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LEWIS ACID PROMOTED ALDOL ADDITIONS OF α-THIOSILYLKETENE ACETALS TO α-ALKOXY ALDEHYDES: DIASTEREOSELECTIVE SYNTHESIS OF syn-α-METHYLENE-β-HYDROXY-γ-ALKOXY ESTERS.

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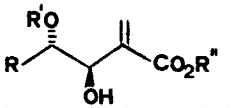
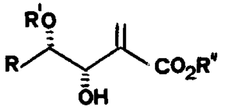
Abstract: MgBr$_2$ mediated addition of Methyl α-methylthio propionate silylketene acetal to α and α,β-alkoxy aldehydes is highly 3,4 syn-selective (18:1). syn-α-methylene-β-hydroxy-γ-alkoxy esters (6) and (8) are synthesized.

We recently reported that t butyl-β-dimethylamino propionate, a synthetic equivalent of t-butyl acrylate, readily reacts with α-alkoxy aldehydes to give anti-α-methylene-β-hydroxy-γ-alkoxy esters (1) (Felkin-Anh products) with high selectivity.[1] The double bond of these compounds and of the corresponding γ-lactones was further elaborated and some branched sugars were obtained in the ribo and arabino series.[2]

As a development of this project, we became interested in the stereoselective synthesis of the syn analogues (2) (chelation-controlled products).



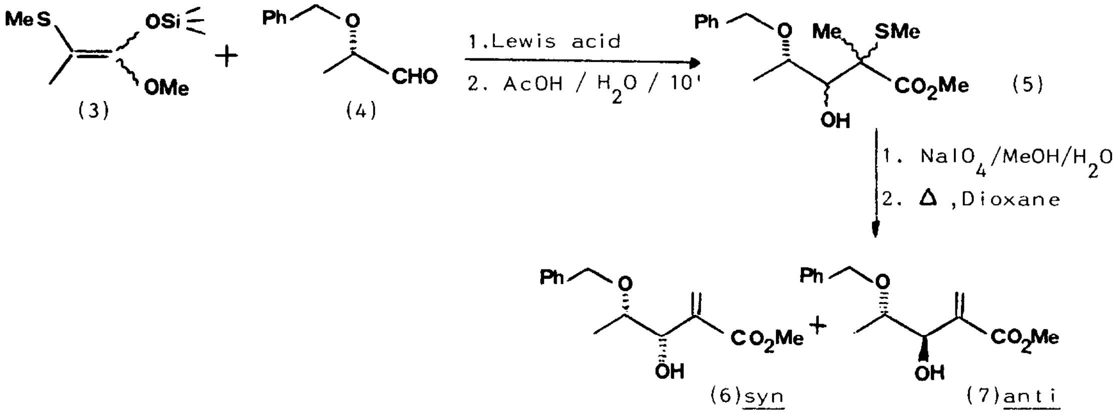
(1), anti

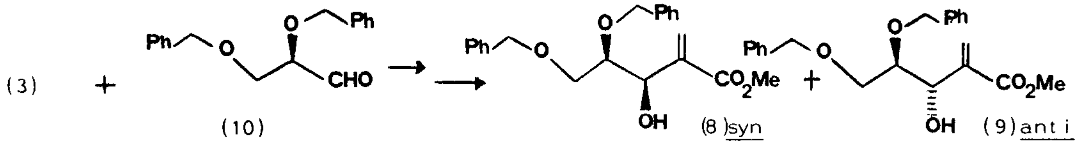


(2), syn

It is well known that silylketene acetals under chelating Lewis acids catalysis give 3,4-syn aldols in the reactions with α-alkoxy aldehydes[3], so that the most straightforward way to achieve our goal seemed to be the use of the thiolactic acid derivative (3)[4] as an acrylate equivalent.[5]

Esters (2) can be easily obtained after reaction of (3) with the appropriate aldehyde, through oxidation and pyrolysis of the resulting sulfoxide. Actually, reaction of (3) with O-benzyllactic aldehyde (4) resulted in a complex mixture of aldols (5) and of their O-silylated derivatives. The crude reaction mixture was treated with AcOH/H$_2$O, in order to hydrolize the silylether and then it was submitted without purification to the oxidation-elimination steps. The same procedure was applied to the glyceraldehyde derivatives; overall yield ranged in all cases from 50 to 65%.





Products (6), (7), (8) and (9) were unambiguously identified by their spectral properties.[6,7]

We examined various Lewis acids and the stereochemical results are summarized in Table. Unexpectedly $TiCl_4$ failed to promote the reaction between (3) and O-benzyllactic aldehyde (entry 1). $SnCl_4$ gave an almost equimolar mixture of (6) and (7) (entry 2) and a syn:anti ratio 1:3 with dibenzyl glyceraldehyde (entry 7). Although $SnCl_4$ is known to be very efficient in promoting α-chelation with α and α,β-alkoxy aldehydes[3,8], when an α-hetero substituted silylketene acetal is involved in the reaction the syn:anti selectivity has been shown to decrease in most cases.[9] Our speculation is that the silylether hetero-atom can disturb the aldehyde α-oxygen coordination to the already coordinatively saturated metal and could be responsible for the observed behaviour. Actually better results were obtained using a coordinatively unsaturated aldehyde-Lewis acid complex (entries 3, 4, 5, 6). With $MgBr_2$ an almost complete α-chelation-controlled diastereofacial preference was obtained with both aldehydes (entries 5, 6)

The application of this procedure to the synthesis of lyxo and xylo monosaccharides is under current investigation.

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Table. Addition of (4) to alkoxy aldehydes.[a]

Entry	Aldehyde	Lewis Acid	Condensation Conditions	*syn*/*anti*[b] ratio
1	(4)	$TiCl_4$	-78 °C → 0 °C[c]	=
2		$SnCl_4$	-78 °C / 1h	1.1 : 1
3		$ZnCl_2$	-40 °C / 3h	2 : 1
4		$MgBr_2$	-40 °C / 3h	11 : 1
5		$MgBr_2$	-78 °C / 8h	18 : 1
6	(10)	$MgBr_2$	-78 °C→ 0 °C / 2h	18 : 1
7		$SnCl_4$	-78 °C / 4h	1 : 3

a. Condensations were carried out by addition of 1.0 mol.-equiv. of the indicated Lewis acid to a solution of the aldehyde in CH_2Cl_2 at the reported temperature, followed by addition of (3) (2.0 mol.-equiv.).

b. Determined by HPLC and ^{1}H-NMR except for entries 6 and 7 which were determined by ^{13}C-NMR.

c. The reaction failed to give the expected products. Raising the temperature to 25 °C resulted in extensive decomposition of reactants.

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2. A.Bernardi, M.G.Beretta, L.Colombo, C.Gennari, G.Poli, C.Scolastico, *J.Org.Chem.*, in press.
3. C.Gennari, A.Bernardi, G.Poli, C.Scolastico, *Tetrahedron Lett.*,2373 (1985), M.T.Reetz *Angew.Chem.Int.Ed.Ingl.*, 556 (1984) and references therein; M.T.Reetz, K.Kesseler, A.Jung, *Tetrahedron*, *40*, 4327 (1984).
4. (3) was synthesized as a 75:25 mixture of diastereoisomers from methyl-2-methylthio propionate by LDA enolization (THF,-78 °C) and Me_3SiCl trapping (-78°C → room temperature). The reaction was worked up by evaporation avoiding water-quenching.
5. The lithium enolate of Ethyl (α-phenylthio)-propionate has been used as an acrylate equivalent in the addition to α-acetoxy aldehydes by Benezra: P.Barbier, C.Benezra,

J.Org.Chem., 48, 2705 (1983).

6. For the configurational assignment of α-methylene-β-hydroxy-γ-alkoxy esters via ^{13}C and ^{1}H-NMR see: L.Banfi, D.Potenza, G.S.Ricca, Org.Magn.Res., 224 (1984).

7. 80MHz ^{1}H-NMR ($CDCl_3/D_2O$) δ

(6): 1.22(3H,d,J=6.4Hz), 3.73(3H,s), 3.55-3.85(1H,m), 4.35-4.70(3H,m), 5.91(1H,t, J=1.2Hz), 6.31(1H,m), 7.30(5H,s).

(7): 1.09(3H,d,J=6.3Hz), 3.73(3H,s), 3.70-4.10(1H,m), 4.35-4.70(3H,m), 6.00(1H,t, J=1.3Hz), 6.31(1H,m), 7.35(5H,s).

25.14MHz ^{13}C-NMR ($CDCl_3$) selected data δ

(8): 51.5, 70.6, 70.8, 73.2, 73.3, 78.5, 126.0, 137.9, 140.2.

(9): 51.6, 69.6, 71.5, 72.2, 73.4, 79.1, 126.3, 138.1, 139.3.

8. The $SnCl_4$ catalyzed reaction between (10) and t-butyl thiopropionate silylketene acetal gave only the α-chelation (3,4-syn) product. C.Gennari et al., submitted for publication in Tetrahedron.

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