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

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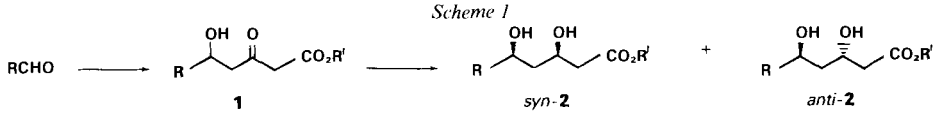
The reduction of δ-hydroxy-β-ketoesters **1** was investigated with three different reducing agents. In several instances, high selectivity in favor of *syn*-1,3-diols was observed.

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.

*Scheme 1*



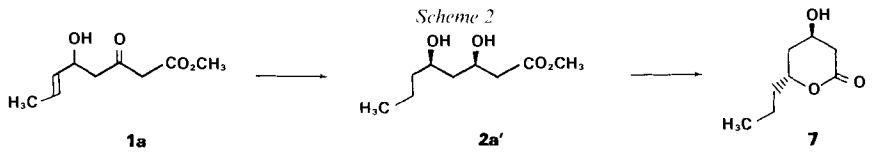

Stereoselective reductions of β-hydroxy-ketones utilizing metal-chelation control have recently been reported in the literature. The boron-chelate method [3], which gives excellent selectivity in favor of the *syn*-diols, invokes cyclic complexes **3** for explaining the stereochemical outcome of the reduction. In the alternative $Zn(BH_4)_2$ 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-

[1]) Present address: *Ciba-Geigy AG*, CH-4002 Basel.

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

*Scheme 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 data[3]) 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**.

Addition[4]) of $FeCl_2$ 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 $FeCl_2$. As the hydrogenation is faster in the presence of $FeCl_2$, 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]) | *syn/anti* Ratios (yield [%]) | | |
|---|---|---|---|---|---|---|
| | | | | *Method A*[b]) | *Method B*[b]) | *Method C*[b]) |
| **1a** | $CH_3CH$=CH (*E*) | $CH_3$ | **2a'** | 90:10(90) | | |
| | | | **2a** | | 90:10(70) | 91:9(69) |
| **1b** | $CH_3CH$=CH | $C_2H_5$ | **2b'** | 76:24(63) | | |
| | | | **2b** | | – | 90:10(80) |
| **1c** | $CH_3CH$=CH | $(CH_3)_3C$ | **2c'** | 70:30(82) | | |
| | | | **2c** | | 85:15(99) | 80:20(87) |
| **1d** | $CH_2$=CH | $C_2H_5$ | **2d'** | 78:22/74) | | |
| | | | **2d** | | 90:10(85) | 89:11(48) |
| **1e** | PhCH=CH (*E*) | $CH_3$ | **2e'** | 79:21(70) | | |
| | | | **2e** | | 90:10(89) | 92:8(60) |
| **1f** | Ph | $C_2H_3$ | **2f** | 66:34(69) | 87:13(34) | 82:18(68) |
| **1g** | $(CH_3)_2CH$ | $C_2H_5$ | **2g** | 75:25(77) | [c]) | 92:8(75) |
| **1h** | $(CH_3)_3C$ | $C_2H_5$ | **2h** | 70:30(85) | [c]) | 75:25(92) |
| **1i** | $(CH_3)_3C$ | $(CH_3)_3C$ | **2i** | 56:44(93) | – | 65:35(76) |
| **1j** | $PhCH_2OCH_2$ | $C_2H_5$ | **2j** | 52:48(25) | 75:25(66) | 60:40(51) |
| **1k** | (*t*-Bu)$Ph_2SiOCH_2$ | $C_2H_5$ | **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:* $FeCl_2$, $H_2$, 50 psi, 20°, MeOH if R'=$CH_3$, otherwise EtOH, 18 h.
*Method B:* $Et_3B$, air, THF, 20°, 2 h; – 78°, $NaBH_4$, 18 h.
*Method C:* $Zn(BH_4)_2$, $Et_2O$, – 20°, 30 min.

[c]) The isolation of diol presented problems due to incomplete hydrolysis of boronates.

[3]) $^{13}$C-NMR ($CDCl_3$) of **2a'** (*syn*-isomer): 172.80; 71.89; 69.00; 51.71; 42.31; 41.61; 40.01; 18.46; 13.99. $^{13}$C-NMR ($CDCl_3$) of **7**: 171.63; 75.91; 61.75; 38.11; 37.18; 35.26; 17.72; 13.44.

[4]) On addition of $FeCl_2$ 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] ($Zn(BH_4)_2$, 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 | *syn*-Isomer | | *anti*-Isomer | |
|---|---|---|---|---|
| | C($\delta$) | C($\beta$) | C($\delta$) | C($\beta$) |
| **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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