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Aldolisation-Type Reaction versus Michael-Type Addition. Hemiacetal Vinylogs: Versatile Synthons.

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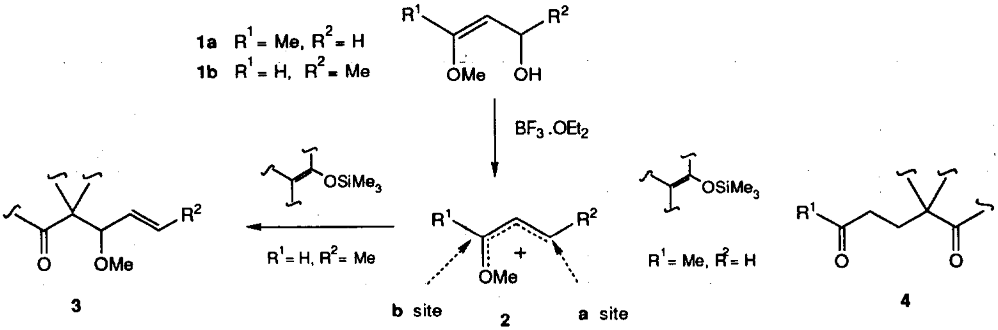
Abstract: Depending on the steric hindrance of the reaction centers, hemiacetal vinylogs **1** in the presence of $BF_3.OEt_2$ can, with enol ethers, lead to a Michael-type addition (**4**) or an aldolisation-type reaction (**3**). Hemiacetal vinylog **1b** always yields the second reaction leading to β-methoxy-γ,δ-ethylenic carbonyl compounds **4** precursors of polyenic carbonyl compounds **5**. Crotonaldehyde and methanol can be used instead of compound **1b**.

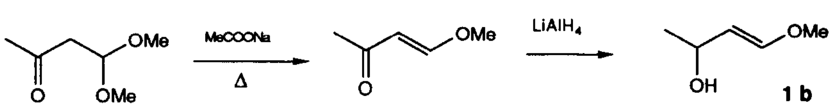
We have previously reported[1] that the hemiacetal vinylog **1a** (R^1 = Me, R^2 = H, synthetic equivalent of methyl vinyl ketone), in the presence of boron trifluoride etherate, leads to a carbocationic species **2** which exhibits two electrophilic reaction centers "**a**" and "**b**". In the presence of an enol ether, the reaction occurred only on the site "**a**" yielding a 1,5-dicarbonyl compound **4** via a Michael-type addition, even with hindered enol ethers (scheme 1).



Scheme 1

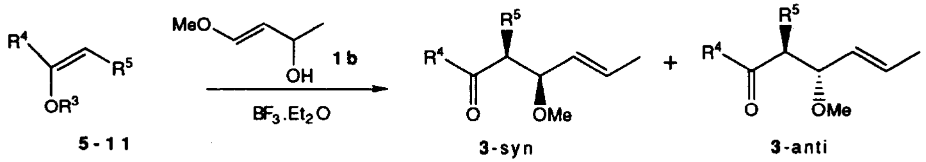
The present paper describes the reaction of isomeric hemiacetal vinylog **1b** (R^1 =H, R^2 = Me, synthetic equivalent of crotonaldehyde) with enol ethers in the presence of boron trifluoride etherate as a catalyst.[2]

Compound **1b** was easily prepared by heating commercially available 4,4-dimethoxy-2-butanone in the presence of sodium acetate followed by reduction of the ketone moiety by $LiAlH_4$ in 49% overall yield (scheme 2)



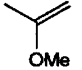
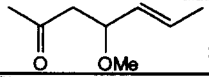
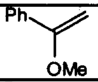
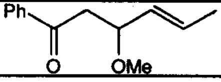
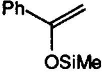
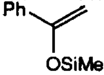
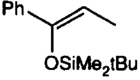
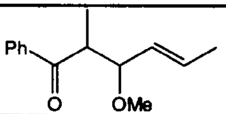
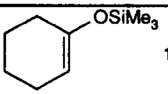
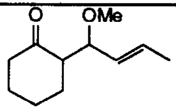
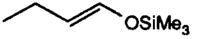
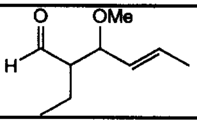
Scheme 2

With enol ethers **5-11**, the aldol reaction product **3** is always obtained without Michael product **4** (Table I).The reaction may be carried out in nitromethane at -25°C as in methylene chloride at -78°C[3] but the yield is always higher in nitromethane. The reaction products obtained (scheme 3) clearly show that enol ethers react exclusively on the "**b**" site of compound **1b** whereas they react exclusively on the "**a**" site of compound **1a**



Scheme 3

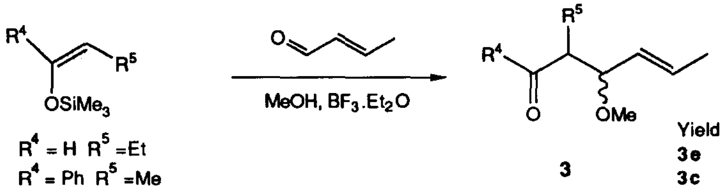
Table I: Preparation of β-alkoxy-γ,δ-ethylenic carbonyl compounds **3**

Entry	Starting enol ether	Method[a]	Reaction product	yield %[b]
1	 **5**	A B	 **3 a**	56 35
2	 **6**	A B	 **3 b**	50 37
3	 **7**	A	**3 b**	30
4	 **8**	A	**3 b**	35
5	 **9**	A	 **3 c**	49 syn/anti = 70/30
6	 **1 0**	A	 **3 d**	51 syn/anti = 70/30
7	 **1 1**	A	 **3 e**	39 syn/anti = 72/28

a) Method A : $MeNO_2$, -25°C, 30 min; Method B : CH_2Cl_2, -78°C, 2 hours. b) yield of product purified by flash chromatography.

Replacing the silyl enol ethers **7** or **8** by the methyl enol ether **6** increased the yield probably due to a higher stability towards the breaking ability of Lewis acid. In the case of enol ethers **9-11** bearing a substituent R^5, the syn-adduct was preferentially obtained (Table I, entries 5-7) as shown by ^1H NMR spectra.[4]

The hemiacetal vinylog **1b** is the synthetic equivalent of crotonaldehyde and as we have shown that hemiacetal vinylog **1a** can be replaced by a mixture of methyl vinyl ketone and an alcohol in stoechiometric conditions,[1f,5] we decided to try using crotonaldehyde and methanol (scheme 4) in this reaction. As anticipated, product **3** was obtained alone.



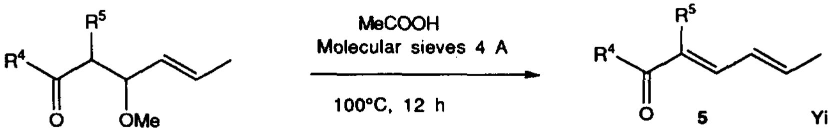
$R^4 = H$ $R^5 = Et$
$R^4 = Ph$ $R^5 = Me$

	Yield %	
3e	40	syn/anti = 72/28
3c	61	syn/anti = 70/30

Scheme 4

For compound **3e** the yield was the same as for the precedent run with hemiacetal vinylog **1b** (entry 7, Table 1) and a little higher for **3c**. The ratio syn/anti products was the same.

The conversion of compounds **3** into polyunsaturated carbonyl compounds was examined under acidic[6a,b,7, 8] and basic[9a,b, 10] conditions. The best results were obtained when compounds **3** were treated by acetic acid in the presence of molecular sieves at 100°C for 12 hours to yield the corresponding polyethylenic carbonyl compounds **5** (scheme 5) in moderate yields.



3a $R^4 = Me$ $R^5 = H$
3b $R^4 = Ph$ $R^5 = H$
3e $R^4 = H$ $R^5 = Et$

	Yield %
5a	46
5b	39
5e	47

Scheme 5

The here reported reactions are of Müller-Cunradi, Pieroh type.[11] The intermediate cationic species **2** ($R^1 = H$, R^2 = alkyl) that we proposed from hemiacetal vinylog **1b** or more conveniently from a mixture of unsaturated aldehydes and alcohols are classically obtained from ketals of conjugated carbonyl compounds.[6, 11-13] Such species also arise from the oxydation of allylic enol ethers.[14]

Thus we have shown that the simple modification of the steric hindrance of the two reaction centers "**a**" and "**b**" of the hemiacetal vinylog **1** is of sufficient importance to change the reaction type completely: a Michael-type addition with compound **1a** or an aldolisation-type reaction with the isomeric structure **1b**. In both cases the hemiacetal vinylog may be replaced by a mixture of unsaturated carbonyl compound and alcohol, MVK for **1a**[1f,5] and crotonaldehyde for **1b**.

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3) To 10 mmol of starting enol ether in 5 mL of nitromethane (or methylene chloride) was added 5 mmol of hemiacetal vinylog (0.5 g) in 5 mL of nitromethane (or methylene chloride). The solution was cooled to -25°C (or -78°C) then 250 µL of boron trifluoride cherate diluted with 240 µL of diethylether was added. Stirring was continued for 30 minutes (or two hours) (CCM control). The mixture was then allowed to warm to 0°C and 5 mL of a saturated aqueous solution of $NaHCO_3$ was added. After extraction with methylene chloride (4 x 10 mL) the organic layers were dried ($MgSO_4$) filtered and evaporated. The compounds **3** were purified by flash chromatography (Et_2O/ light petroleum: 8/100).

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