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Z- OR *E*-CONFIGURATED γ-ALKYLIDENEBUTENOLIDES FROM A 2-(TRIMETHYLSILOXY)FURAN AND IODOMETHACROLEIN – STEREOSELECTIVE SYNTHESIS OF *Z*- AND *E*-FREELINGYNE

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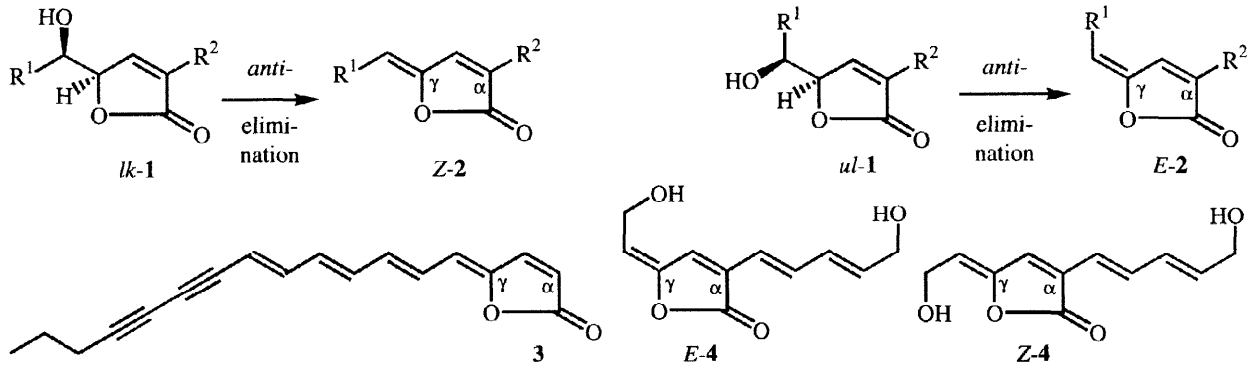
Abstract: The γ-(α-hydroxylalkyl)butenolides *lk*-**5** and *ul*-**5** were prepared by Mukaiyama aldol additions between iodoaldehyde **10** and the trimethylsiloxy-substituted furan **6** in the presence of BF_3•OEt_2 and $ZnBr_2$, respectively. Couplings of these butenolides with 3-ethynylfuran followed by *anti*-eliminations of water mediated by DEAD/PPh_3 led to *Z*-freelingyne (*Z*-**11**; *ds* = 92:8) and *E*-freelingyne (*E*-**11**; *ds* = 98:2).

γ-Lactones and α,β-unsaturated γ-lactones („Δ^2-butenolides") constitute the core of many natural and unnatural compounds as do certain alkylidene derivatives thereof like α-methylene-γ-lactones or – to a lesser extent – γ-alkylidene substituted α,β-unsaturated γ-lactones **2**.[1] For the latters we have been developing a synthesis based on the dehydration of γ-(α-hydroxyalkyl)butenolides **1** through *anti*-eliminations (Scheme 1).[2,3] Ideally, these eliminations are stereospecific so that stereopure γ-(α-hydroxyalkyl)butenolides *lk*-**1** (*ul*-**1**) give stereopure γ-alkylidenebutenolides *Z*-**2** (*E*-**2**). So far, we eliminated compounds **1** with triflic anhydride and pyridine and obtained dihydroxerulin (**3**),[2] the isolissoclinolid *E*-**4** [3] or the isotetrenolin *Z*-**4**.[3] Here, we describe a different elimination protocol. It was essential for realizing stereoselective syntheses of *Z*-freelingyne (*Z*-**11**; constituent of wood oil from *Eremophila freelingii*) [4] and its isomer *E*-**11**. Previous syntheses of freelingyne suffered from the absence of stereocontrol [5,6] or led cleanly to *Z*-freelingyne but not to *E*-freelingyne.[7,8]



Scheme 1.

We desired to reach the type-**1** precursors of our target butenolides *Z*- and *E*-**11** by diastereoselective Mukaiyama aldol additions between *E*-3-iodomethacrolein (**10**) [9] and the trimethylsiloxylated furan **6** [10] noting precedence for such diastereoselectivity in additions between α-*chiral* aldehydes and heterocycles akin to **6**.[11] In fact, in the presence of BF_3•OEt_2 aldehyde **10** took up furan **6** with perfect stereocontrol (Scheme 2). After hydrolysis we isolated a single product [12] *lk*-**5** [13] in 56% yield. The opposite stereochemical preference was observed when aldehyde **10** was combined with furan **6** in the presence of $ZnBr_2$. Hydrolysis and flash chromatography furnished 52% of the previously not formed aldol adduct *ul*-**5** [14] in the early and 9% *lk*-**5** in the late fractions. Each aldol adduct was coupled under Pd(0) catalysis with ethynylfuran **7**; this reagent had been generated by a Peterson olefination of furancarbaldehyde **9** with lithio(trimethylsilyl)diazomethane.[15] The coupling products *lk*- and *ul*-**8** formed diastereomerically pure in 70 and 76% yield, respectively. To our consternation, the *anti*-eliminations *lk*-**8**→*Z*-**11** and *ul*-**8**→*E*-**11** did not even yield trace amounts of product when tried with the elsewhere successful [2,3] triflic anhydride / pyridine mixture. On the other hand, eliminations with excess DEAD / excess PPh_3 [16] were high-yielding (94% *Z*-**7**, 87% *E*-**7**) and *anti*-selective so that natural freelingyne (*Z*-**11**) resulted as a 92:8 *Z*:*E*- and the unnatural isomer *E*-**11** as a 98:2 *E*:*Z*-mixture. The feasibility of an *aldol addition* / β-elimination approach to γ-alkylidenbutenolides has thereby been established.

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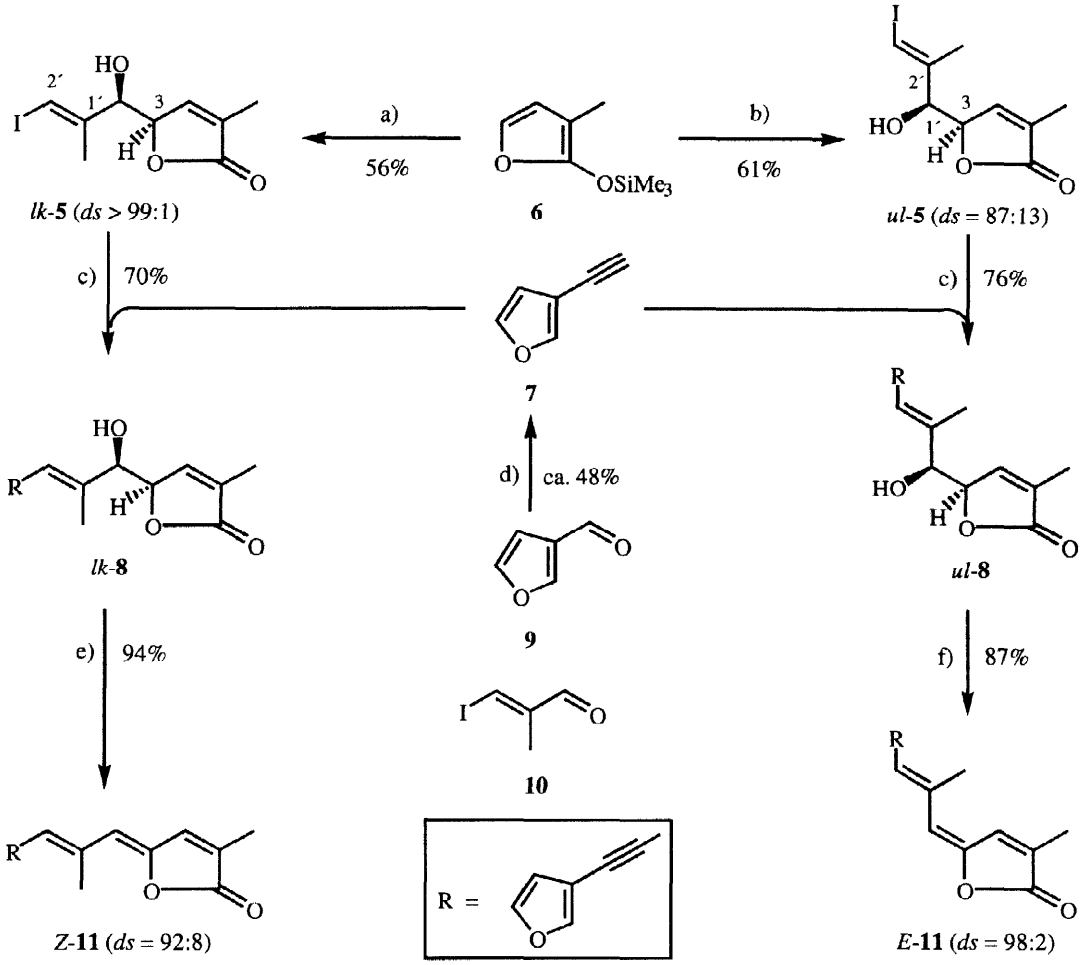

Scheme 2. a) $BF_3{\bullet}OEt_2$ (1.0 equiv.), **10** (1.0 equiv.), CH_2Cl_2, -78°C, 2.5 h.– b) $ZnBr_2$ (1.0 equiv.), **10** (1.0 equiv.), CH_2Cl_2, -78°C, 2.5 h– c) **7** (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol-%), CuI (0.1 equiv.), THF/$(iPr)_2NEt$ (4:1), room temp., 30 min.– d) LDA (1.2 equiv.), Me_3SiCHN_2 (1.2 equiv.), THF, -78°C, 30 min; **9** (1.0 equiv.), -78°C, 1 h; room temp., 30 min.– e) DEAD (6.0 equiv.), PPh_3 (6.0 equiv.), THF, -40°C, 5 h; 0°C, 30 min.– f) Same as e) at 0°C, 2 h.

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