Pergamon

Tetrahedron, Vol. 53, No. 4, pp. 1361-1368, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01048-4

Lipase-assisted Preparation of Enantiopure Ferrocenyl Sulfides Possessing Planar Chirality and their Use in the Synthesis of Chiral Sulfoxides

Angela Patti, Daniela Lambusta, Mario Piattelli, Giovanni Nicolosi*

Istituto del CNR per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico#

Via del Santuario, 110, I- 95028 Valverde, Italy

Patrick McArdle, Desmond Cunningham, Martin Walsh

Chemistry Department, University College, Galway, Ireland

Abstract: Racemic 2-hydroxymethyl-1-phenylthioferrocene **5** and 2-hydroxymethyl-1-*tert*-butylthioferrocene **6** were subjected to kinetic resolution via acetylation catalysed by lipase from *Candida antarctica* (Novozym® 435) or *Mucor miehei* (Lipozyme® IM). The obtained enantiopure thioethers underwent chemical oxygenation at the sulfur atom to give the corresponding ferrocenyl sulfoxides with settled central/planar chirality.

The interest in chiral ferrocenyl derivatives is mainly due to their possible use as catalysts in asymmetric synthesis or starting materials in the stereospecific synthesis of more complex molecules.[1] Concerning their catalytic properties, ferrocenyl sulfides and sulfoxides have been used, in both racemic and, sometimes, enantiopure form.[2] The few enantiopure sulfur-containing ferrocenes reported in the literature have been mainly prepared either by modifying substituents in enantiomerically pure ferrocenes[3] or by diastereoselective synthesis from enantiomerically pure dimethylaminoethylferrocene via a standard route to 1,2-disubstituted ferrocenes with settled planar and central chirality.[4] In this field the use of biocatalysis is as yet little studied but appears promising. Yamazaki and Hosono have obtained ferrocenyl sulfoxides with central or planar chirality, or C_2 symmetry by stereoselective oxygenation of sulfides with *Corynebacterium equi* or *Penicillium frequentans*.[5] In our laboratory lipases of different origin have been used in the resolution of racemic 2-hydroxymethyl-1-methylthioferrocene **1**.[6]

In the present paper we wish to report the enzymatic resolution of racemic ferrocenyl sulfides **5** and **6** and their chemical conversion into ferrocenyl sulfoxides with defined central and planar chirality.

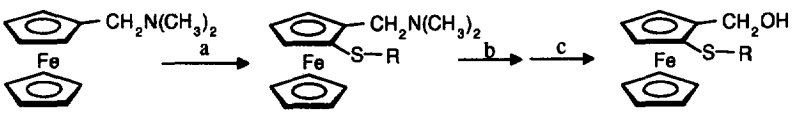
RESULTS AND DISCUSSION

Racemic ferrocenyl sulfides (±)-**5** and (±)-**6** have been prepared from dimethylaminomethylferrocene, **2**, according to the standard procedure for the synthesis of 1,2-disubstituted ferrocenes. Lithiation with *n*-BuLi

Associated to the National Institute for the Chemistry of Biological Systems-CNR

followed by treatment with diphenyldisulfide or di-*tert*-butyldisulfide yielded respectively the dimethylaminothioethers (±)-**3** and (±)-**4**, which were converted into the corresponding hydroxythioethers (±)-**5** and (±)-**6** (Scheme 1).

Scheme 1



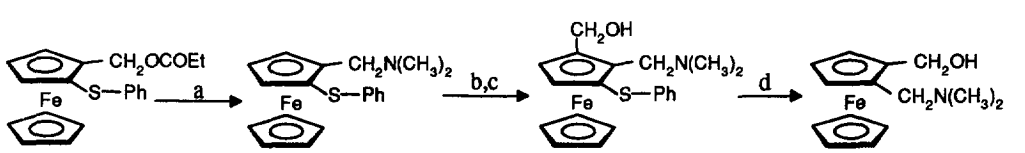
2 (±)-**3** R = Ph (±)-**4** R = *t*-Bu (±)-**5** R = Ph (±)-**6** R = *t*-Bu

Reagents: a) *n*-BuLi; R-S-S-R ; b) Ac_2O; c) $MeOH/K_2CO_3$

Initially, for the resolution of (±)-**5** we took into consideration the reaction with vinyl acetate catalysed by lipase from *Candida antarctica* (Novozym® 435) or *Mucor miehei* (Lipozyme® IM), previously used successfully in the resolution of methylthio derivative (±)-**1** (Table 1, entries 1 and 2). The reaction catalysed by Novozym is fast, but the enantioselectivity is unsatisfactory, since at 42% conversion the enantiomeric excess of the recovered ester (+)-**5a** is less than 80% (entry 3). The Lipozyme catalysed esterification has a similar course in terms of reaction rate and enantioselectivity (entry 5).

For a better result a vinyl ester with a more bulky acyl group, namely vinyl propionate, was then tried. While no improvement was observed with Lipozyme as the catalyst (entries 5 and 6), a significant increase in enantioselectivity was obtained in the reaction promoted by Novozym. In this case propionic ester (+)-**5b** had e.e. near 90% at high levels of conversion (entry 4). In a preparative run quenched at 40% conversion, ester (+)-**5b** was isolated with 90% e.e., along with unreacted alcohol (–)-**5** with 60% e.e. In a parallel experiment prolonged until 55% conversion the e.e. of the unchanged (–)-**5** reached 95%. The absolute stereochemistry of (+)-**5b** was assessed by chemical correlation with the known (–)-**8**[7] (scheme 2). Reaction of (+)-**5b** with dimethylamine in methanol afforded the dimethylamino derivative (–)-**3**. This was converted, through lithiation at the position *ortho* to the dimethylaminomethyl group followed by reaction with trioxane, into the trisubstituted (+)-**7**, which was treated with Raney Ni to yield (–)-**8**.

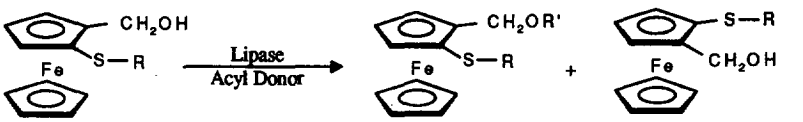
Scheme 2



(+)-**5b** (–)-**3** (+)-**7** (–)-**8**

Reagents: a) $NH(CH_3)_2/MeOH$; b) *n*-BuLi; c) $C_3H_6O_3$; d) Raney Ni

Table 1. Enzymatic esterification of compounds (±)-1, (±)-5 and (±)-6[a]



(±)-1 R= Me (+)-1a R'=Ac (+)-1

(±)-5 R= Ph (+)-5a R'=Ac (+)-5b R'=-OCEt (−)-5

(±)-6 R= *t*-Bu (+)-6a R'= Ac (+)-6

Entry	R	Lipase	Acyl donor[b]	Time, h	Conv., %[c]	e.e. Ester[d]	E[e]	Stereo-preference	e.e. Alcohol[f]
1[g]	Me	Novozym	A	0.9	32	90	30	1*R*	48
2[g]		Lipozyme	A	0.4	46	81	20	1*R*	69
3	Ph	Novozym	A	1	42	79	15	1*R*	58
4		Novozym	P	1	45	88	34	1*R*	72
5		Lipozyme	A	1	42	79	15	1*R*	58
6		Lipozyme	P	0.3	37	76	11	1*R*	45
7	*t*-Bu	Novozym	A	22	30	76	10	1*R*	32
8		Lipozyme	A	2.5	35	90	30	1*R*	48

[a]Experimental conditions: substrate 20 mg/mL, solvent diisopropyl ether, lipase 40 mg/mL, vinyl ester (10 eqv). [b]A=vinyl acetate, P=vinyl propionate. [c]Determined by ^{1}H-NMR analysis of the reaction mixture. [d]Determined after reductive deacylation with $LiAlH_4$ by ^{1}H-NMR in the presence of Eu(hfc)$_3$. [e]Calculated according to ref. 8. [f]Determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$. [g]Data from ref. 6.

Regarding the resolution of (±)-**6**, with Novozym as the catalyst the reaction rate is very slow and the enantioselectivity moderate. In fact, yet at low level of conversion (30%) the ester formed has a moderate e.e. (76%, entry 7). The same reaction catalysed by Lipozyme proceeds with satisfying reaction rate and enantioselectivity and, at 35% conversion, ester (+)-**6a** has 90% e.e.(entry 8). A preparative run with Lipozyme quenched after 3 h incubation gave an ester with good chemical yield (40%) and e.e. (88%). When the reaction time was prolonged until conversion reached 55% the unreacted alcohol (+)-**6** was recovered in 43% yield and 95% e.e. Esterification of *t*-Bu-thioether (±)-**6** proceeded with the same 1*R* stereopreference, as confirmed by X-ray crystallographic analysis of the corresponding sulfoxide (see below).

Ferrocenyl sulfides (+)-**1**, (−)-**5** and (+)-**6**, all with 1*S* planar chirality and high e.e. (ca. 95%), were oxidised with sodium metaperiodate to the corresponding ferrocenyl sulfoxides. With (+)-**1** the reaction is scarcely selective giving sulfoxides (−)-**9** and (+)-**10** in a 3:2 ratio. The absolute configuration of these

compounds, the planar chirality being known, was assigned by comparison of their ^{1}H-NMR spectra. It is in fact known[4] that in this class of compounds the more stable conformation is the one in which the lone pair is directed towards the Fe atom ("*endo*"). The presence in the spectrum of (+)-**10** of a signal (dd) at δ 2.24 due to an alcoholic proton hydrogen-bonded to the oxygen of the sulfoxide function is only compatible with the 1*S*,*R* configuration (Fig. 1). This signal is obviously absent from the spectrum of (–)-**9**, whose configuration is 1*S*,*S*.

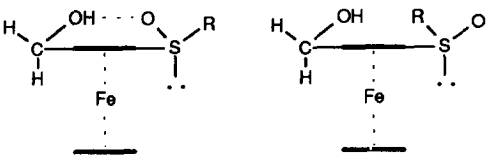
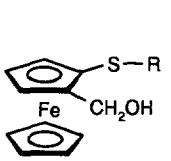


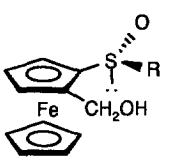
Fig. 1

Oxidation of (–)-**5** is slower but more stereoselective giving diastereoisomers (–)-**11** and (+)-**12** in a 1:3 ratio. In this case also, the presence of a hydrogen-bonded OH in the spectrum of (+)-**12** but not (–)-**11** allowed to assign to these sulfoxide the 1*S*,*R* and 1*S*,*S* stereochemistry, respectively.

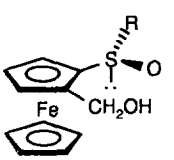
Table 2. $NaIO_4$ oxidation of homochiral ferrocenyl sulfides



(+)-**1** R= CH_3
(–)-**5** R= Ph
(+)-**6** R=*t*-Bu



(–)-**9** R= CH_3
(–)-**11** R= Ph
(+)-**13** R=*t*-Bu

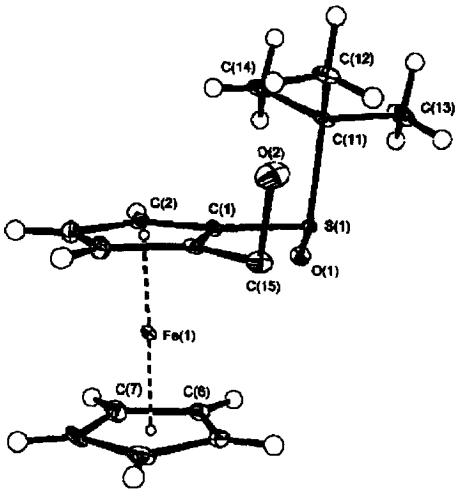


(+)-**10** R= CH_3
(+)-**12** R= Ph

Sulfide	Time, h[a]	Product	Config[b]	Product	Config[b]	Diast. ratio[c]
(+)-**1**	2	(-)-**8**	1*S*,*S*	(+)-**9**	1*S*,*R*	3:2
(–)-**5**	20	(-)-**10**	1*S*,*S*	(+)-**11**	1*S*,*R*	1:3
(+)-**6**	2	(+)-**12**	1*S*,*S*			-

[a]At total conversion. [b]The first and the second letter refers to the planar and central chirality, respectively. [c]Determined by ^{1}H-NMR analysis of the reaction mixture.

In contrast with (+)-**1** and (–)-**5**, oxidation of (+)-**6** is highly stereoselective and gives a single sulfoxide, (+)-**13**. Although its ^{1}H-NMR spectrum does not contain the resonance for a hydrogen-bonded OH, unavailability of the diastereoisomer of opposite chirality at the sulfur atom (in an attempt to prepare it by oxidation of (+)-**6** with 3-chloroperbenzoic acid, which is reported to have stereoselectivity opposite to sodium metaperiodate,[4] a product was obtained with the same spectral and chiroptical properties of (+)-**13**) did not allow an unambiguous assignment of the stereochemistry. A single crystal X-ray crystallographic analysis gave definite proof of the 1*S*,*S* configuration (Fig. 2)



$C_{15}H_{20}FeO_2S$. M=320.22
Orthorhombic, $P2_12_12_1$
a=7.315(2); b=10.258(2); c=19.193(3)
Final R_1=4.11%; wR_2=10.83%

Fig. 2. ORTEX drawing of sulfoxide (+)-**13** (40% ellipsoids)

CONCLUSION

Racemic 2-hydroxymethyl-1-methylthioferrocene (±)-**1**, 2-hydroxymethyl-1-phenylthioferrocene (±)-**5** and 2-hydroxymethyl-1-*tert*-buthylthioferrocene (±)-**6** can be efficiently resolved by irreversible acetylation catalysed by Novozym (lipase from *Candida antarctica*) or Lipozyme (lipase from *Mucor miehei*). Chemical oxygenation at the sulfur atom in the three homochiral thioethers (all with 1*S* planar stereochemistry) affords the corresponding sulfoxides, as a mixture of diastereoisomers for (+)-**1** and (–)-**5** while (+)-**6** yielded a single product, namely the 1*S*,*S*-isomer.

EXPERIMENTAL

General

^{1}H-and ^{13}C-NMR were recorded in $CDCl_3$ at 250.13 and 62.9 MHz, respectively, on a Bruker AC 250 spectrometer. Optical rotations were measured with a Jasco DIP-370 polarimeter. Lipozyme® IM (immobilised lipase from *Mucor miehei*) and Novozym® 435 (immobilised lipase from *Candida antarctica*) are registered marks from Novo Nordisk. All reagents were analytical grade. Column chromatography was performed on LiChroprep Diol 40-63 μm (Merck). Europium (III) tris(3-heptafluoropropyl)hydroxymethylene-(+)-camphorate [Eu(hfc)$_3$] was used as chiral shift reagent.

Preparation of (±)-3 and (±)-4

Dimethylamminomethylferrocene, **2**, was subjected to lithiation with *n*-BuLi followed by treatment with diphenyldisulphyde or di-*t*-butyldisulphyde according to a described procedure[2] to give (±)-**3** and (±)-**4**, respectively.

2-Dimethylamino-methyl-1-phenylthioferrocene, (±)-3: ^{1}H-NMR δ 2.04 (6H, s, $N(CH_3)_2$), 3.43 and 3.47 (AB system, each 1H, d, *J*=13.2 Hz, $CH_2N(CH_3)_2$), 4.18 (5H, s, C'p), 4.34 (1H, t, *J*=2.5 Hz, Cp), 4.48 (1H, m, Cp), 4.53 (1H, m, Cp), 7.05 (1H, m, Ph), 7.13 (4h, bs, Ph); ^{13}C-NMR δ 44.95, 56.62, 69.00, 70.22, 71.18, 75.48, 76.26, 87.41, 124.71, 126.07, 128.34, 140.05. Anal. Calcd for $C_{19}H_{21}FeNS$: C, 64.96; H, 6.03; N, 3.99. Found: C, 64.73; H, 6.05; N, 3.92.

*2-Dimethylaminomethyl-1-*tert*-butylthioferrocene, (±)-4*: mp 64-65 °C; ^{1}H-NMR δ 1.23 (9H, s, $C(CH_3)_3$), 2.23 (6H, s, $N(CH_3)_2$), 3.18 and 3.53 (AB system, each 1H, d, *J*=13.3 Hz, $CH_2N(CH_3)_2$), 4.08 (5H, s, C'p), 4.21 (1H, t, *J*=2.5 Hz, Cp), 4.36 (1H, bs, Cp), 4.42 (1H, m, Cp); ^{13}C-NMR δ 31.07, 45.81, 57.58, 67.99, 70.20, 70.70, 76.56, 88.90. Anal. Calcd for $C_{17}H_{25}FeNS$: C, 61.67; H, 7.60; N, 4.23. Found: C, 61.85; H, 7.52; N, 4.26.

Preparation of (±)-1, (±)-5 and (±)-6

2-Hydroxymethyl-1-methylthioferrocene (±)-1 was obtained from **2** as reported previously.[6]

2-Hydroxymethyl-1-phenylthioferrocene, (±)-5. Ac_2O (10 mL) was added to a solution of (±)-**3** (1 g, 2.85 mmol) in 10 mL of *t*-BME and the resulting mixture refluxed for 1 h. After removal of solvent and excess Ac_2O by distillation under vacuum, the residue was dissolved in methanol (10 mL) containing K_2CO_3 (500 mg) and the suspension stirred for 1 h at 40 °C. Water (40 mL) was then added and the product extracted with ether. Removal of the solvent afforded (±)-**5** (445 mg, 51% yield); mp 87-88 °C; ^{1}H-NMR δ 4.26 (5H, s, Cp), 4.36 (1H, t, *J*=2.5 Hz, Cp), 4.46 (1H, m, Cp), 4.51 (3H, m, Cp and CH_2OH), 7.05 (3H, m, Ph), 7.18 (2H, m, Ph); ^{13}C-NMR δ 59.42, 69.10, 69.96, 70.48, 75.57, 90.85, 125.16, 125.75, 128.88, 140.18. Anal. Calcd for $C_{17}H_{16}FeOS$: C, 62.98; H, 4.97. Found: C, 63.20; H, 5.01.

*2-Hydroxymethyl-1-*tert*-butylthioferrocene, (±)-6*. Treatment of (±)-**4** (1 g, 3.01 mmol) as above afforded (±)-**6** (505 mg, yield 55%); mp 74-75 °C; ^{1}H-NMR δ 1.17 (9H, s, $C(CH_3)_3$), 4.08 (1H, m, Cp), 4.10 (5H, s, C'p), 4.20 (1H, t, *J*=2.5 Hz, Cp), 4.33 (1H, m, Cp), 4.37 and 4.49 (AB system, each 1H, d, *J*=12.3 Hz, CH_2OH); ^{13}C-NMR δ 30.65, 45.80, 59.27, 68.45, 69.14, 69.67, 76.80, 77.31, 91.47. Anal. Calcd for $C_{15}H_{20}FeOS$: C, 59.22; H, 6.63. Found: C, 59.05; H, 6.58.

Preliminary experiments of enzymatic acylation

Lipase of choice (40 mg) and vinyl acetate (20 μL/mL) were added to a solution of ferrocenyl derivative (20 mg) in DIPE (2 mL) and the suspension was shaken (300 rpm) at 45 °C. At the appropriate time (Table 1) the reaction was stopped filtering off the enzyme, the conversion determined by ^{1}H-NMR analysis of an aliquot and the remaining material subjected to chromatography. The enantiomeric excess of the ester was determined, after reductive deacylation with $LiAlH_4$, by ^{1}H-NMR analysis in the presence of $Eu(hfc)_3$ using for each enantiomer integrated areas of the resonances relative to the cyclopentadienyl ring or the *tert*-butyl group.

Lipase catalysed esterification of (±)-5

Novozym 435 (500 mg) and vinyl propionate (0.85 mL) were added to a solution of (±)-**5** (500 mg, 1.54 mmol) in 50 mL of DIPE and the mixture incubated at 45 °C under shaking (300 rpm). After 90 min, when the conversion of the substrate had reached 40%, the enzyme was filtered off and the filtrate taken to dryness in vacuum. Column chromatography of the residue afforded unreacted (–)-**5** (290 mg, 58% yield, 60% e.e.) and ester (+)-**5b** (223 mg, 38% yield, 90% e.e.).

(1R)-1-phenylthio-2-propionyloxyferrocene, (+)-**5b**, $[\alpha]_D$ +73 (*c* 0.68, $CHCl_3$), ^{1}H-NMR δ 0.94 (3H, t, *J*=7.5 Hz, CH_3CH_2CO), 2.00 (2H, m, CH_3CH_2CO), 4.24 (5H, s, C'p), 4.38 (1H, m, Cp), 4.49 (1H, bs, Cp), 4.53 (1H, bs, Cp), 4.95 and 5.08 (AB system, each 1H, d, *J*=11.8 Hz, CH_2OCOEt), 7.03 (3H, m, Ph), 7.13 (2H, m, Ph); ^{13}C-NMR δ 8.82, 27.11, 60.76, 69.47, 70.07, 71.67, 76.01, 76.89, 85.24, 124.77, 125.95, 128.32, 140.10, 173.87. Anal. Calcd for $C_{20}H_{20}FeO_2S$: C, 63.17; H, 5.30. Found: C, 63.28; H, 5.36.

In an experiment in which the reaction was allowed to proceed up to 55% conversion the unchanged alcohol (–)-**5** was recovered with 95% e.e., $[\alpha]_D$ –50 (*c* 1.14, $CHCl_3$).

Determination of absolute configuration of (+)-5b

Aqueous dimethylamine (33%, 10 mL) was added to a solution of (+)-**5b** (1 g, 2.63 mmol, 90% e.e.) in methanol (10 mL) and the mixture was left at 45 °C for 12 h. Conventional work up, as described by Gokel *et al.* for the preparation of *N,N*-dimethyl-1-ferrocenylethylamine,[9] afforded (–)-**3** (490 mg, 53% yield), $[\alpha]_D$ –51 (*c* 0.64, $CHCl_3$). An aliquot (300 mg, 0.85 mmol) was dissolved in 4 mL of anhydrous ether, treated with 1.1 eqv of *n*-BuLi and the mixture refluxed for 1 h. Then 150 mg of $(CH_2O)_3$ in ether (6 mL) was added dropwise and the solution refluxed. After 6 h the reaction was stopped and the products extracted with ether. Evaporation of the solvent left a residue which was subjected to chromatographic purification (MeOH:THF 1:1 vol/vol as the eluent) to give (+)-**7** (25 mg , yield 7%).

3-Dimethylaminomethyl-2-hydroxymethyl-1-methylthioferrocene (+)-7. $[\alpha]_D$ +169 (*c* 0.09, $CHCl_3$); ^{1}H-NMR δ 1.93 (6H, s, $N(CH_3)_2$), 3.25 and 3.85 (AB system, each 1H, d, *J*=12.9 Hz, $CH_2N(CH_3)_2$), 4.13 (5H, s, C'p), 4.18 and 4.77 (AB system, each 1H, d, *J*=12.3 Hz, CH_2OH), 4.42 (1H, d, *J*=2.5 Hz, Cp), 4.48 (1H, d, *J*=2.5 Hz, Cp), 7.10 (5H, m, Ph). Anal. Calcd for $C_{20}H_{23}FeNOS$: C, 62.99; H, 6.08; N, 3.67. Found: C, 63.20; H, 6.04; N, 3.71.

Treatment of (+)-**7** in MeOH with Raney-Ni afforded a compound whose spectroscopic and optical properties were in agreement with those of (1*S*)-1-hydroxymethyl-2-dimethylaminomethylferrocene, (–)-**8**.[7]

Lipase catalysed esterification of (±)-6

Lipozyme (500 mg) was added to a solution of (±)-**6** (250 mg, 0.82 mmol) in DIPE (25 mL) containing vinyl acetate (0.8 mL) and the suspension incubated at 45 °C under shaking (300 rpm). After 3 h (conversion ca. 42%) the enzyme was filtered off and the filtrate taken to dryness in vacuum. Column chromatography of the residue afforded unreacted (+)-**6** (140 mg, 57 % yield, 64 % e.e.) and (+)-**6a** (114 mg, 40% yield, 88% e.e.)

*(1R)-2-acetoxymethyl-1-*tert*-butylthioferrocene, (+)-6a.* $[\alpha]_D$ +3.5 (*c* 1.3, $CHCl_3$); ^{1}H-NMR δ 1.20 (9H, s, $C(CH_3)_3$), 2.01 (3H, s, CH_3CO), 4.15 (5H, s, C'p), 4.30 (1H, m, Cp), 4.43 (1H, m, Cp), 4.46 (1H, m, Cp), 4.99 and 5.06 (AB system, each 1H, d, *J*=11.8 Hz, CH_2OAc); ^{13}C-NMR δ 20.80, 30.65, 45.49, 60.94, 69.27, 69.94, 71.03, 77.21, 77.38, 84.97, 170.58. Anal. Calcd for $C_{17}H_{22}FeO_2S$: C, 58.97; H, 6.40. Found: C, 59.15; H, 6.42.

In an experiment in which the reaction was allowed to proceed up to 55% conversion the unchanged alcohol (+)-**6** was recovered with 95% e.e., $[\alpha]_D$ + 63 (*c* 1, $CHCl_3$).

Oxidation of (+)-1, (–)-5 and (+)-6

A solution of $NaIO_4$ (1.1 mmol) in water (2 mL) was added to a solution of compound (0.55 mmol) in dioxane (2 mL) and the mixture stirred at room temperature until complete conversion of the sulfides (Table 2). Water was then added and the product extracted with CH_2Cl_2. After drying with Na_2SO_4 the solvent was evaporated and the residue chromatographed on Si gel to afford pure sulfoxide(s).Thus, sulfoxides (–)-**9** and (+)-**10** were obtained from (+)-**1**, sulfoxides (–)-**11** and (+)-**12** from (–)-**5**, and sulfoxide (+)-**13** from (+)-**6**

(1S,S)-2-hydroxymethyl-1-methylsulfinylferrocene, (–)-9: 80 mg (52% yield); $[\alpha]_D$ –56 (*c* 0.06, $CHCl_3$); ^{1}H-NMR δ 2.79 (3H, s, SOCH3), 4.30 (1H, m, Cp), 4.41 (5H, m, C'p), 4.44 (3H, m, Cp and CH_2OH), 4.73 (1H, m, Cp); ^{13}C-NMR δ 41.64, 58.45, 67.65, 68.10, 70.38, 71.99, 89.18. Anal. Calcd for $C_{12}H_{14}FeO_2S$: C, 51.82; H, 5.07. Found: C, 51.67; H, 5.11.

(1S,R)-2-hydroxymethyl-1-methylsulfinylferrocene (+)-*10*: 50 mg (33% yield); $[\alpha]_D$ +221 (*c* 0.07, $CHCl_3$); ^{1}H-NMR δ 2.24 (1H, dd, *J*= 6 and 5.4 Hz, OH), 2.77 (3H, s, $SOCH_3$), 4.37 (7H, bs, C'p and Cp), 4.48 (2H, m, CH_2OH), 4.68 (1H, m, Cp); ^{13}C-NMR δ 43.65, 58.92, 64.88, 68.45, 70.18, 71.00, 87.01, 93.30. Anal. Calcd for $C_{12}H_{14}FeO_2S$: C, 51.82; H, 5.07. Found: C, 51.97; H, 5.09.

(1S,S)-2-hydroxymethyl-1-phenylsulfinylferrocene (–)-11: 40 mg (22% yield); mp 137-138 °C; $[\alpha]_D$ –247 (*c* 0.13, $CHCl_3$), ^{1}H-NMR δ 4.10 (2H, m, CH_2OH), 4.29 (1H, t, *J* =4.0 and 2.5 Hz, Cp), 4.38 (1H, m, Cp), 4.51 (5H, m, C'p), 4.73 (1H, m, Cp), 7.45 (3H, m, Ph), 7.57 (2H, m, Ph); ^{13}C-NMR δ 57.97, 67.90, 69.85, 70.48, 72.50, 89.14, 90.47, 124.10, 129.06, 130.58, 144.14. Anal. Calcd for $C_{17}H_{16}FeO_2S$: C, 60.02; H, 4.74. Found: C, 59.84; H, 4.80.
(1S,R)-2-hydroxymethyl-1-phenylsulfinylferrocene (+)-12: 130 mg (70% yield); mp 123-124 °C; $[\alpha]_D$ +710 (*c* 0.1, $CHCl_3$); ^{1}H-NMR δ 2.05 (1H, dd, *J*=4.8 and 6.6 Hz, OH), 4.32 (1H,t, *J*=2.5 Hz, Cp), 4.41 (5H, s, C'p), 4.52 (4H, m, Cp and CH_2OH), 7.43 (3H, m, Ph), 7.70 (2H, m, Ph); ^{13}C-NMR δ 58.88, 65.24, 68.80, 70.31, 70.85, 88.20, 94.67, 124.35, 129.00, 130.63, 146.12. Anal. Calcd for $C_{17}H_{16}FeO_2S$: C, 60.02; H, 4.74. Found: C, 59.78; H, 4.82.
*(1S,S)-2-hydroxymethyl-1-*tert*-butylsulfinylferrocene (+)-13*: 160 mg (91% yield); mp 173-174 °C; $[\alpha]_D$ +281 (*c* 1, $CHCl_3$); ^{1}H-NMR δ 1.16 (9H, s, $C(CH_3)_3$), 4.40 (5H,s, C'p), 4.49 (4H, m, Cp and CH_2OH), 4.73 (1H, m, Cp); ^{13}C-NMR δ 22.96, 55.96, 58.88, 66.00, 69.14, 69.95, 70.45, 77.19, 90.83.

Crystallographic analysis

The diffraction data was collected at 100 °K using the DESY synchrotron on wiggler beam line bw7b at a wavelength of 0.59400 Å. The structure was solved by direct methods, SHELXS-86,[10] and refined by full matrix least squares using SHELXL-93.[11] SHELX operations were rendered paperless using ORTEX which was also used to obtain the drawings.[12] Data were corrected for Lorentz and polarisation effects but not for the absorption. Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Silicon Graphics R4000 computer.

Acknowledgement: Authors thank Dr. Patrizia Mertoli (CNR) for the assistance in the preparation of ferrocenylsulfoxides. Thanks are due to Novo Nordisk for a kind gift of Novozym® 435 and Lipozyme® IM.

REFERENCES AND NOTES

1. Togni, A.; Hayashi, T. *Ferrocenes*, VCH, New York, 1995.
2. Shen, L.-H; Okoroafor, M. O.; Brubaker, C.H. *Organometallics* **1988**, *7*, 825
3. Yamazaki, Y.; Hosono, K.; Matsuda, H.; Minami, N.; Asai, M.; Nakanishi, H. *Biotech. Biong.* **1991**, *38*, 1218.
4. a) Hermann, R.; Hubener, G.; Ugi, I. *Tetrahedron* **1985**, *41*, 941. b) Pastor, S.D. *Tetrahedron* **1988**, *44*, 2883. c) Deus, N.; Hubener, G.; Herrmann, R. *J. Organometal. Chem.* **1990**, *384*, 155. d) Togni, A.; Pastor, S.D. *J. Org. Chem.* **1990**, *55*, 1649.
5. a) Yamazaki, Y.; Hosono, K. *Biotechnol. Lett.* **1989**, 2, 627. b) Yamazaki, Y.; Hosono, K. *Agric. Biol. Chem.* **1990**, *54*, 2183.
6. Lambusta, D.; Nicolosi, G.; Patti, A.; Piattelli, M. *Tetrahedron Lett.* **1996**, *37*, 127.
7. Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron Asymm.* **1994**, *5*, 1275.
8. Chen, C.-S., Fujimoto, Y.; Girdauskas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
9. Gokel, G. W.; Marquading, D.; Ugi, I. *J. Org. Chem.* **1972**, *37*, 3052.
10. Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467.
11. Sheldrick, G. M., SHELXL-93 a computer program for crystal structure determination, University of Gottingen 1993.
12. McArdle, P. *J. Appl. Cryst.* **1995**, *28*, 65.

(*Received in UK* 10 *September* 1996; *revised* 8 *November* 1996; *accepted* 14 *November* 1996)