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# ENANTIOMERICALLY PURE KETALS IN SYNTHESIS. DIASTEREOSELECTIVE FORMATION OF β-KETO AND β-HYDROXY KETALS

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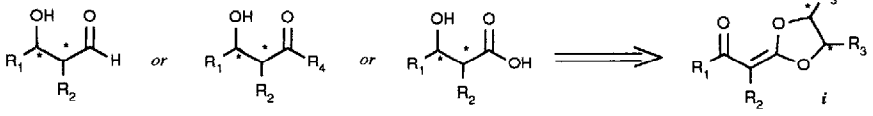
***Abstract:*** *Enantiomerically pure acylketene acetals were employed to generate a homochiral β-keto ketal through a highly diastereoselective lithium enolate quench. The β-keto ketal, which was also prepared through a desymmetrization ketalization reaction on a meso dione, was employed in the synthesis of the isomers of the insect pheromone sitophilure.*

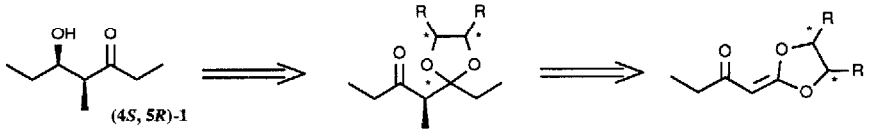
We recently reported that achiral acylketene acetals undergo conjugate hydroboration-reduction and conjugate organolithium addition reactions. With organolithium reagents, the resulting lithium enolate could be quenched with methyl iodide in good yield.[1] From these results, we hypothesized that a homochiral acylketene acetal (such as ***i***) would follow the same reaction pathway and undergo a diastereoselective enolate quench. In addition, diastereoselective reduction of the resultant monoprotected β-dicarbonyl compounds would lead to a new, non-aldol route to chiral, nonracemic β-hydroxy carbonyls.[2] Such a protocol would allow for a unified approach to the array of β-hydroxy carbonyl compounds of different oxidation states and substitution pattern, as shown below.[3] Herein we report our studies in this area. Further,

**Figure 1**



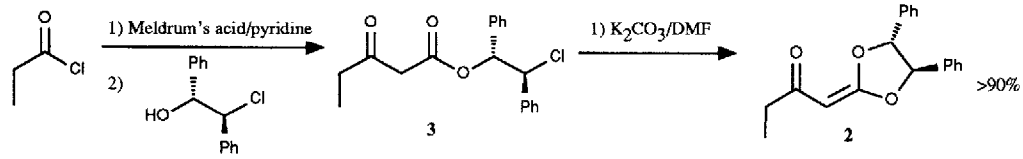

we document our preliminary work on the diastereoselective monoketalization of a prochiral dione with an enantiomerically pure diol.

We chose to test our ideas with the synthesis of 5-hydroxy-4-methyl-3-heptanone (**1**), of which the 4*S*, 5*R* isomer is the insect pheromone sitophilure.[4] All four possible isomers of sitophilure have been previously prepared and identified.[4b] The strategy, shown in retrosynthetic form below, was to add ethyllithium to a



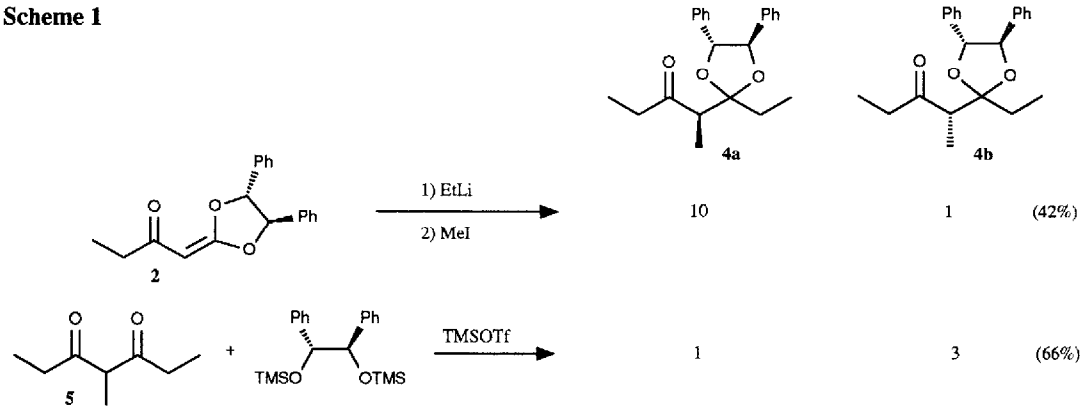

homochiral acylketene acetal and quench the resulting enolate diastereofacially with methyl iodide. The resulting β-keto acetal, having the correct methyl stereochemistry, would be reduced stereoselectively to β-hydroxy acetal. Removal of the acetal auxiliary would give sitophilure.

Acylketene acetal **2** is prepared from the reaction of propionyl chloride with Meldrum's acid,[5] followed by reaction of the product with (1*R*,2*S*)-2-chloro-1,2-diphenylethanol[6] to afford desired β-ketoester **3**.[7] Treatment with $K_2CO_3$ in DMF[1,8] yields **2** in greater than 90% isolated yield from acid chloride.




The addition of ethyllithium to **2** at 0°C in THF, followed by $CH_3I$ quench, gave the diastereomers **4a** and **4b** in 42% combined, isolated yield (Scheme 1). Neither gas chromatographic analysis nor HPLC were able to differentiate between the diastereomers, but $^1H$ NMR at 300 MHz indicated the ratio of **4a** to **4b** to be in excess of 10 to 1, respectively. Additionally, significant amounts of stilbene oxide were formed in the course of the reaction and could not be avoided. Analysis of test reactions indicated that when more than one equivalent of ethyllithium was used, the yield of **4** would significantly diminish and the amount of stilbene oxide would increase. This may be the result of acetal fragmentation of the lithium enolate. A similar situation was observed with boron enolates.[1]

**Scheme 1**

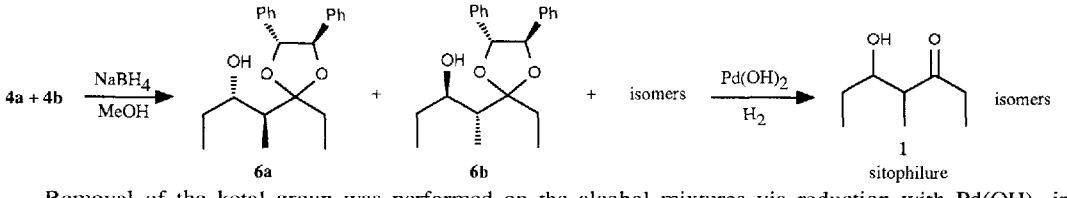



While the diastereoselectivity for the production of **4** was gratifying, the yield was modest and the reaction was difficult to scale-up. Thus, our attention was drawn to an alternative approach to **4** which recognized that sitophilure could be derived from a single enantioselective reduction of one of the ketone functionalities of 4-methyl-3,5-heptanedione (**5**). We chose to pursue this idea in a diastereoselective manner via the Noyori ketalization protocol.[9] To our knowledge, this methodology has never been employed on a prochiral dione with an enantiomerically pure diol. In the event, (*R*, *R*)-hydrobenzoin[10] was reacted with trimethylsilyl chloride in THF with triethylamine to form the bis-TMS ether. This was reacted directly with **5** in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to form **4a** and

**4b** in 66% isolated yield as a 1:3 mixture of diastereomers (Scheme 1). Although enzymes are known to differentiate enantiotopic groups in meso compounds, there are relatively few synthetic examples of this type of desymmetrization process.[11]

With ample quantities of **4** in hand, we turned to the problem of selective reduction of the ketone functionality. Best results were obtained with $NaBH_4$ in MeOH at 0°C, which afforded the *anti* isomers **6a** and **6b** in 28:1 and 37:1 ratios from **4a** and **4b**, respectively, in 84% isolated yield. Unfortunately, while the *anti* and *syn* pairs were separable from one another, the two *anti* compounds and the two *syn* compounds proved inseparable from one another by both conventional and chiral-column HPLC.

To understand our reduction results, we undertook a preliminary computer-assisted molecular model investigation of **4a** and **4b**.[12] Both space-filling models and computational studies indicate a very hindered system as a result of the phenyl groups. Therefore, metal complexation with an acetal oxygen for controlled hydride transfer does not appear to be in operation. Minimized structures of **4a** and **4b** indicate that the methyl group seems to have little steric effect on hindering either face of the carbonyl. By comparison, the effect imparted by the ethyl group attached to the central carbon of the acetal moiety is substantial. A hydride moiety on its trajectory toward the carbonyl carbon[13] would experience significant hindrance to approach to the *pro-R* face caused by the ethyl group. This effect is small on the *pro-S* face.




**6a** **6b** **1** sitophilure

Removal of the ketal group was performed on the alcohol mixtures via reduction with $Pd(OH)_2$ in quantitative yield.[4c] Crude product **1** was derivatized with (*S*)-MTPA-Cl[14] to afford a mixture of isomers in the corresponding ratios to those present prior to hydrogenolysis. Comparison of the $^{19}F$ NMR shifts with those published by Mori and coworkers[4b] established the absolute configuration of compounds **4** and **6**.

In conclusion, the synthesis of enantiomerically pure acylketene acetals from simple starting material have been developed. The products are stable if kept below 0°C away from moisture.

The oxidation state of the β-carbon of acylketene acetals can be manipulated in a predictable manner, and the transformations necessary to produce the triad of β-hydroxy carbonyl compounds depicted in Figure 1 from the point of view of the β-carbon are in place.[1,3] Such β-keto acetals and ketals are useful intermediates in organic synthesis,[15] and this protocol adds to the growing list of approaches to the monoacetals of β-dicarbonyl compounds.[16]

Stereochemical induction in the alkyllithium/MeI treatment of homochiral acylketene acetals appears to be quite high. However, the yield is modest at best, and more work is needed before this protocol is synthetically viable. The alternative asymmetric synthesis of **4** *via* the differentiation of a meso dione allows for the facile synthesis of β-keto ketals. Both routes are flexible, since the chiral auxiliary employed in each is available in either enantiomeric series. Finally, the stereoselectivity in the reduction of α-substituted-β-keto ketals is very high and affords *anti* product. While not of particular interest for the synthesis of the natural isomer of sitophilure, *anti* isomers are difficult to obtain by the conventional aldol reaction.

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