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Stereoselective Synthesis of Substituted Oxetanes

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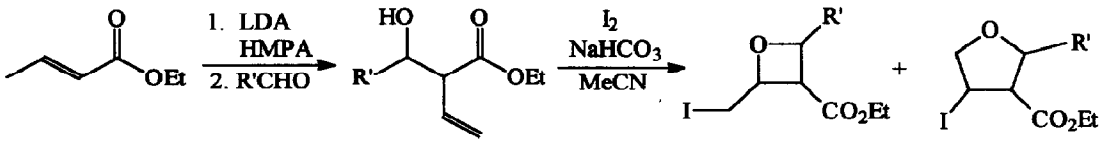
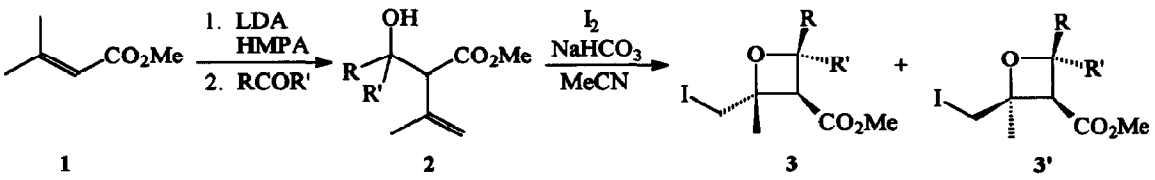
ABSTRACT: The stereospecific synthesis of substituted oxetanes was shown to be feasible through the use of a deconjugative aldol-cyclization sequence.

The discovery of anti-viral compounds, such as oxetanocin, that contain oxetane rings has sparked an interest in the synthesis of these cyclic ethers.[1] In preliminary efforts[2], we investigated a deconjugative aldol-cyclization sequence for the construction of cyclic ethers. In this system we noted a dichotomy in the reaction manifolds that the intermediate homoallylic alcohols could undergo (see scheme 1). In studies of halolactonization, it was noted that the regiochemistry could be controlled by the substitution pattern.[3] The positioning of a methyl group could direct the mode of attack on the olefin. Indeed, the addition of a methyl group to the terminal end of the olefin in the deconjugated aldol product resulted in exclusive formation of the tetrahydrofuran ring system.[2]

Scheme I



We wished broaden the scope of this deconjugative aldol-cyclization sequence by modifying the substitution pattern in order to only form oxetanes. With this in mind, ester **1**[4] was chosen as our starting material. Deprotonation of **1** using conditions previously described[2] afforded the corresponding dienolate that upon exposure to a variety of aldehydes and ketones produced aldol products **2** (see table 1). In the cases where diastereomers of **2** were formed, the *syn* and *anti* aldols (approximately a 1:1 ratio) could be separated by chromatography and their stereochemical assignments were based on ^{13}C NMR chemical shift of methine and carbinol resonances.[2]



1 2 3 3'

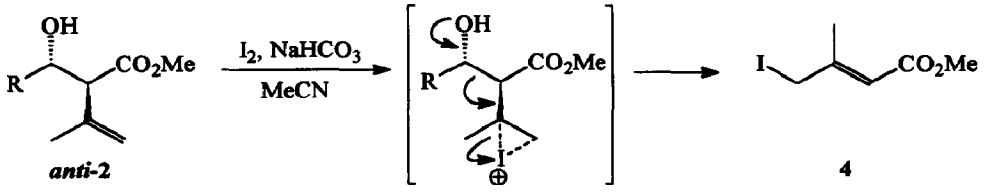
With **2** in hand the cyclization chemistry was investigated. This was carried out by treating these compounds with iodine and sodium bicarbonate in acetonitrile at RT in the dark for 24 h. As expected, the positioning of the methyl group completely shut down tetrahydrofuran ring formation and now directed cyclization solely towards oxetane formation in fair to good yields (see table 1). Compounds **3** and **3'** are the

TABLE 1. Product Distribution From Tandem Aldol-Cyclization Sequence With Ester 1

ENTRY	ALDOL (2)	YIELD (%)	OXETANE	YIELD (%)
1	*syn* R=H, R'=Me	66	**3** (R=H, R'=Me)	71
2	*anti* R=Me, R'=H		**3**:**3'**=1:1 (R=Me, R'=H)	44[a]
3	*syn* R=H, R'=Ph	78	**3** (R=H, R'=Ph)	48
4	*anti* R=Ph, R'=H		**3**:**3'**=1:1 (R=Ph, R'=H)	17[b]
5	R=R'=Me	32	**3** (R=R'=Me)	47
6	R=R'= -$(CH_2)_4$-	39	**3** (R=R'= -$(CH_2)_4$-)	49
7	R=R'= -$(CH_2)_5$-	42	**3** (R=R'= -$(CH_2)_5$-)	54

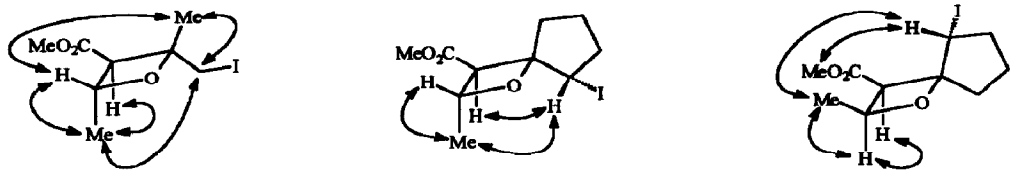
a) isolated along with 16% of **4**. b) isolated along with 28% of **4**.

two products possible from addition to either side of the olefin in **2**. In the cases of table 1, entries 2 and 4, the resultant oxetanes **3** and **3'** were formed as an unseparable mixture of isomers (1:1 ratio determined by NMR). Also observed in entries 2 and 4 was the formation of compound **4**. For reasons still unclear, the intermediate iodonium ion activates these two systems for the retro-aldol reaction. In a control reaction in which the experiment was run in the absence of iodine, $NaHCO_3$ present, one could only recover starting material. As a consequence, this side product diminishes the yield of cyclized material.

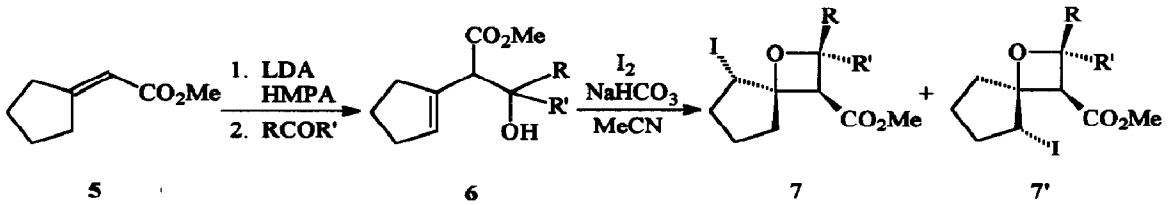


The relative stereochemistry of the oxetanes was determined by comparing trends in high-field ^1H and ^{13}C NMR chemical shifts and by difference NOE measurements (see scheme 2).

Scheme 2. Representative Nuclear Overhauser Enhancements



As an initial step at determining the scope and limitations of this chemistry, a derivative of 1 was constructed. Reaction of trimethylphosphonoacetate with cyclopentanone afforded 5 in 98% yield. This compound was subjected to similar conditions and the results are outlined in table 2. This modification



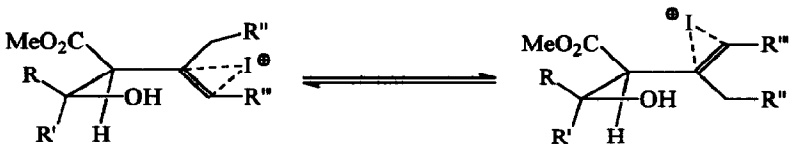
5 6 7 7'

TABLE 2. Product Distribution From Tandem Aldol-Cyclization Sequence With Ester 5

ENTRY	ALDOL (6)	YIELD (%)	OXETANE	YIELD (%)
1	*syn* R=H, R'=Me	92	7 (R=H, R'=Me)	94
2	*anti* R=Me, R'=H		7' (R=Me, R'=H)	53
3	*syn* R=H, R'=Ph	82	7 (R=H, R'=Ph)	88
4	*anti* R=Ph, R'=H		7' (R=Ph, R'=H)	89
5	R=R'=Me	61	7 (R=R'=Me)	90
6	R=R'= -$(CH_2)_4$-	55	7 (R=R'= -$(CH_2)_4$-)	65
7	R=R'= -$(CH_2)_5$-	66	7 (R=R'= -$(CH_2)_5$-)	64

improved the yields on both the aldol and cyclization steps. Furthermore, no mixture of diastereomers and no formation of 4 was observed in the cyclization step. For entries 1,3,5-7 in both tables, product was derived solely from addition to the same side of the olefin in the aldol product. For entries 2 and 4 in both tables, an erosion of the selectivity for addition to the olefin was observed for the first series of reactions and a complete reversal of selectivity for the second series of reactions. In our earlier work[2] all aldol products cyclized through the same transition state to generate the corresponding tetrahydrofurans. The reaction of the *anti* aldol products in these reactions stands in sharp contrast to those results. One rational for this anomalous behavior was gleaned from molecular mechanics calculations. PCModel[5] calculates that for entries 2 and 4 in both tables, 3' and 7' are more stable than 3 and 7 respectively. This leads to the conclusion, that for these reactions, the transition state is late and/or is more product-like. Alternatively, one

could also directly examine the two possible transition structures for the cyclization step, **8** (olefin anti to ester group) and **9** (olefin syn to ester group). Allylic strain would render **9** less stable than **8** which is consistent with the majority of our observations. However for the *anti* aldol products in this study, transannular or torsional effects exacerbated by this small ring may reverse the transition structure stability thereby explaining the reversal in selectivity.



8 **9**

In summary, we have shown the versatility of the deconjugative aldol-cyclization sequence for the construction of substituted oxetanes with the ability to control relative stereochemistry around the ring. We are currently developing an enantioselective process based on this chemistry and will report those results in due time.

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