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AN APPLICATION OF THE IRELAND REACTION TO THE STEREOSPECIFIC SYNTHESIS OF FUSED CARBOCYCLIC SYSTEMS.

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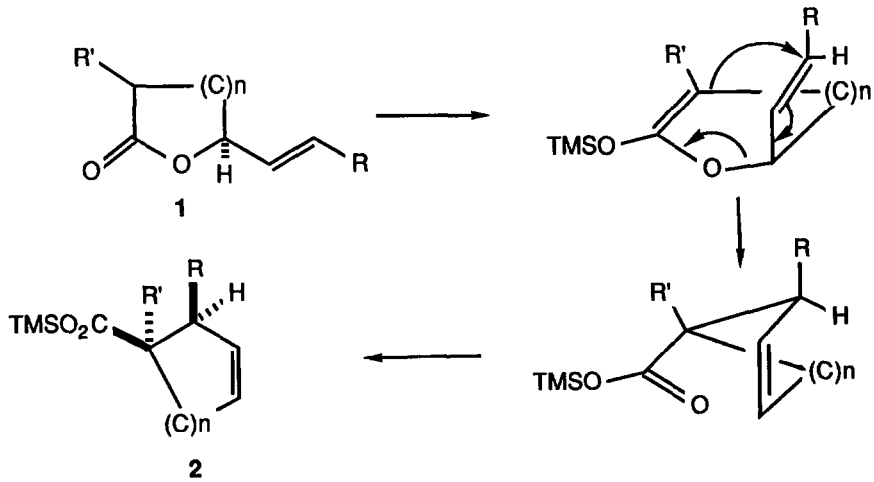
Abstract: The sequence : group transfer Michael addition, aldol / lactonization and Claisen rearrangement provides access to the title compounds.

The importance of deliberately planned bond reorganization reactions in organic synthesis can hardly be exaggerated[1,2]. The Ireland silyl keteneacetal variation of the Claisen rearrangement [3a,b] has certainly played a critical role in addressing sophisticated issues of stereochemical communication in complex settings[4]. The margin of overall stereoselectivity of the acyclic Ireland reaction rests on two bases. The first is the remarkable control which can be exercised over enolate geometry (*E or Z*) by adjustment of experimental conditions. The second control element is the topographic character ("chair" or "boat") of the transition state. Barring unusual constraints[4] the chair transition state, with a pre-*E* disposition of the evolving carbon-carbon double bond, is preferred in the Ireland reaction[3a,b].

Some years ago, our laboratory demonstrated a lactonic version of the ester enolate Claisen rearrangement (cf. **1**--> **2**)[5,6]. Of course with six and seven membered lactones (n= 3 or 4, respectively) the constraint of the cyclic structure imposes an obligatory cis geometry (*E*) on the enolate equivalent. Also, these types of cyclic structures impose a boat like character on the transition state of the reorganization and dictate the formation of a cis double bond. Thus, from the standpoint of stereochemistry, the lactonic version of the Ireland reaction offers enhanced opportunities for rigorous control of the outcome. We first demonstrated the applicability of these ideas in the context of a stereospecific synthesis of widdrol[7]. Since that time, the lactonic version of the Ireland reaction has been applied effectively in a variety of novel contexts[8,9,10].

The logic implied in the transformation of **1**-->**2** lends itself to the synthesis of fused carbocycles, given technology to generate the precursor lactones with stereochemical definition in systems containing other chiral elements. A timely

disclosure by Mukaiyama, in a different context[11], carried with it an implicit solution to the synthesis of the required substrates. In the light of the Mukaiyama advance we have reinvestigated anew the potentialities of this methodology. Scheme I sets forth our findings in this regard.



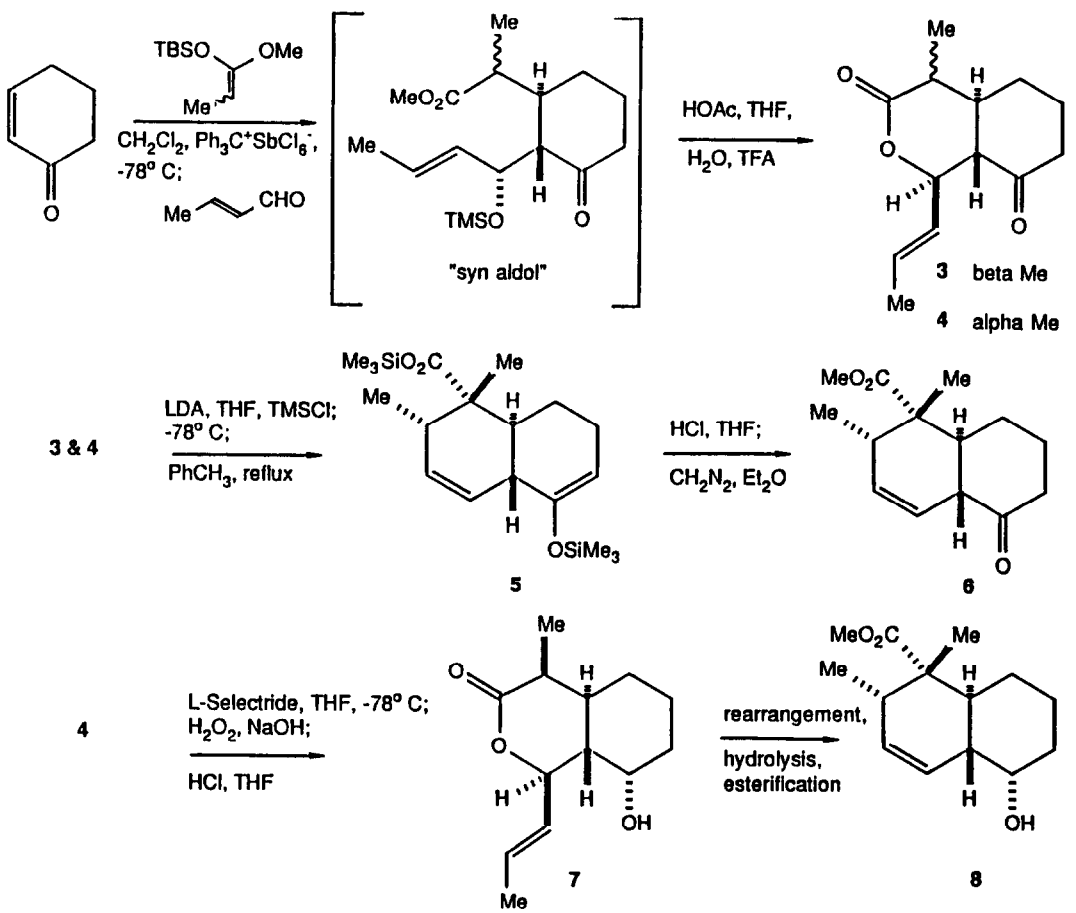
Treatment of cyclohexenone with the t-butyldimethylsilyl keteneacetal of methyl propionate (Scheme I) under the Mukaiyama protocol[11] (CH_2Cl_2 , Ph_3CSbCl_6 , -78 C ; trans-crotonaldehyde ; HOAc, THF, H_2O, TFA, R.T.) affords roughly a 1 : 1.5 mixture of **3** and **4** in 65 % yield. This result again demonstrates the low diastereoselectivity of the Michael reaction of ester enolates with cyclic ketones (of little consequence in the present context)[12]. However the selectivity of the aldol addition was quite high[11] allowing for isolation of lactones **3** and **4**, both arising from syn aldol formation.

Since both lactones **3** and **4** afford the same silyl keteneacetal, they can be processed together in the Claisen sequence (THF, xs LDA, TMSCl, - 78 C ; $PhCh_3$, reflux 4H). Under this treatment, the precursor to rearrangement is the silyl keteneacetal silyl enol ether (not characterized). *It will be noted that the product , compound **5**, contains a potentially exploitable silyl enol ether functionality.* In the case at hand, **5** was treated as shown to afford ketone **6** .

Alternatively the lactone **4** was reduced (L-Selectride®, THF, -78 C ; NaOH, H_2O_2 ; 1 M HCl) to afford hydroxy lactone **7** in 85 % yield. Application of the Claisen protocol gave rise to hydroxy ester **8** in 93 % overall yield. The conciseness and high margin of control in the elaboration of the five stereogenic centers of compound 8 are attractive features of this approach[13].

The functionalized hydronaphthalene structural types available through this sequence could well prove to be useful in synthesis of various natural products. including mevinolin. Efforts in our laboratory toward such ends are well underway.

Scheme I



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