

85. Stereoselective Reduction of δ -Hydroxy- β -ketoesters

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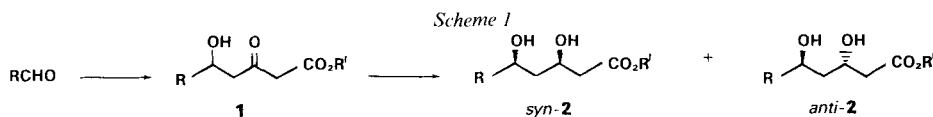
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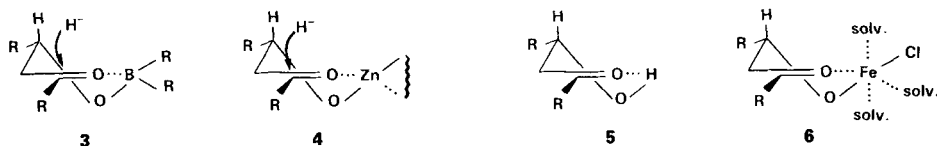
The reduction of δ -hydroxy- β -ketoesters **1** was investigated with three different reducing agents. In several instances, high selectivity in favor of *syn*-1,3-diols was observed.

Stereoselective preparation of the 1,3-diol function has great utility in synthetic organic chemistry due to the occurrence of these fragments in several natural products. In connection with our work on compactin analogues [1], we needed an efficient and general method for preparing *syn*-1,3-diols.

Towards this objective, we have prepared [2] a series of δ -hydroxy- β -ketoesters **1** (Scheme 1) by the addition of acetoacetate dianion to the respective aldehydes and investigated their reductions with different agents.



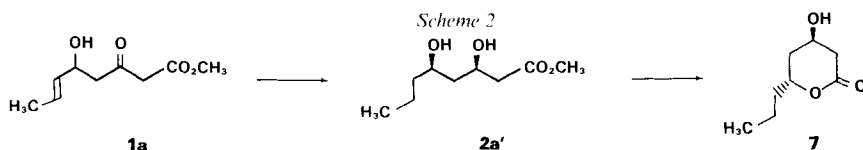
Stereoselective reductions of β -hydroxy-ketones utilizing metal-chelation control have recently been reported in the literature. The boron-chelate method [3], which gives excellent selectivity in favor of the *syn*-diols, invokes cyclic complexes **3** for explaining the stereochemical outcome of the reduction. In the alternative $\text{Zn}(\text{BH}_4)_2$ method [4], the setup for the reduction is presumed to be **4**.



At the outset of our investigations with δ -hydroxy- β -ketoesters, we were intrigued by the possibility that a simple H-bond as shown in **5** may provide a sufficiently strong bridge for achieving the desired *syn*-selectivity. Accordingly, we examined the hydrogenation of **1a**²⁾ using 5% Pt/C (room temperature, 50 psi) in MeOH. Under these condi-

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²⁾ All the hydroxy-ketoesters **1a-k** described are derived from the addition of acetoacetate dianion to the corresponding aldehydes, following [2].



tions, the hydrogenation of the olefinic double bond was faster than that of the desired C=O bond. When the hydrogenation was allowed to proceed for three days, the diol **2a'** was isolated in 60% yield. Interestingly, the product was found to be stereochemically completely homogeneous, and the spectroscopic data³⁾ indicated it to be pure *syn*-isomer. The relative configuration of the two OH groups was further confirmed by the transformation to the *trans*-lactone **7**.

Addition⁴⁾ of FeCl₂ to the hydrogenation mixture enhanced the reduction rate of the carbonyl group, possibly *via* complex **6**, but gave a *syn/anti* diastereoisomeric ratio of 9:1. On the other hand, **1d** and **1e** (see Table 1) exhibited the same selectivity with or without FeCl₂. As the hydrogenation is faster in the presence of FeCl₂, this method (*Method A*) was examined in greater detail. It turned out that the ratio of the *syn*- and *anti*-isomers formed in these hydrogenations is dependent on the size of groups R and R' present in the

Table 1. Stereoisomer Ratios in the Reduction of δ -Hydroxy- β -ketoesters

Starting Ketone	R	R'	Product ^{a)}	<i>syn/anti</i> Ratios (yield [%])		
				<i>Method A</i> ^{b)}	<i>Method B</i> ^{b)}	<i>Method C</i> ^{b)}
1a	CH ₃ CH=CH (<i>E</i>)	CH ₃	2a'	90:10(90)		
			2a		90:10(70)	91:9(69)
1b	CH ₃ CH=CH	C ₂ H ₅	2b'	76:24(63)		
			2b		–	90:10(80)
1c	CH ₃ CH=CH	(CH ₃) ₃ C	2c'	70:30(82)		
			2c		85:15(99)	80:20(87)
1d	CH ₂ =CH	C ₂ H ₅	2d'	78:22/74		
			2d		90:10(85)	89:11(48)
1e	PhCH=CH (<i>E</i>)	CH ₃	2e'	79:21(70)		
			2e		90:10(89)	92:8(60)
1f	Ph	C ₂ H ₅	2f	66:34(69)	87:13(34)	82:18(68)
1g	(CH ₃) ₂ CH	C ₂ H ₅	2g	75:25(77)	^{c)}	92:8(75)
1h	(CH ₃) ₃ C	C ₂ H ₅	2h	70:30(85)	^{c)}	75:25(92)
1i	(CH ₃) ₃ C	(CH ₃) ₃ C	2i	56:44(93)	–	65:35(76)
1j	PhCH ₂ OCH ₂	C ₂ H ₅	2j	52:48(25)	75:25(66)	60:40(51)
1k	(<i>t</i> -Bu)Ph ₂ SiOCH ₂	C ₂ H ₅	2k	51:49(62)	90:10(82)	92:8(87)

^{a)} All the primed numbers (**2a'**, etc.) correspond to those diols in which the olefin was reduced by hydrogenation.

^{b)} *Method A*: FeCl₂, H₂, 50 psi, 20°, MeOH if R'=CH₃, otherwise EtOH, 18 h.

Method B: Et₃B, air, THF, 20°, 2 h; – 78°, NaBH₄, 18 h.

Method C: Zn(BH₄)₂, Et₂O, – 20°, 30 min.

^{c)} The isolation of diol presented problems due to incomplete hydrolysis of boronates.

³⁾ ¹³C-NMR (CDCl₃) of **2a'** (*syn*-isomer): 172.80; 71.89; 69.00; 51.71; 42.31; 41.61; 40.01; 18.46; 13.99.

¹³C-NMR (CDCl₃) of **7**: 171.63; 75.91; 61.75; 38.11; 37.18; 35.26; 17.72; 13.44.

⁴⁾ On addition of FeCl₂ to the β -ketoester, the solution turns dark red; the color disappears on complete hydrogenation.

starting ketoesters: the smaller the size of R and R', the better the selectivity in favor of the *syn*-isomer.

With these results in hand, we turned our attention to the applicability of literature methods, *i.e.* the boron-chelate method [3] (BEt_3 , air, THF, 20°, 2 h; – 78°, NaBH_4 , 18 h; *Method B*) and the zinc-borohydride method [4] ($\text{Zn}(\text{BH}_4)_2$, ether, – 20°; *Method C*), for the stereoselective reduction of the above hydroxy-ketoesters. The results are presented in *Table 1*. It appears that *Methods B* and *C* are generally comparable in their *syn*-selectivity and that the selectivity does not depend on the substituents R and R' except when R contains a competing chelating atom (see **1j**).

The *syn/anti* ratio was estimated on the basis of the relative intensity of the two sets of C(13) signals of the stereogenic [5] C-atoms. The chemical shift values are listed in *Table 2*. The accuracy of the ^{13}C -NMR method was counter-checked by HPLC with **1c** and **1i**.

Table 2. ^{13}C Chemical Shifts of the Two Stereogenic C-Atoms in the Diols **2** and **2'**

Compound	<i>syn</i> -Isomer		<i>anti</i> -Isomer	
	C(δ)	C(β)	C(δ)	C(β)
2a	72.57	68.12	69.70	65.42
2a'	71.89	69.00	68.53	65.58
2b	72.53	68.15	69.70	65.44
2b'	71.92	69.06	68.56	65.67
2c	72.59	68.39	69.85	65.70
2c'	71.80	69.23	68.53	65.82
2d	72.56	68.17	68.87	65.41
2d'	73.26	68.85	69.91	65.47
2e	72.51	68.16	69.78	65.49
2e'	71.37	68.93	68.28	65.62
2f	74.28	68.53	71.04	65.50
2g	76.91	69.15	73.32	65.76
2h	79.89	69.29	75.66	65.99
2i	80.12	69.73	75.63	66.17
2j	70.43	68.87	67.60	65.35
2k	71.64	68.83	67.61	65.11

Further work on the selective reductions of related optically active hydroxy-ketoesters, which could result in synthetically useful 1,3-diol derivatives, is in progress.

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