Lipase-Mediated Separation of the Stereoisomers of 1-(1-Hydroxyethyl)-2-(hydroxymethyl)ferrocene

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Because of the increasing interest in catalytic asymmetric synthesis, numerous enantiopure organometallic compounds valuable as chiral auxiliaries, most of which are ferrocene derivatives, have been described in the last years.[1a-c] On the other hand, the chemoenzymatic methodology relying on the enantioselectivity or prochiral selectivity of lipases in the transesterification of mono- and polyhydroxy alcohols has been successfully applied to metallocenes, and examples of synthesis of optically active ferrocenyl alcohols with central or planar chirality have been described. Thus, Y.-F. Wang *et al.*[2] and N. W. Boaz[3] obtained both enantiomers of 1-ferrocenylethanol (the *R* form as ester) in good optical purities, while M.-J. Kim *et al.*[4] and D. Lambusta *et al.*[5] efficiently resolved (2-hydroxypropyl)ferrocene and 1,1′-bis(1-hydroxyethyl)-ferrocene, respectively. The feasibility of the resolution of planar chiral (hydroxymethyl)ferrocenes[6] and [4](1,2)-ferrocenophanes[7] has been demonstrated by T. Izumi's group. Finally, Nicolosi *et al.* made use of the planar prochiral selectivity of lipases to obtain both enantiomers of 1-[(acetyloxy)methyl]-2-(hydroxymethyl)ferrocene from the *meso* compound 1,2-bis(hydroxymethyl)ferrocene using as the catalyst different enzymatic preparations.[8] Some of the above compounds are possible precursors in the preparation of chiral ligands for homogeneous asymmetric catalysis.[9a,b]

A logical extension of our previous work on the enzymatic manipulation of ferrocene derivatives was to examine a compound having both central and planar chirality as substrate for enzyme-catalyzed transesterification, and we report herein the results obtained with both racemates of 1-(1-hydroxyethyl)-2-(hydroxymethyl)ferrocene.

The substrates for the optical resolution were prepared from [(dimethylamino)methyl]ferrocene essentially according to one of the procedures described by C. Moise *et al.*[10] Lithiation with *n*-BuLi and subsequent treatment with acetaldehyde gave 2-[(dimethylamino)methyl]-1-(1-hydroxyethyl)ferrocene (HDMF) as a mixture of two racemates, which were separated by column chromatography. Each individual racemic HDMF was reacted with methyl iodide to give the quaternary ammonium salt wherefrom the relevant racemate of 1-(1-hydroxyethyl)-2-(hydroxymethyl)ferrocene was obtained by treatment with alkali. On the basis of our previous work, immobilized lipase from *Pseudomonas cepacia* was examined for the transesterification of the two racemic diols in toluene using vinyl acetate as irreversible acyl donor. Experiments were carried out at different conversions of the substrate. At the end of the incubation time, the reaction was quenched by filtering off the enzyme and the reaction mixture was analyzed by ^{1}H NMR spectroscopy or separated by column chromatography. In each case enantiomeric excess (ee) of products was estimated by ^{1}H NMR spectral analysis in the presence of a chiral shift reagent. The results are listed in Table 1.

Table 1. Transesterification of 1-(1-Hydroxyethyl)-2-(hydroxymethyl)ferrocene Catalyzed by *Pseudomonas cepacia* Lipase[a]

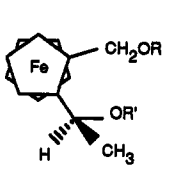
Racemate A

reaction time	diol 1a		monoester 2b		diester 2d	
	yield, %[b]	ee, %	yield, %[b]	ee, %	yield, %[b]	ee, %
4	75	27	25	79	–	–
12	52	59	48	50	–	–
24	27	>97	59	23	14	>97
36[c]	22	>97	55	10	18	>97

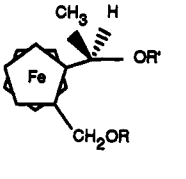
Racemate B

reaction time	diole 3a		monoester 4b		diester 3d	
	yield, %[b]	ee, %	yield, %[b]	ee, %	yield, %[b]	ee, %
3	73	28	27	78	–	–
6	50	61	50	61	–	–
12	41	>95	59	58	–	–
24	32	>95	68	42	–	–
42[c]	–	–	78	27	17	>95

[a] Conducted according to the standard procedure described in the Experimental Section. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] A small amount (5%) of secondary monoester is also present in the reaction mixture.



1a R=R'=H
1c R=H R'=Ac



2a R=R'=H
2b R=Ac R'=H
2c R=H R'=Ac
2d R=R'=Ac

The first racemate (A: equimolecular mixture of **1a** and **2a**) gave initially a monoester, (1*S*)-[(1*R*)-hydroxyethyl]-(2*R*)-[(acetyloxy)methyl]ferrocene[11] (**2b**), whose ee value declined with the reaction progress. After 24 h, the reaction mixture contained, along with **2b** of low optical purity, unreacted (1*R*)-[(1*S*)-hydroxyethyl]-(2*S*)-(hydroxymethyl)ferrocene (**1a**) (27%, theoretical maximum yield 50%) and (1*S*)-[(1*R*)-(acetyloxy)ethyl]-(2*R*)-[(acetyloxy)methyl]ferrocene (**2d**) (14%), both optically pure (ee > 97%).

(1) (a) Watanabe, M.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2218. (b) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857 and refs therein. (c) Watanabe, M.; Hashimoto, N.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1992**, *57*, 742.

(2) Wang, Y.-F.; Lalonde, J. J.; Momogan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200.

(3) Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061.

(4) Kim, M.-J.; Cho, H.; Chol, K. *J. Am. Soc., Perkins Trans. 1* **1991**, 2270.

(5) Lambusta, D.; Nicolosi, G.; Patti, A.; Piattelli, M. *Tetrahedron: Asymmetry* **1993**, *4*, 919.

(6) Izumi, T.; Hino, T. *J. Chem. Tech. Biotechnol.* **1992**, *55*, 325.

(7) Izumi, T.; Tamura, F.; Sasaki, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2784.

(8) Nicolosi. G.; Morrone, M.; Patti, A.; Piattelli, M. *Tetrahedron: Asymmetry* **1992**, *3*, 753.

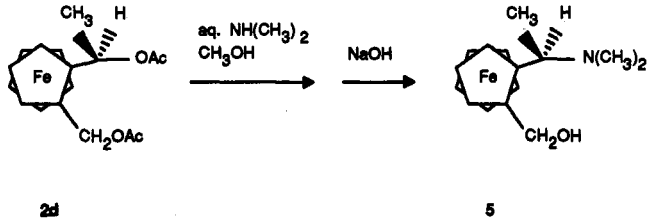
(9) (a) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138. (b) Hayashi, T.; Yamamoto, A.; Hojo, M.; Kishi, K.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Organomet. Chem.* **1989**, *370*, 129.

(10) Moise, C.; Sautrey, D.; Tirouflet, J. *Bull. Soc. Chim. Fr.* **1971**, *12*, 4562.

(11) Different systems have been proposed for specification of metallocenes chirality. The Schlögl–Cahn–Prelog system (Schögl, K. *Top. Stereochem.* **1967**, 39) is used in this paper.

0022-3263/94/1959-0251$04.50/0

Scheme 1

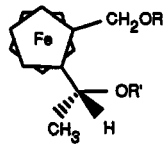


2d 5

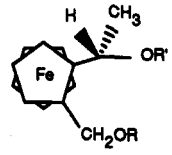
The chemical yield of **2d** increased by prolonging the reaction time, and a preparative run (see Experimental Section) with 120-h incubation time allowed isolation of this diester in 30% yield without appreciable loss of optical purity. It is to be noted that for incubation times longer than 24 h an additional component was detectable through the appearance of separate signals in the ^1H NMR spectrum of the crude reaction mixture (a singlet for an acetate at δ 1.98, a quartet for an oxygen-bearing methine at δ 5.95, and a doublet for a methyl at δ 1.66). This new compound was not isolated, but tentatively identified on the basis of the presence of above resonances, as 1-[(1-acetyloxy)ethyl]-2-(hydroxymethyl)ferrocene (**1c** and/or **2c**). Since chemical hydrolysis of **2d** gave diol **2a** with very high ee, resolution of the first racemate was positively achieved.

Assignment of the absolute structure of the resulting diols was ascertained by converting diacetate **2d** to the reported compound **5** by reaction with aqueous dimethylamine followed by hydrolysis (see Scheme 1).[12a,b] Thus the absolute structure of diol **2a** was determined to be 1*S*,2*R*,*R* and consequently that of **1a** is 1*R*,2*S*,*S*. The stereochemistry of monoacetate **2b**[13] was determined by hydrolysis with base and comparison of the chiroptical properties of the obtained diol with those of **2a**.

Reaction of the second racemate (**B**: equimolecular mixture of **3a** and **4a**) under the same conditions initially proceeded comparatively faster and resulted in the formation of (1*S*)-[(1*S*)-hydroxyethyl]-(2*R*)-[(acetyloxy)-methyl]ferrocene (**4b**), whose optical purity decreased by increasing the reaction time. After 12 h conversion of



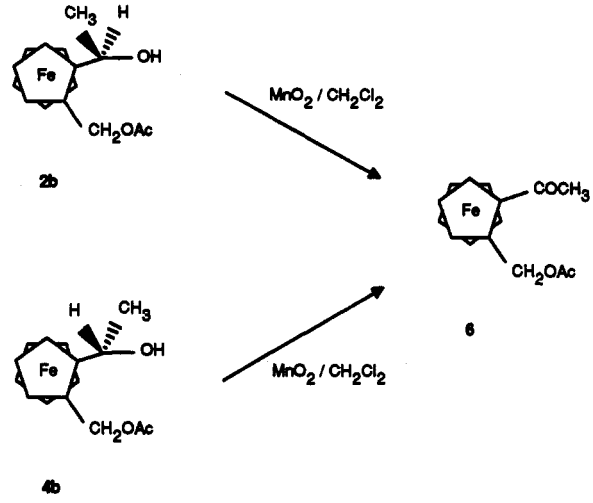
3a R=R'=H
3b R=Ac R'=H
3c R=H R'=Ac
3d R=R'=Ac



4a R=R'=H
4b R=Ac R'=H
4c R=H R'=Ac

substrate was 59% and unreacted (1*R*)-[(1*R*)-(hydroxy)-ethyl]-(2*S*)-(hydroxymethyl)ferrocene (**3a**) could be isolated with high optical purity (ee > 97%), while **4b** was obtained with a lower ee (58%). In order to obtain a sample of **4b** of better optical purity, a run of the transesterification was stopped after 3 h. Chromatographic separation of the monoester fraction from the unreacted diol gave **4b** in 24% chemical yield with 78% ee. After prolonged reaction time (36 h) the starting material was no longer present in the mixture which contained, in addition to

Scheme 2



primary monoacetate **4b** of very low optical purity, significant amounts (17%) of diacetate **3d** along with lesser amounts of a secondary monoacetate (stereochemistry not assessed, **3c** and/or **4c**).

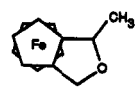
The absolute configuration of monoacetate **4b** was established as 1*S*,2*R*,*S* by MnO_2 oxidation to ketone **6**, which had the same sign of optical rotation as that of the ketone prepared by oxidation of **2b** (see Scheme 2). This implies that the unreacted diol **3a** is 1*R*,2*S*,*R*. The stereochemistry of diester **3d** followed from the sign of the optical rotation of the product of its alkaline hydrolysis, which was the same as that of diol **3a**.

Optimization of the ee value of **4b** (and consequently of diol **4a** from its hydrolysis) in the direct acetylation mode would imply a infinitesimally small reaction time and, consequently, a vanishingly low chemical yield. A possible strategy to enhance the ee value of the faster reacting enantiomer was the adoption of the double kinetic resolution methodology,[14] in which the product of the first kinetic resolution (in the case in hand, monoacetate **4b**) is subjected to a lipase-catalyzed hydrolysis. Unfortunately, attempts at utilizing this two-step strategy gave in our case unsatisfactory results, due to the lability of the substrate in the hydrolysis step.

In conclusion, in this study lipase from *P. cepacia* was found to be effective for the resolution of both racemates of a ferrocene derivative, 1-(1-hydroxyethyl)-2-(hydroxymethyl)ferrocene, having planar chirality owing to the 1,2 unsymmetrical substitution and containing in addition a chiral carbon atom in one of the substituents. Three of the optically active forms (1*S*,2*R*,*R*, 1*R*,2*S*,*S*, and 1*R*,2*S*,*R*)

(12) (a) Marquading, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (b) Gokel, G.; Marquading, D.; Ugi, I. *J. Org. Chem.* **1972**, *37*, 3052.

(13) A sample of **2b** on standing at room temperature for a period of 2 weeks was completely converted into a compound whose structure was determined as 6-methyl-7-oxa-[3](1,2)ferrocenophane (i) from ^1H and ^{13}C NMR spectra:



(i)

^1H NMR δ 1.55 (d, J = 6.4 Hz, 3H, CH_3CHOCH_2), 3.99 (s, 5H, Cp'), 3.94 and 4.36 (AB system, d, J = 10.7 Hz, each 1H, CH_2OCH), 4.26 (m, 2H, Cp), 4.43 (m, 1H, Cp), 4.32 (m, 1H, CH_3CHOCH_2); ^{13}C NMR δ 22.06 (CH_3CHOCH_2), 61.75 (CH_2OCH), 65.40 (CH_3CHOCH_2), 66.28 (Cp), 68.23 (Cp), 69.37 (Cp'), 69.52 (Cp), 82.89, 88.64.

(14) Brown, S.; Davies, S.; de Sousa, J. *Tetrahedron: Asymmetry* **1993**, *4*, 813.

were obtained in excellent optical purity and the fourth one (1*S*,2*R*,*S*) with good enantiomeric excess. Transesterification of the ferrocene diols appears to be controlled initially by both the chemodifferentiation between primary and secondary hydroxyl groups (the former reacting faster) and the enzymatic recognition of the planar chirality. Indeed, for both racemates it is observed that the enantiomer in which the primary hydroxyl group is in position 2*R* is acylated preferentially, in accordance with a previous observation on the prochiral compound 1,2-bis(hydroxymethyl)ferrocene.[6] When a large proportion of starting diol has been converted into primary monoacetate, this begins to undergo acylation at the secondary hydroxyl, and the steric course of this second step appears to be dictated essentially by the central chirality and, as expected from the known stereopreference of *P. cepacia* lipase,[15] the *R* stereogenic center is preferentially acylated. Since this center in the case of racemate A is embodied in the faster-formed monoester (i.e. **2b**) and in the case of racemate B in the slower-formed monoester (i.e. **3b**), the diester preferentially synthesized in the two instances (**2d** or **3d**) has the same or, respectively, the opposite configuration to that of the corresponding isolated primary monoacetate.

Experimental Section

General. [(Dimethylamino)methyl]ferrocene (DMAF) was from Aldrich. All reagents were analytical grade. Lipase from *P. cepacia* was obtained from Amano Pharmaceutical Co. Immobilization of the enzyme on Hyflo Super Cel was performed as reported previously.[16] Vinyl acetate was distilled prior to use. Column chromatography was carried out using 40–63 μm LiChroprep Si Diol, unless otherwise stated.

Optical rotations were measured in $CHCl_3$ solutions. IR spectra were recorded in $CHCl_3$. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ at 250.13 and 62.9 MHz, respectively. Europium(III) tris-[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorate] [(+)-Eu(hfc)$_3$] and europium(III) tris[3-[(trifluoromethyl)hydroxymethylene]-(+)-camphorate] [(+)-Eu(tfc)$_3$] were used as chiral shift agents.

Preparation of the Starting Material. Synthesis of the two racemates of 1-(1-hydroxymethyl)-2-(hydroxymethyl)ferrocene was carried out according essentially to a procedure of Moise *et al.*[10] A solution of DAMF (4 mL, 0.02 mol) in dry ether (15 mL) was treated with *n*-BuLi (0.024 mol) and the mixture left at room temperature for 2 h. Acetaldehyde (5 mL, 0.09 mol) in ether (10 mL) was then added dropwise and the mixture was kept at 0 °C for 3 h. After addition of water, the organic layer was separated, dried over sodium sulfate, and evaporated under reduced pressure. Chromatography of the residue on Si gel 63–200 μm (MeOH/ether 1:1 as the eluent) afforded 1.70 (30% yield) and 1.15 g (20% yield) of the two racemic forms of 2-[(dimethylamino)methyl]-1-(1-hydroxyethyl)ferrocene, whose ^1H-NMR spectra agreed with those reported.[10] Each racemate was individually treated with MeI in CH_3CN for 4 h at room temperature. Addition of ether to the reaction mixture resulted in the precipitation of the quaternary ammonium salt, which was collected by filtration, recrystallized from ethanol, and treated with NaOH to give the corresponding racemate of 1-(1-hydroxyethyl)-2-(hydroxymethyl)ferrocene.

Racemate A (equimolecular mixture of 1a and 2a): orange needles from benzene/hexane, mp 68 °C;[17] IR 3382, 3010, 2936, 1469, 1411, 1373, 1281, 1226, 1106, 1083, 1068, 1000 cm^{-1}; ^1H NMR δ 1.55 (d, J = 6.4 Hz, 3H), 4.08 (bs, 6H), 4.20 (m, 1H), 4.25 (m, 1H), 4.32 and 4.66 (AB system, d, J = 12.0 Hz, each 1H), 4.93 (q, J = 6.4 Hz, 1H); ^{13}C NMR δ 21.08, 59.93, 65.29, 66.35, 66.62, 68.88, 70.03, 85.55, 90.75.

Racemate B (equimolecular mixture of 3a and 4a). After recrystallization from benzene/hexane: mp 56 °C;[17] IR 3407, 3012, 2978, 2931, 2883, 1451, 1377, 1280, 1249, 1106, 1068, 1001 cm^{-1}; ^1H NMR δ 1.44 (d, J = 6.4 Hz, 3H), 4.13 (t, J = 2.4 Hz, 1H), 4.23 (bs, 7H), 4.33 and 4.42 (AB system, d, J = 12.2 Hz, each 1H), 4.66 (q, J = 6.4 Hz, 1H); ^{13}C NMR δ 24.21, 59.25, 64.19, 66.07, 66.56, 68.51, 69.46, 85.29, 93.71.

Enzymatic Acylation. The lipase-mediated transesterification was carried out according to the following typical experimental procedure. To a solution of racemic diol (200 mg, 19.2 mM) in toluene (40 mL) containing vinyl acetate (8.5 μL/mL) was added lipase from *P. cepacia* immobilized on Hyflo Super Cel (50 mg/mL). The suspension was shaken in a stoppered vial at 45 °C under 300 rpm. At the time reported in Table 1 the reaction mixture was filtered to remove the enzyme and the filtrate evaporated under reduced pressure to remove the solvent and excess vinyl acetate. Conversion of substrate and ratio of the products were determined by ^1H NMR spectroscopy of the residue. Column chromatography (AcOEt/petroleum ether 1:4) gave recovered diol and products which were characterized through their spectroscopic properties. Enantiomeric excesses were measured by ^1H NMR analysis in the presence of a chiral reagent [(+)-Eu(hfc)$_3$ for racemate A and (+)-Eu(tfc)$_3$ for racemate B], using the integrated areas of the resonances attributable to the corresponding enantiomers and relative to the unsubstituted cyclopentadienyl rings (Cp') or the acetate groups. Also the doublets for the methyls of the hydroxyethyl side chain appear at distinctly different fields. Optical purities of diacetates were measured after hydrolysis to the corresponding diols.

Lipase-Mediated Esterification of Racemate A. For preparative purposes, three separate experiments were run according to the above general procedure with different incubation times. A first run (4-h incubation) allowed isolation of **2b** in 22% yield and 79% ee. A second run (24-h incubation) gave **1a** in 24% isolated yield and ee > 97%, and **2d** in 11% yield (ee > 97%). Diester **2d** was isolated in better yield (30%) and high optical purity (ee > 97%) from a third run with 120 h of incubation. **2a** was obtained by chemical hydrolysis of **2d**.

1(*R*)-[1(*S*)-Hydroxyethyl]-2(*S*)-(hydroxymethyl)-ferrocene (1a): $[\alpha]_D$ = −42.5° (*c* 0.7). ^1H and ^{13}C NMR spectra were identical with those described above for racemate A.

1(*S*)-[1(*R*)-(Acetyloxy)ethyl]-2(*R*)-[(acetyloxy)methyl]-ferrocene (2d): $[\alpha]_D$ = −93.9° (*c* 0.6); IR 3024, 3013, 1733, 1457, 1373, 1256, 1107, 1056, 1020 cm^{-1}; ^1H NMR δ 1.59 (d, J = 6.5 Hz, 3H), 2.00 (s, 6H), 4.13 (s, 5H), 4.22 (t, J = 2.6 Hz, 1H), 4.33 (d, J = 2.6 Hz), 4.85 and 5.02 (AB system, d, J = 12.1 Hz, each 1H), 6.00 (q, J = 6.5 Hz, 1H); ^{13}C NMR δ 19.42, 20.92, 21.23, 61.10, 67.38, 67.66, 67.85, 69.30, 71.45, 80.17, 86.83, 170.03 and 170.60. Anal. Calcd for $C_{17}H_{20}FeO_4$: C, 59.30; H, 5.81. Found: C, 59.15; H, 5.83.

1(*S*)-[1(*R*)-Hydroxyethyl]-2(*R*)-(hydroxymethyl)-ferrocene (2a). Hydrolysis of **2d** (25 mg) with NaOH in ethanol afforded **2a** (16 mg, 85% yield): $[\alpha]_D$ = +40.0° (*c* 0.5). ^1H and ^{13}C NMR spectra were identical with those described above for racemate A.

1(*S*)-[1(*R*)-Hydroxyethyl]-2(*R*)-[(acetyloxy)methyl]ferrocene (2b): $[\alpha]_D$ = −43.6° (*c* 0.9); IR 3026, 3011, 2937, 1730, 1450, 1373, 1240, 1225, 1107, 1082, 1067, 1003 cm^{-1}; ^1H NMR δ 1.55 (d, J = 6.4 Hz, 1H), 2.02 (s, 3H), 4.12 (bs, 5H), 4.20 (m, 1H), 4.30 (m, 2H), 4.86 (q, J = 6.4 Hz, 1H), 4.95 and 5.15 (AB systems, d, J = 12.0 Hz, each 1H); ^{13}C NMR δ 21.00, 21.42, 61.64, 64.32, 66.81, 67.68, 69.06, 70.84, 79.35, 91.57, 171.09. Anal. Calcd for $C_{15}H_{18}FeO_3$: C, 59.60; H, 5.96. Found: C, 59.55; H, 5.94. Standard hydrolysis of **2b** with NaOH in ethanol afforded **2a**.

Lipase-Mediated Esterification of Racemate B. Diol **3a** was isolated in 37% yield and ee value of >95% from a preparative run with a 12-h reaction time. Monoester **4b**, obtained in 24% yield and 78% ee in a second run with 3-h incubation, was subjected to chemical hydrolysis to give **4a**. A third run (42-h incubation) gave **3d** (14% yield, >95% ee), monoacetate **4b** (75% yield, 27% ee) and a small amount of 1-[(1-acetyloxy)ethyl]-2-

(15) Xie, Z.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 733.
(16) Nicolosi, G.; Piattelli, M.; Sanfilippo, C. *Tetrahedron* **1993**, *49*, 3143.
(17) The reported mp's of racemate A and B (see ref 10) are not in agreement with our values.

(hydroxymethyl)ferrocene of undetermined stereochemistry (3c and/or 4c).

1(*R*)-[1(*R*)-Hydroxyethyl]-2(*S*)-(hydroxymethyl)-ferrocene (3a): $[\alpha]_D = -38.2°$ (*c* 0.5). ^1H and ^{13}C NMR spectra were identical with those described above for racemate B.

1(*S*)-[1(*S*)-Hydroxyethyl]-2(*R*)-[(acetyloxy)methyl]ferrocene (4b): $[\alpha]_D = +26.4°$ (*c* 0.5); IR 3014, 1733, 1451, 1376, 1250, 1107, 1021, 1001 cm^{-1}; ^1H NMR δ 1.37 (d, J = 6.4 Hz, 3H), 2.02 (s, 3H), 4.17 (m, 1H), 4.21 (bs, 6H), 4.31 (m, 1H), 4.63 (q, J = 6.4 Hz), 4.91 and 4.97 (AB system, d, J = 12.1 Hz, each 1H); ^{13}C NMR δ 20.90, 24.69, 61.38, 64.09, 65.93, 67.35, 68.74, 70.59, 79.12, 95.50, 170.80. Anal. Calcd for $C_{15}H_{18}FeO_3$: C, 59.60; H, 5.96. Found: C, 59.70; H, 5.98.

1(*S*)-[1(*S*)-Hydroxyethyl]-2(*R*)-(hydroxymethyl)-ferrocene (4a). Hydrolysis of **4b** (40 mg) with NaOH in ethanol afforded **4a** (30 mg, 88% yield), $[\alpha]_D = +29.6°$ (*c* 0.5). The ^1H and ^{13}C NMR spectra were identical with those described above for racemate B.

1(*R*)-[1(*R*)-(Acetyloxy)ethyl]-2(*S*)-[(acetyloxy)methyl]-ferrocene (3d): $[\alpha]_D = +6.0°$ (*c* 0.5); IR 3014, 2932, 1733, 1374, 1064, 1022, 1107 cm^{-1}; ^1H NMR δ 1.40 (d, J = 6.4 Hz, 3H), 2.01 (s, 3H), 2.17 (s, 3H), 4.13 (bs, 5H), 4.17 (t, J = 2.5 Hz, 1H), 4.24 (m, 1H), 4.28 (m, 1H), 4.90 and 4.98 (AB system, d, J = 12.1 Hz, each 1H), 5.86 (q, J = 6.4 Hz, 1H); ^{13}C NMR δ 19.55 and 20.83, 23.05, 61.58, 67.05, 67.41, 68.80, 69.22, 70.38, 78.71, 90.07, 170.00 and 170.67. Anal. Calcd for $C_{17}H_{20}FeO_4$: C, 59.30; H, 5.81. Found: C, 59.45; H, 5.78. Alkaline hydrolysis of **3d** afforded **3a**.

1-[(1-Acetyloxy)ethyl]-2-(hydroxymethyl)ferrocene (3c and/or 4c): ^1H NMR δ 1.43 (d, J = 6.5 Hz, 3H), 2.17 (s, 3H), 4.13 (bs, 5H), 4.20 and 4.35 (m, 5H), 5.91 (q, J = 6.5 Hz, 1H).

Determination of the Absolute Stereochemistry of 2d. Compound **2d** (50 mg, >97% ee) was treated with $NH(CH_3)_2$ and MeOH for 2 days at room temperature according a procedure previously reported.[12b] The reaction mixture after dilution with ether was extracted with 10% aqueous citric acid. To the aqueous layer was added 20% NaOH to pH 8.5 and then extracted with ether. Evaporation of the solvent gave **5** (35 mg, 81% yield): $[\alpha]_D = +118.0°$ (*c* 0.5), lit.[12a] $[\alpha]_D = +121.5°$, whose ^1H NMR spectrum and elemental analysis agreed with those reported.[12a]

Determination of the Absolute Stereochemistry of 4b. Oxidation of (+)-**4b** (20 mg, 78% ee) with 20 mg of MnO_2 in CH_2Cl_2 at room temperature for 12 h afforded 18 mg (91% yield) of 1(*S*)-acetyl-2(*R*)-[(acetyloxy)methyl]ferrocence (**6**): $[\alpha]_D = -335.0°$ (*c* 0.5); IR 3024, 3012, 2933, 1733, 1666, 1435, 1372, 1253, 1107, 1003 cm^{-1}; ^1H NMR δ 2.07 (s, 3H), 2.49 (s, 3H), 4.21 (s, 5H), 4.45 (m, 1H), 4.62 (m, 1H), 4.70 (m, 1H), 5.23 and 5.33 (AB system, d, J = 12.1 Hz, each 1H); ^{13}C NMR δ 21.03, 28.25, 61.86, 70.49, 70.93, 72.44, 74.52, 77.82, 83.43, 170.91, 194.61. Anal. Calcd for $C_{15}H_{16}FeO_3$: C, 60.00; H, 8.89. Found: C, 60.10; H, 8.91. Ketone **6** had the same chiroptical properties of the compound obtained by oxidation of **2b** in the same conditions ($[\alpha]_D = -341.0°$, *c* 0.5).

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