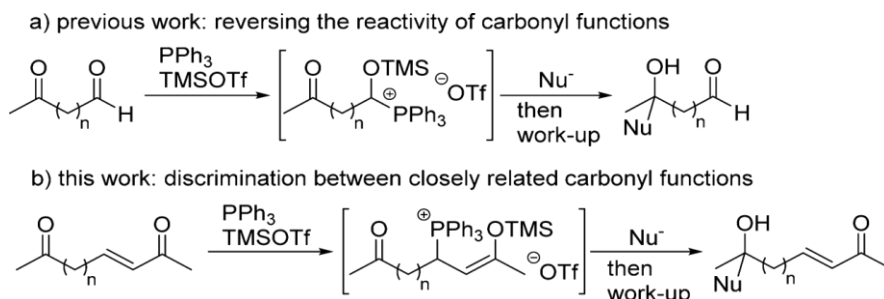
Enones selectively react with a combination of  $\text{PPh}_3$  and  $\text{TMSOTf}$  to produce phosphonium silyl enol ethers, which work as protective groups of enones during the reduction of other carbonyl functions and can be easily deprotected to regenerate parent enones at workup. Furthermore, the first ketone selective alkylations in the presence of enones were also accomplished. This in situ protection method was applied to concise asymmetric total syntheses of decytospolides A and B.

## INTRODUCTION

Ketones and  $\alpha,\beta$ -unsaturated ketones display nearly identical reactivity, although ketones generally have slightly higher reactivity toward nucleophiles than enones. In the past, only three different methods have been reported to describe selective reductions of ketones in the presence of enones. Ward et al. described a ketone-selective reduction in the presence of enones using  $\text{NaBH}_4$  in  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ . Ranu et al. realized that  $\text{Zn}(\text{BH}_4)_2$  in DME can also be employed to perform selective reductions of ketones. Although these methods are applicable to selective reductions of aliphatic ketones, they cannot be used to differentiate aromatic ketones from enones owing to their highly similar reactivities. Maruoka et al. described a procedure for chemoselective reductions of saturated aldehydes and a ketone in the presence of unsaturated carbonyls that employs a bulky tin hydride and Lewis acid. Although this method was effective in the discrimination of aldehydes, the yield of the ketone reduction was moderate. In addition, the key organotin reagent needs to be prepared using a multistep sequence.

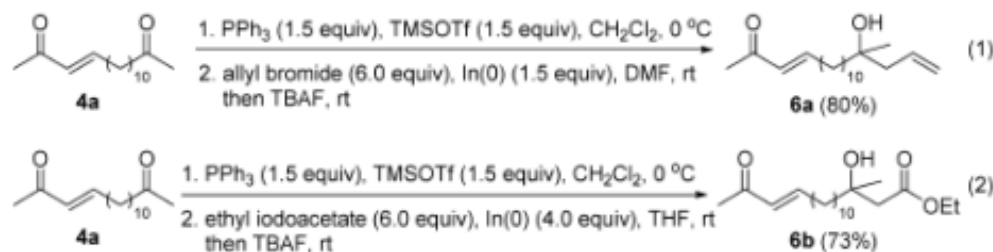


As described above, although there are a few methodologies succeeding in the selective transformation between closely related carbonyl functions, ketones, and enones, there is no general method for selective reduction of carbonyl functions in the presence of  $\alpha,\beta$ -unsaturated enones, let alone the method for selective alkylation. In our previous studies, we have developed procedures for reversing the reactivity of carbonyl functions that relies on the use of a combination of  $\text{TMSOTf}$  and phosphines to temporarily protect aldehydes and ketones (Scheme 1 a).



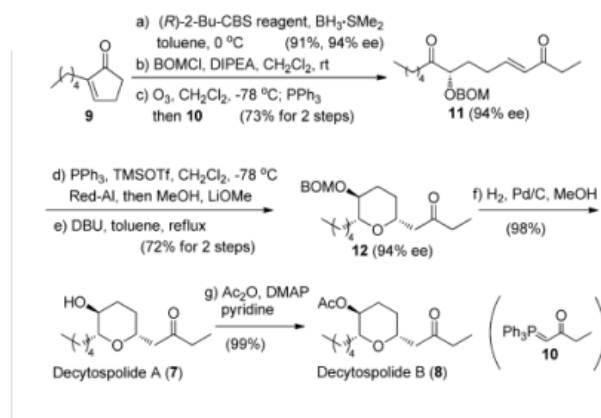
**Scheme 1. *In Situ* Protection Method for Selective Transformation**

In these processes, aldehydes and ketones are temporarily protected by being O,P-acetal-type phosphonium salt intermediates. In the course of this study, we found that the  $\text{PPh}_3$  and  $\text{TMSOTf}$  combination, even when used in excess, does not transform ketones to their corresponding phosphonium salts. On the other hand, Kozikowski et al., Kim et al., and Lee et al. separately reported  $\beta$ -alkylation reactions of enones using  $\text{PPh}_3$  and  $\text{TBSOTf}$  take place via initial phosphoniosilylation processes. We then expected that the combination of  $\text{PPh}_3$  and silyl triflate would react with  $\alpha,\beta$ -unsaturated ketones selectively in the presence of ketones. Although the phosphonium salts were generated as reactive intermediates in the previous reports,<sup>4</sup> we presumed that if the phosphonium silyl enol ethers could survive during the transformation of remaining ketones, an in situ protection method for discriminating between closely related functional groups would be established (Scheme 1 b).



**Scheme.2.Ketone-Selective Allylation (Equation.1) and Reformatsky Reaction (Equation.2)**

To demonstrate the synthetic utility of this method, we carried out the asymmetric total synthesis of decytopolides A (7) and B (8), which were isolated from *Cytospora* sp., an endophytic fungus from *Ilex canariensis*.<sup>7</sup> Decytopolide B (8) shows in vitro cytotoxic activity toward tumor cell lines A549 and QGY. To date, two reports exist describing the totalsynthesis of these natural products, and those synthetic routes involve multiple processes. Our synthetic route for the target natural products was summarized in Scheme 3. Corey–Bakshi–Shibata reduction of commercially available 2-pentyl-2-cyclopenten-1-one (9) afforded a chiral allylic alcohol. Protection of the hydroxyl group with BOM group was followed by a one-pot ozonolysis–Wittig reaction sequence to give the key keto-enone 11. Following in situ protection of the enone group, diastereo- and chemoselective reduction of ketone moiety in 11 with Red- Al proceeded smoothly, and 12, which has desired stereochemistry, was constructed by DBU-promoted isomerization. It is notable that the chiral center in 11 was not epimerized through this sequence of reactions. Finally, BOM group in 12 was detached by hydrogenolysis to give decytopolide A (7), which was acetylated to afford decytopolide B (8). These enantioselective syntheses were accomplished in six and seven steps from commercially available cyclopentenone 9, with overall yields of 47% for decytopolide A and 46% for decytopolide B.



**Scheme.3.Assymetric total synthesis of Decytopolides A and B**

## CONCLUSION

A convenient and versatile in situ protection method for enones has been developed. The process,performed by using a combination of PPh<sub>3</sub> and TMSOTf, generates phosphonium silyl enol ether intermediates. This method can be employed to discriminate between enones and ketones. By using this procedure, the first ketone selective alkylation reactions of a keto-enone were developed. Finally, we demonstrated the asymmetric total synthesis of decytopolides A and B by using the developed method as a key reaction. The route employed for the preparation of these natural products is the most concise and efficient of those developed thus far. Additional investigations of the applicability of other reagents and the protection of  $\alpha,\beta$ -unsaturated carbonyl substrates having other substituent patterns are currently underway.

## REFERENCES

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