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Diastereoselectivity in the Bakers Yeast Reduction of [1-^{2}H](Sorbaldehyde)Fe(CO)$_3$

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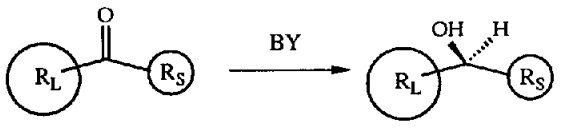
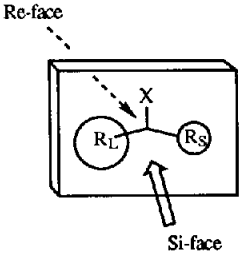
Abstract: Bakers yeast reduction of the faster reacting (2*S*) enantiomer of [1-^{2}H](sorbaldehyde) Fe(CO)$_3$ proceeds with complete diastereoselectivity. Little or no diastereoselectivity is observed in bakers yeast reduction of the slower reacting (2*R*) enantiomer or in the reduction of the racemic complex with $NaBH_4$.

INTRODUCTION

Biotransformations using bakers yeast have received much attention in recent years, particularly (but not exclusively) in the asymmetric reduction of carbonyl compounds.[1] Though several exceptions have been reported, the reactions may generally be viewed as proceeding according to Prelog's rule[2] *via* hydrogen transfer to the *re* face of a prochiral carbonyl with R_L and R_S representing large and small substituents adjacent to the carbonyl group.





For ketones containing chiral substituents, bakers yeast reductions have been widely used for resolution in both organic[1] and, to a lesser extent, in organometallic systems.[3] Such resolutions depend either on differences in the rate of reduction of the enantiomers of the racemate, or since the *re* selectivity is essentially maintained for both enantiomers, formation of separable diastereoisomers from which the optically pure ketones can be regenerated by oxidation. In the case of non-deuteriated aldehydes, such diastereoisomer formation is not possible, and relatively few examples of kinetic resolution of organic aldehydes have been reported;[4] the use of bakers yeast for resolution of organometallic aldehydes having planar chirality is more extensive.[5] Though several achiral organic[6] and organometallic[3b, 5b, 7] deuteroaldehydes have been reduced with high enantioselectivity to (*S*)-RCHD(OH) derivatives, we are not aware of any study of the

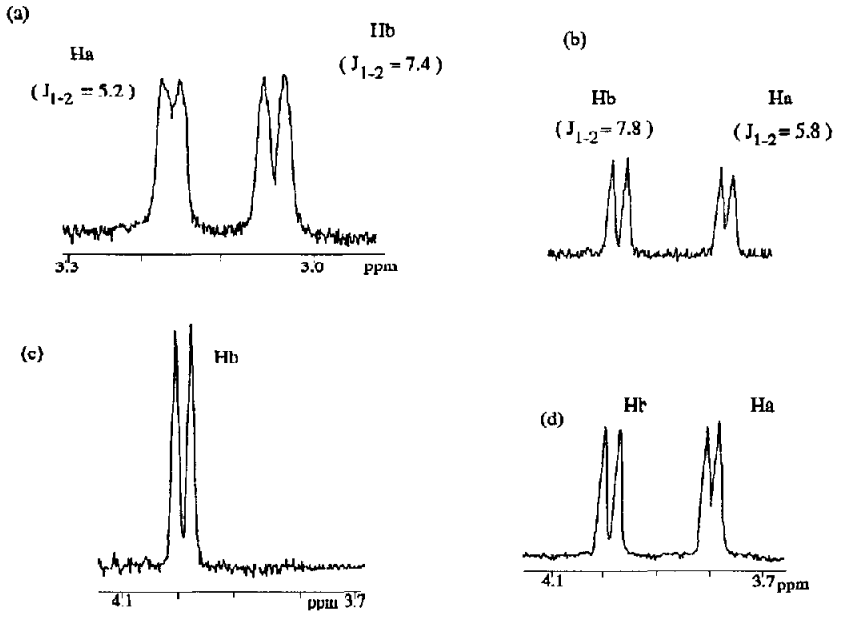
relative diastereoselectivity of bakers yeast reduction of a chiral organometallic or organic deuterioaldehyde. Following our successful kinetic resolution of (sorbaldehyde)Fe(CO)3 using bakers yeast,[5c] we wish to report here our results on the diastereoselectivity of the reduction of (2*S*)- and (2*R*)-[1-^{2}H](sorbaldehyde)Fe(CO)3 which demonstrate the importance of both planar chirality and aldehyde configuration in the diastereoselection process.

RESULTS AND DISCUSSION

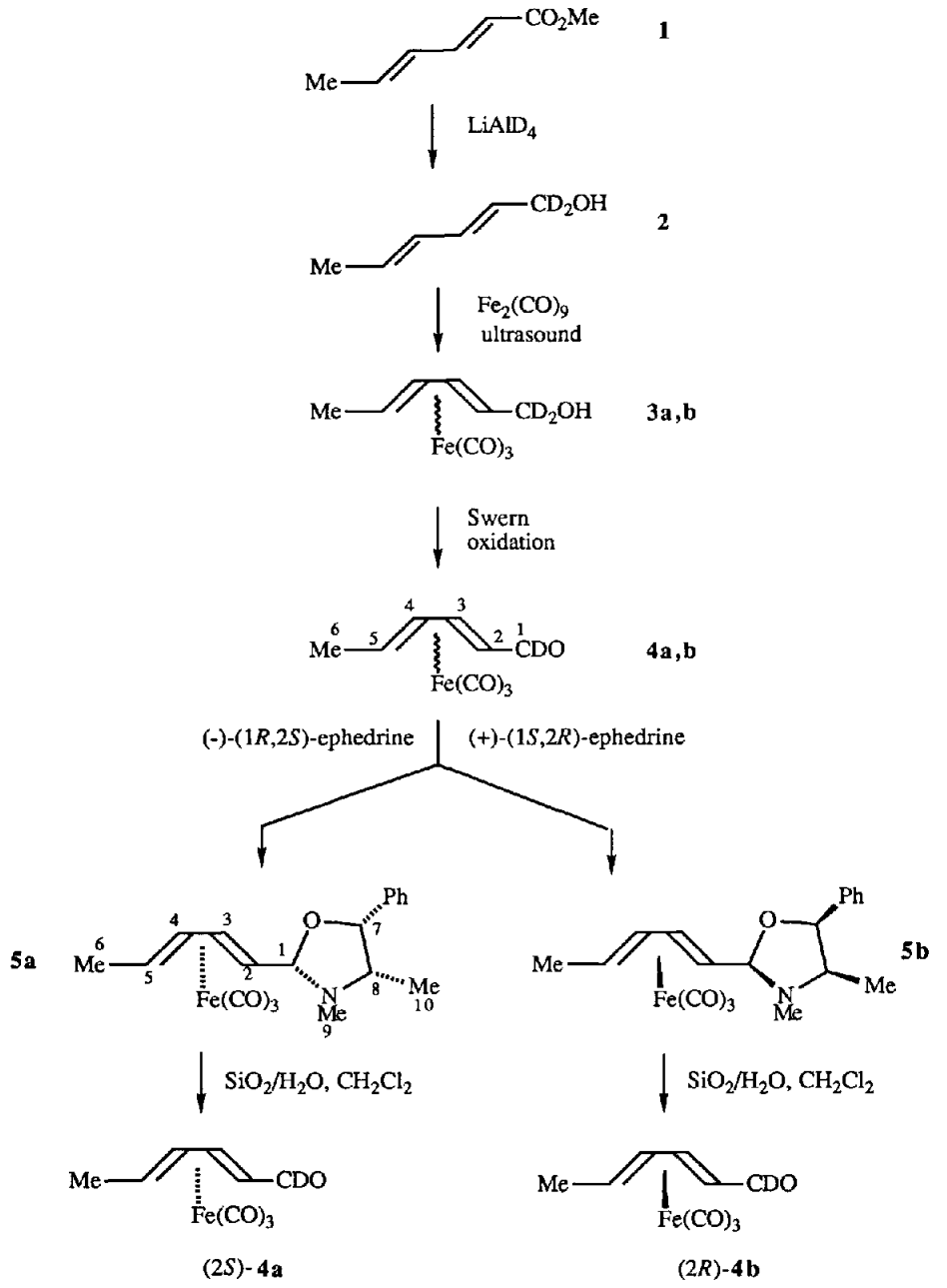
The [1-^{2}H] derivative **4** was prepared by reduction of methyl sorbate **1** with LiAlD4 (98 %) to give **2** followed by complexation and Swern oxidation to give racemic **4**. To avoid any ambiguity in the bakers yeast reduction, **4a,b** was resolved at this stage by treatment with either (-)- or (+)-ephedrine.[8] Fractional crystallisation provided the enantiomers **5a,b** of defined absolute configuration[9] from which the enantiomerically pure deuterioaldehyde was regenerated by mild hydrolysis.

Consistent with our results on kinetic resolution,[5e] the (2*S*) enantiomer is rapidly consumed (4 hours) by bakers yeast to yield the alcohol **6a** whose NMR spectrum in the H1 region contains only a single doublet resonance, consistent with complete diastereoelectricity in the reduction process. In contrast, consumption of **4b** is much slower (50 % after 15 hours) and the NMR spectrum in the H1 (Figure 1) region contains two doublets of equal intensity assignable to **6b** and **7b**, indicating no diastereoselection in the reduction process.

Figure 1. ^{1}H NMR Spectra of Monodeuteriated Alcohols and Acetates (C_6D_6)



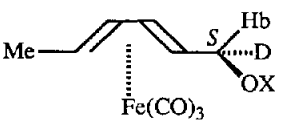
(a) 6b/7b from BY reduction of 4b
(b) 8b/9b from BY reduction of 4b
(c) 8a from BY reduction of 4a
(d) 8a,b/9a,b from $NaBH_4$ reduction of 4a,b

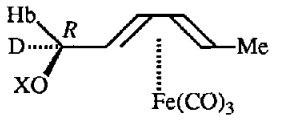


Scheme 1

Spectra which are sharper (due to the absence of O-H coupling) and with a greater chemical shift difference may be obtained by conversion to the acetates **8a** and **8b/9b** (Figure 1), though integration and coupling

constants clearly show a reversal of the chemical shift ordering of Ha and Hb. Molecular modelling studies,[10] coupled with several crystallographic studies,[11] indicate that the OH or OAc group will occupy the least sterically hindered position shown below, perpendicular to the diene plane. Ha and Hb will thus differ in chemical shift and coupling to H2.

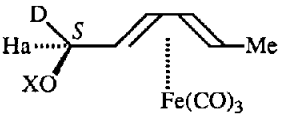




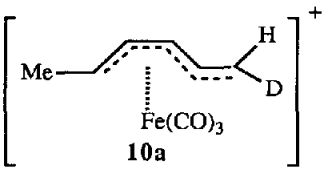
6a X = H
8a X = CH_3CO

6b X = H
8b X = CH_3CO

CD_2Cl_2, -25 °C | + HSO_3F - HOAc

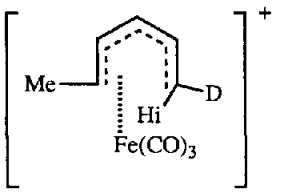


7b X = H
9b X = CH_3CO

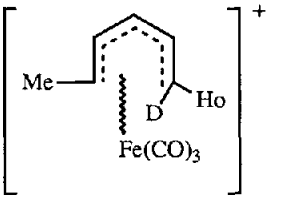


10a

rapid



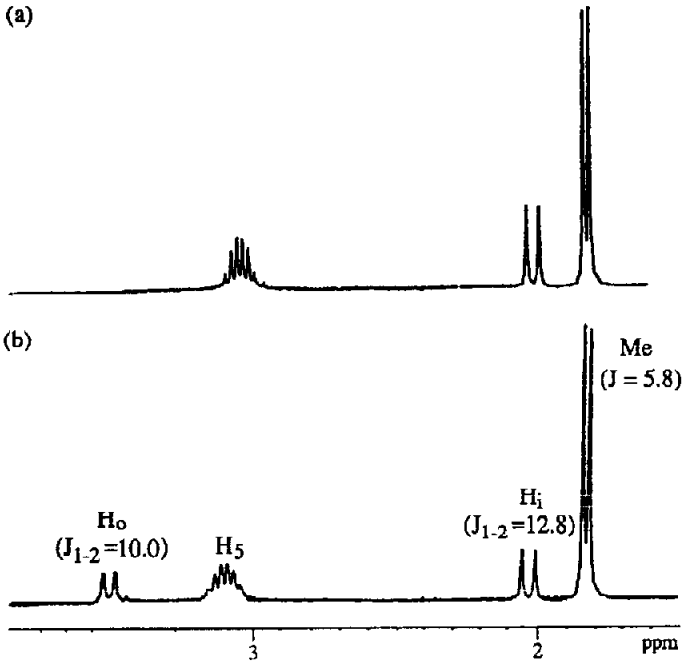
11a



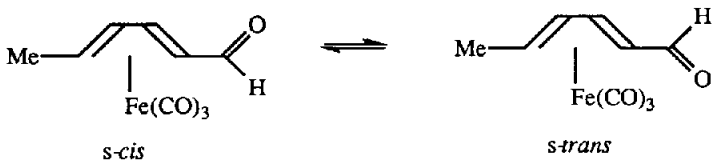
12a,b

The (*S*)-C1 stereochemistry assigned to **6a** is consistent with reduction of other deuteriated aldehydes by bakers yeast, and has been confirmed by *in situ* protonation of the acetate **8a** using HSO_3F/CD_2Cl_2 at low temperature. Literature data[12] on protonation of **7** and **8** with methyl in place of deuterium show that protonation is stereospecific at low temperature, and extension to **8a** predicts that protonation/elimination should yield the initial intermediate *trans*-pentadienyl cation **10a** which rapidly undergoes bond rotation to give the *cis*-cation **11a**. The high field part of the ^1H NMR spectrum of the resultant cation **11a** is illustrated in Figure 2a, together in 2b with that of a racemic mixture of **11a,b** and **12a,b** produced by protonation of a 1:1 mixture of the racemic acetates **8a,b/9a,b** derived *inter alia* from $NaBH_4$ reduction of **4a,b** (*vide infra*). In Figure 2b, two doublet resonances are seen at 2.05 and 3.51 ppm assignable to the inner (Hi) and outer (Ho) terminal dienyl protons respectively[12] of the **11a,b/12a,b** mixture. In Figure 2a, the low field doublet is entirely absent, indicating the presence of only **11a**. This cation is configurationally stable, exhibiting no deuterium scrambling between Hi and Ho over a period of hours at +10 °C.

Figure 2. ^{1}H NMR Spectra of Dienyl Cations (HSO_3F / CD_2Cl_2, - 25°C)



NMR studies clearly show that [1-^{1}H] analogues of **4** exist in solution in an s-*cis*/s-*trans* equilibrium with respect to rotation about C1-C2.[9,13]



Though the barrier for s-*cis*/s-*trans* interconversion is too low to measure by NMR for the tricarbonyl complex, low temperature spectra for $Fe(CO)_2PR_3$ complexes[9] establish J_{1-2} values of ≤ 2 Hz for the s-*cis* isomer and 8 Hz for the s-*trans* isomer. For the [1-^{1}H] analogue of **4**, the average value of J_{1-2} in MeOD at 25 °C is 4.7 Hz, indicating an approximately equal concentration of both conformers. If Prelog's rule is obeyed, the results for **4a** thus indicate preferential reaction with only the s-*trans* conformer in which the *re* face of the aldehyde is exposed to attack. For **4b**, in which the *re* face is exposed in the s-*cis* conformer, no diastereoselectivity is observed. Thus, lack of recognition of planar chirality is accompanied by a lack of discrimination between conformational isomers. A similar diastereoselectivity is seen in the asymmetric allylboration of (sorbaldehyde)$Fe(CO)_3$[14] where the faster and slower reacting enantiomers also exhibit greatly different diastereoselectivities in the creation of the new chiral centre.

These results may be compared to the $NaBH_4$ reduction of racemic **4a,b** where the spectrum of the derived acetate (Figure 1) indicates only a slight excess of **6a,b** relative to **7a,b.** The spectrum of the acetate obtained by $NaBD_4$ reduction of (1-^{1}H)(sorbaldehyde)$Fe(CO)_3$ is identical but with the intensities of the Ha/Hb resonances reversed. Diastereoselectivity in this case broadly reflects the position of the conformational equilibrium.

Finally, it may be noted that coordination to iron protects the dienal from further double bond reduction by bakers yeast which occurs in the free ligand series.[15] In addition, literature results[16] indicate that nucleophilic displacement of acetate from **8a** should occur with complete retention of configuration, thus providing access to a wider range of enantiomerically pure CHD derivatives.

EXPERIMENTAL

NMR spectra were recorded using a JEOL GSX270 spectrometer; chemical shifts are relative to tetramethylsilane. Methyl sorbate[17] and [1-^{1}H](sorbaldehyde)$Fe(CO)_3$[8b] were prepared by literature methods. Preparative thin layer chromatography was performed on a Harrison Research 7924 Chromatotron using 2 mm silica gel (type PF60254) plates. Diethyl ether was distilled from $LiAlH_4$. Pyridine was distilled from KOH. DMSO and Et_3N were distilled from CaH_2 and stored over molecular seives under argon. CH_2Cl_2 was distilled from P_2O_5 under argon. Oxalyl chloride was distilled under argon and stored over molecular seives. Bakers yeast was obtained locally in Paris.

(a) Preparation of [1-^{2}H](sorbaldehyde)$Fe(CO)_3$ 4

A suspension of $LiAlD_4$ (98 %) (1.0 g, 23.8 mmol) in diethylether (30 ml) was cooled to -78 °C under nitrogen. With stirring, a solution of methyl sorbate (2.67 g, 23.8 mmol) in diethyl ether (30 ml) was added dropwise and the reaction was allowed to warm to room temperature. On completion (as judged by tlc), water (30 ml) was added followed by 10 % H_2SO_4 to dissolve the precipitate. After separation, the aqueous layer was extracted with chloroform (3 x 40 ml) and the combined organic extracts were washed with 10 % $NaHCO_3$ solution and dried over $MgSO_4$. Removal of solvent gave [1-$^2H_2$]2,4-hexadien-1-ol **2** as an oily solid (2.0 g, 85 %). NMR ($CDCl_3$): 5.6 - 6.3 (m, H2-5), 1.72 (dd, Me, J_{5-6} = 6.6, J_{4-6} = 1.2).

Compound **2** (1.0 g, 10.2 mmol) and $Fe_2(CO)_9$ (10.9 g, 30 mml) were stirred in toluene (30 ml) under argon in an ultrasonic bath until completion of reaction as judged by tlc. Diethyl ether (20 ml) was added and the suspension was filtered through celite. After removal of solvent, the crude product was purified by column chromatography (alumina IV, 4:1 petroleum ether (30-40): ethyl acetate) to give **3** as a brown oil (1.37 g, 56 %). A spectroscopic sample was purified by short-path distillation (125 °C, 0.1 mm Hg). Infrared (hexane): 2043, 1981, 1971 cm^{-1}; NMR ($CDCl_3$): 5.10 (m, H3,4), 1.04 (d, H2, J_{2-3} = 8.4), 1.21 (m, H5, J_{5-6} = 6.0), 1.38 (d, H6); the CH_2 resonance at 3.60 of the [1-$^1H_2$] complex is absent.

DMSO (0.39 ml, 5.06 mmol) in CH_2Cl_2 (1.0 ml) was added under argon to a stirred solution of oxalyl chloride (0.23 ml, 2.53 mol) in CH_2Cl_2 (5 ml) at -78 °C. After 10 minutes stirring, complex **3** (0.569 g, 2.3 mmol) in CH_2Cl_2 (0.5 ml) was added dropwise and the reaction was stirred at -78 °C for 25 minutes. NEt_3 (1.6 ml) was added and the reaction was allowed to warm to 10 °C. After addition of water (15 ml) and further CH_2Cl_2 (15 ml), the mixture was shaken vigorously to produce an orange/yellow two phase solution. Separation and extraction of the aqueous phase (CH_2Cl_2, 3 x 100 ml), followed by drying over $MgSO_4$ and

removal of solvent gave a brown oil which was purified by chromatotron (4:1 petroleum ether (30 - 40): ethyl acetate) to give **4** as a golden oil (0.25 g, 45 %). Infrared (hexane): 2059, 1999, 1983 cm^{-1}; NMR (C_6D_6): 0.66 (H2, d, J_{2-3} = 8.1), 5.08 (m, H3), 4.26 (m, H4), 0.83 (m, H5, J_{5-6} = 6.5), 1.48 (d, H6); the CHO resonance at 9.0 of the [1-^{1}H] complex is absent.

(b) Resolution of 4a,b

Details are given for the [1-^{1}H] analogue of **4**. (Sorbaldehyde)Fe(CO)3 (0.88 g, 3.73 mmol) and (-)-ephedrine (0.62 g, 3.73 mmol) were stirred in dichloromethane at room temperature under N_2 until infrared monitoring indicated complete consumption of starting material (ca. 2 hours). The mixture was filtered through celite and the solvent removed. Fractional crystallisation from petroleum ether (60-80) gave yellow crystals of the [1-^{1}H] analogue of **5a** (0.49 g, 34 %) as a yellow solid. M.p. 123-124 °C; analysis: calc. C-59.6, H-5.52, N-3.66 %, found C-59.8, H-5.60, N-3.49 %; infrared (hexane): 2047, 1983, 1975 cm^{-1}; NMR ($CDCl_3$): 3.35 (d, H1, J_{1-2} = 8.5), 0.97 (t, H2, J_{2-3} = 7.5), 5.18 (m, H3, J_{3-4} = 5.4), 5.02 (m, H4, J_{4-5} = 8.0), 1.26 (m, H5, J_{5-6} = 5.8), 1.37 (d, H6), 4.94 (d, H7, J_{7-8} = 8.1), 2.79 (m, H8, J_{8-10} = 6.6), 2.23 (s, H9), 0.57 (d, H10). Diastereoisomeric purity was assessed using either H1 or H7, which in the crude diastereoisomer mixture exhibit well distinguished additional doublet resonances at 3.72 and 4.88 ppm respectively. Treatment of **4a,b** with (-)- and (+)-ephedrine in a similar way provides **5a** and **5b** whose NMR spectra are identical and differ only from the [1-^{1}H] analogue in the absence of H1 resonances and the absence of H1-H2 coupling (doublet rather than triplet resonance for H2).

(c) Hydrolysis of 5a,b

Details are given for the [1-^{1}H] analogue of **5a**. Water (0.3 g) and 70-235 mesh silica gel (3 g) were mixed and suspended in CH_2Cl_2 (7 ml). Complex **5a** (1.0 g, 2.61 mmol) was added and the reaction monitored to completion by infrared (ca. 4 hours). Filtration and evaporation of solvent gave (+)-(2*S*)-(sorbaldehyde)Fe(CO)3 (0.55 g, 89 %) which was shown to be enantiomerically pure (within the limits of ^{1}H detection) by examination of the CHO resonance in C_6D_6 in the presence of tris [heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III); (+)-(2*S*): $[\alpha]_D^{20}$+110 (c=1, $CHCl_3$), (-)-(2*R*): $[\alpha]_D^{20}$-110 (c=1, $CHCl_3$). Enantiomerically pure samples of the [1-^{2}H] analogues **4a** and **4b** were obtained in the same way through hydrolysis of **5a** and **5b** respectively.

Hydrolysis of the residue from fractional recrystallisation provides material of about 70 % enrichment in the opposite enantiomer.

(d) Bakers yeast reduction of 4a/4b

Water (100 ml, degassed with argon), bakers yeast (10 g) and glucose (2.5 g) were stirred at 25 °C for 30 minutes. Complex **4a** (0.28 g, 1.18 mmol) in distilled ethanol (2 ml) was added with stirring. Tlc monitoring indicated complete consumption after 4 hours. The product was extracted with diethylether (3 x 500 ml), dried with $MgSO_4$, and the solvent removed to give **6a** as a yellow oil (0.23 g, 81 %). Infrared (hexane): 2052, 1980, 1972 cm^{-1}; NMR (C_6D_6): 4.31 (m, H4), 4.50 (m, H3), 0.70 (m, H2, H5), 1.01 (d, H6, J_{5-6} = 6.1), 3.15 (d, H1b, J_{1-2} = 7.4).

Reduction of **4b** in the same manner using bakers yeast proceeded only to 50 % completion over 15 hours. The NMR spectrum is identical to that of **6a**, but with the addition of a doublet resonance due to H1a

at 3.28 ppm (J_{1-2} = 5.2). The **6b/7b** mixture was converted to the acetate **8b/9b** [see part (f)] and then separated from unreacted **4b** by chromatotron.

(e) $NaBH_4$ reduction of 4a,b

$NaBH_4$ (0.016 g, 0.422 mmol) was added with stirring at 0 °C under nitrogen to a solution of racemic **4** (0.1 g, 0.42 mmol) in dry methanol (10 ml). After 30 minutes, water (15 ml) and diethyl ether (20 ml) were added. After separation, the aqueous layer was extracted with diethyl ether (2 x 30 ml) and the combined extracts dried over $MgSO_4$. Removal of solvent gave **6a,b/7a,b** (80 mg, 79 %).

$NaBD_4$ (98 %) reduction of [1-^{1}H(sorbaldehyde)Fe(CO)3 was carried out in the same way. NMR spectra are identical to those of **6a,b/7a,b**, differing only in the relative intensities of the H1a/H1b resonances.

(f) Esterification of 6a

Complex **6a** (0.23 g, 0.96 mmol) was dissolved in dry pyridine (3.5 ml) under nitrogen and cooled to 0 °C. Acetic anhydride (0.102 ml, 1.08 mmol) was added and the reaction stirred at room temperature overnight. After removal of solvent, the residue was purified by chromatotron (4:1 petroleum ether (30-40)/ethyl acetate) to give **8a** as a yellow oil (0.19 g, 70 %). Infrared (hexane): 2043, 1983, 1975 cm^{-1}; NMR (C_6D_6): 4.58 (m, H3), 4.28 (m, H4), 0.6-0.8 (m, H2,H5), 0.96 (d, H6, J_{5-6} = 5.5), 1.69 (s, OAc), 3.99 (d, H1b, J_{1-2} = 7.8); $[\alpha]_D^{20}$ -17 (c=1, $CHCl_3$). Examination of the acetate singlet in the presence of tris[heptafluoropropylhydroxy-methylene)-(+)-camphorato]europium (III) showed no loss of optical purity of planar chirality during the bakers yeast reduction.

Esterification of **6b/7b** in the same way gave **8b/9b** having an identical NMR spectrum, but with the addition of a doublet resonance due to H1a at 3.79 ppm (J_{1-2} = 5.8). Esterification of the products of $NaBH_4/NaBD_4$ reduction of [1-^{2}H]/(1-^{1}H)(sorbaldehyde)Fe(CO)3 gave acetates having identical NMR spectra, differing only in the relative intensities of the H1a/H1b resonances.

(g) In situ Protonation

The acetate (10-15 mg) was dissolved in CD_2Cl_2 (1.5 ml) in a 5 mm NMR tube, degassed with nitrogen and cooled to -80 °C. After addition of HSO_3F (0.1 ml, triply distilled) by syringe, the solution was mixed by shaking and placed in the NMR spectrometer and warmed to -20 °C.

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