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 trimethysilyl enol ether **2** (2 equiv.) and $BF_3{\cdot}OEt_2$ (2 equiv.) at −60 °C for a few hours, affording a diastereoisomerically enriched monoprotected 1,3-diketone **3**, (Scheme 1).

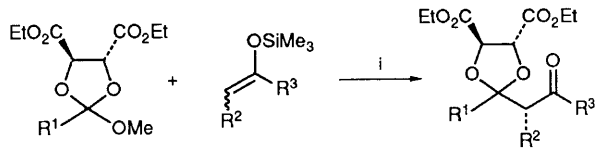
Table 1 shows some representative data obtained from pure *Z*[3] and *E*[4] silyl enol ethers.† The level of diastereoselectivity that can be obtained using mixtures of silyl enol ethers prepared *via* metallation–silylation (using lithium diisopropylamide, in tetrahydrofuran at −78 °C followed by addition of Me_3SiCl) 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	*Z*	65	0
3b	*Z*	61	0
3c	*E* : *Z* = 7 : 3	75	72
3d	*E*	70	90
3e	*E*	60	84
3f	*E*	90	88

[a] The reactions were carried out by mixing **1** (1 mmol), **2** (2 mmol) and $BF_3{\cdot}OEt_2$ (2 mmol) in anhydrous CH_2Cl_2 (10 ml) at −60 °C for 3h. After quenching with sat. $NaHCO_3$ 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 $Me_3SiCH_2CO_2Et$ and cat. $Bu_4N^+F^-$ at −78 °C; pure *E* compounds (*E* : *Z* >98 : 2) were obtained *via* oxidation of configurationally pure vinyllithium derivatives with $Me_3SiOOSiMe_3$.

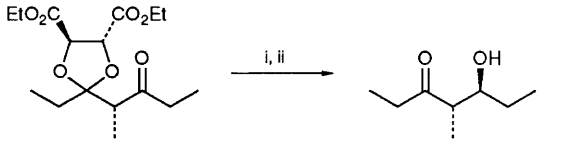


a: $R^1 = R^2 = Me$, $R^3 = Et$
b: $R^1 = Me$, $R^2 = Et$, $R^3 = Pr^n$
c: $R^1 = R^3 = Et$, $R^2 = Me$
d: $R^1 = R^2 = R^3 = Et$
e: $R^1 = Et$, $R^2 = R^3 = Pr^n$
f: $R^1 = Ph$, $R^2 = R^3 = Pr^n$

Scheme 1 *Reagents and conditions*: i, $BF_3{\cdot}OEt_2$, 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 $BF_3{\cdot}OEt_2$ in MeOH–CH_2Cl_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 configuration 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-one[5] have a positive specific rotation value.¶



3c
d. e. = 72%

4
anti / *syn* = 5 : 1[a]
$[\alpha]_D^{25}$ + 24.2° (*c* 0.8 in Et_2O)
[a] determined by GC and NMR

Scheme 2 *Reagents and conditions*: i, Bu^i_2AlH (5 equiv.), Et_2O, −80 °C; ii, $BF_3{\cdot}OEt_2$, MeOH, CH_2Cl_2, room temp.

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.

We thank the Consiglio Nazionale delle Ricerche, 'Progretto Chimica Fine 2,' Roma, for financial support.

Received, 15th October 1990; Com. 0/04635C

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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 ^{13}C NMR spectrum. For **4** $[\alpha]_D^{25}$ + 24.2° (*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 $BF_3{\cdot}OEt_2$ in MeOH–CH_2Cl_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*) $[\alpha]_D^{23}$ −37.8° (*c* 1.20 in diethyl ether), (4*S*,5*S*) $[\alpha]_D^{22}$ +36.8° (*c* 1,25 in diethyl ether), (4*R*,5*S*) $[\alpha]_D^{20}$ −26.7° (*c* 1.52 in diethyl ether), (4*S*,5*R*) $[\alpha]_D^{20}$ +27.0° (*c* 1.24 in diethyl ether).[5]