

Enantioselective Acylation of Enolates; the reaction of (4*R*)-*trans*-Diethyl 2-Alkyl-2-methoxy-1,3-dioxolane-4,5-dicarboxylates with *E*- and *Z*-Silyl Enol Ethers

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The stereoselectivity of the Lewis acid induced acylation of open-chain silyl enol ethers by chiral orthoesters is strongly affected by the C=C bond configuration: both *Z* and *E* silyl enol ethers are acylated in good isolated yields, but the *Z* isomers give rise to a 1:1 ratio of diastereoisomeric monoprotected 1,3-diketones, while excellent stereoselectivities are obtained with *E* enols.

The acylation of enolates represents an alternative to the more common aldol condensation for the synthesis of 1,3-difunctional compounds. While the number of methods for the enantioselective aldol condensation has increased recently, very few methods have been concerned with controlling the absolute stereochemistry of the acylation reaction.¹

Recently we have introduced optically active orthoesters as precursors of chiral acyl cation equivalents, and reported their diastereoselective reaction with trimethylsilyl enol ethers derived from cyclic ketones.² Here we show the results obtained with open chain silyl enol ethers, in particular stressing the effect of the configuration of the enolic double bond.

The chiral orthoester **1** is reacted with a trimethylsilyl enol ether **2** (2 equiv.) and BF₃·OEt₂ (2 equiv.) at -60 °C for a few hours, affording a diastereoisomerically enriched monoprotected 1,3-diketone **3**, (Scheme 1).

Table 1 shows some representative data obtained from pure *Z*³ and *E*⁴ silyl enol ethers.† The level of diastereoselectivity

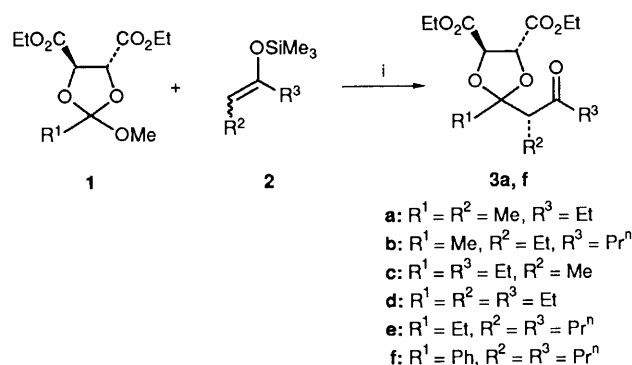
that can be obtained using mixtures of silyl enol ethers prepared *via* metallation-silylation (using lithium diisopropylamide, in tetrahydrofuran at -78 °C followed by addition of Me₃SiCl) of the parent ketone is also reported. The yields are only marginally dependent on the configuration of the enolic double bond, but the stereoselectivity is dramatically affected: *E* silyl enol ethers **2d**, **2e** and **2f** afford diastereoisomeric

Table 1 Acylation of configurationally defined trimethylsilylenol ethers^a

Product	Config. of 2	Yield (%) ^b	D.e. (%) ^c
3a	<i>Z</i>	65	0
3b	<i>Z</i>	61	0
3c	<i>E</i> : <i>Z</i> = 7:3	75	72
3d	<i>E</i>	70	90
3e	<i>E</i>	60	84
3f	<i>E</i>	90	88

^a The reactions were carried out by mixing **1** (1 mmol), **2** (2 mmol) and BF₃·OEt₂ (2 mmol) in anhydrous CH₂Cl₂ (10 ml) at -60 °C for 3h. After quenching with sat. NaHCO₃ solution (10 ml), compounds **3a-e** were purified by flash chromatography. ^b Yields refer to purified isolated products. ^c Determined by NMR.

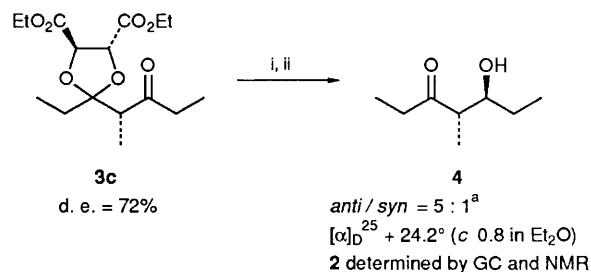
† *Z*-Silyl enol ethers (*Z*:*E* >98:2) were prepared by treatment of the parent ketones with Me₃SiCH₂CO₂Et and cat. Bu₄N⁺F⁻ at -78 °C; pure *E* compounds (*E*:*Z* >98:2) were obtained *via* oxidation of configurationally pure vinylolithium derivatives with Me₃SiOOSiMe₃.



Scheme 1 Reagents and conditions: i, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -60°C

excess (d.e.) values slightly superior to those obtained with cyclic compounds,² while *Z* silyl enol ethers **2a** and **2b** are completely non-stereoselective, giving a 1:1 mixture of diastereoisomers. Of course the behaviour of the *E*:*Z* mixture **2c** is intermediate. Investigations aimed at finding a rationale for such a different trend are in progress.

To establish the absolute configuration of the stereocentre generated by the acylation reaction we transformed compound **3c** into 4-methyl-5-hydroxyheptan-3-one by reduction with excess diisobutylaluminium hydride and deprotection with $\text{BF}_3 \cdot \text{OEt}_2$ in $\text{MeOH}-\text{CH}_2\text{Cl}_2$ as shown in Scheme 2. According to Cram's and Felkin's rules the *anti* product is predominantly formed (*anti*:*syn* = 5:1).[‡] After carefully checking that no epimerization could have occurred in the critical deprotection step§ we concluded that the configura-



Scheme 2 Reagents and conditions: i, Bu^i_2AlH (5 equiv.), Et_2O , -80°C ; ii, $\text{BF}_3 \cdot \text{OEt}_2$, MeOH , CH_2Cl_2 , room temp.

tion at C-4 in **4** is the same as in **3c**. Since the mixture obtained from the reduction-deprotection sequence showed a positive optical rotation, we attribute the (4*S*,5*S*) configuration to the major isomer. In fact both the *anti* and the *syn* isomers of (4*S*)-4-methyl-5-hydroxyheptan-3-one⁵ have a positive specific rotation value.¶

As a consequence we can say that the configuration of **3c** is (*S*) and on this basis we can assume that the *Si* face of the silylenol ether is preferentially acylated by (*R,R*) orthoesters.

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‡ The ¹H NMR spectrum (Varian Gemini-300, C_6D_6 solution) of the mixture showed two signals at δ 3.48 (dt, *J* 8.1 and 4.1 Hz) and at δ 3.64 (m) in a 5:1 integral ratio that were respectively attributed to the *anti* and *syn* isomer by comparison with the values reported in ref. 5. An analogous agreement with the reported values was found in the ¹³C NMR spectrum. For **4** $[\alpha]_{\text{D}}^{25} + 24.2^\circ$ (c 0.8 in Et_2O).

§ To eliminate this possibility, *syn*-4-(1-hydroxyhexyl)hexan-3-one, independently prepared in a configurationally pure form according to G. P. Boldrini, F. Mancini, E. Tagliavini, C. Trombini and A. Umani-Ronchi, *J. Chem. Soc., Chem. Commun.*, 1990, 1680, was stirred with a five-fold excess of $\text{BF}_3 \cdot \text{OEt}_2$ in $\text{MeOH}-\text{CH}_2\text{Cl}_2$ for 24 h. After quenching with aq. NaHCO_3 and extraction with diethyl ether the ¹H NMR spectrum of the product (although some decomposition occurred) allowed any conversion to the *anti* isomer to be excluded.

¶ All four stereoisomers of 4-methyl-5-hydroxyheptan-3-one have been prepared; they show the following specific rotations: (4*R*,5*R*) $[\alpha]_{\text{D}}^{23} - 37.8^\circ$ (c 1.20 in diethyl ether), (4*S*,5*S*) $[\alpha]_{\text{D}}^{22} + 36.8^\circ$ (c 1.25 in diethyl ether), (4*R*,5*S*) $[\alpha]_{\text{D}}^{20} - 26.7^\circ$ (c 1.52 in diethyl ether), (4*S*,5*R*) $[\alpha]_{\text{D}}^{20} + 27.0^\circ$ (c 1.24 in diethyl ether).⁵