Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3687–3692

TETRAHEDRON: *ASYMMETRY*

Preparation of chiral C_2-symmetrical 1,1′-disubstituted ferrocenes

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Received 27 June 2000; accepted 7 August 2000

Abstract

A biocatalytic procedure for the resolution and concurrent desymmetrization of tetraacetoxyferrocene (±, *meso*)-**2** is described. Enantiomerically pure (*R*,*R*)- and (*S*,*S*)-forms have been converted into the corresponding epoxide **6**, a useful starting material for the preparation of polyfunctional C_2-symmetric ferrocenes.

1. Introduction

Homogeneous asymmetric catalysis with transition metal complexes is an active area of research[1] and great interest is directed toward the design and development of efficient ligands.

Ferrocene ligands have gained much attention due to their peculiar chemical features, namely diastereoselective metallation on the cyclopentadienyl ring[2] and retentive nucleophilic displacement on the benzylic position,[3] which allow the preparation of a broad range of substituted derivatives. Numerous ferrocenyl ligands incorporating both planar and central chirality have proved very effective in several asymmetric catalytic processes.[4] More recently several C_2-symmetrical ferrocenes have been synthesized[5] and some ferrocenyldiphoshines have been used as catalysts in palladium-catalyzed reactions[6] or rhodium-catalyzed hydrogenation and hydrosilylation.[7]

Stereoselective reduction of 1,1′-ferrocenyldiketones provides access to C_2-symmetrical ferrocenes possessing only central chirality[8] and the related 1,1′-ferrocenyldiamines have been used successfully as ligands for ruthenium-catalyzed transfer hydrogenation.[9]

We have recently developed a chemoenzymatic method to prepare chiral ferrocenyl derivatives with a stereogenic carbon β to the cyclopentadienyl ring.[10] Here we report the extension of that procedure to 1,1′-bis[(2,3-dihydroxy)propyl]ferrocene, (±, *meso*)-**1** whose (*R*,*R*)- and (*S*,*S*)-forms

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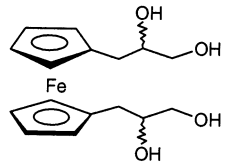
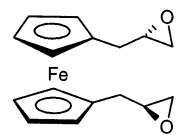
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00299-8

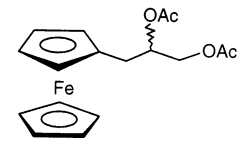
could in turn be converted into both enantiomers of 1,1′-ferrocenyldiepoxide **6**, a useful starting material for the preparation of highly functionalised C_2-symmetrical ferrocenes.



(±, *meso*)-**1**



(*S,S*)-**6**



(±)-**3**

The resolution of the racemic form and the desymmetrization of the *meso* form of (±, *meso*)-**1** were simultaneously achieved using a lipase-catalyzed reaction, and the results obtained are discussed.

2. Results and discussion

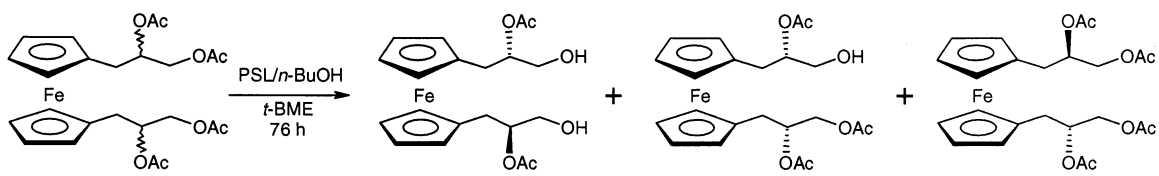
Conventional metallation of ferrocene with *n*-BuLi/TMEDA[11] and electrophilic quenching with benzylglycidyl ether gave, after the removal of benzylic groups, compound (±, *meso*)-**1** in about 45% yield and 1:1 diastereoisomeric ratio.[12] Attempts of separation of the racemic and the *meso* forms of **1** by chromatography or crystallization procedures failed, so the whole diastereoisomeric mixture was considered.

Due to the low solubility of (±, *meso*)-**1** in the common apolar organic solvents, the corresponding tetraacetate (±, *meso*)-**2** was chosen as a better substrate for enzymatic reactions.

It was known from previous work[10b] that lipase from *Candida antarctica* (immobilised, Novozyme® 435) catalyzed the alcoholysis of the diacetate (±)-**3** in a two-step sequential fashion, yielding the optically active diol and monoacetate. Conversely, in the same reaction carried out in the presence of lipase from *Pseudomonas cepacia*, only the stereospecific alcoholysis of the primary acetoxy group was promoted.

The latter enzyme was then chosen for the alcoholysis of (±, *meso*)-**2**, in order to prevent the formation of the tetrahydroxyferrocenyl compound and its possible precipitation on the enzyme surface.

When (±, *meso*)-**2** was subjected to alcoholysis with *n*-BuOH in *tert*-butyl methyl ether in the presence of *P. cepacia* lipase, after 76 h the reaction mixture contained three products in about a 1:2:1 ratio, as determined by HPLC analysis (Scheme 1).



(±, *meso*)-**2**

(+)-**4**
23%
(97% ee)

(–)-**5**
53%
(96% ee)

(–)-**2**
24%
(98% ee)

Scheme 1.

After purification on silica gel, diacetate (+)-**4**, triacetate (−)-**5** and unreacted tetraacetate (−)-**2** were isolated and characterized.

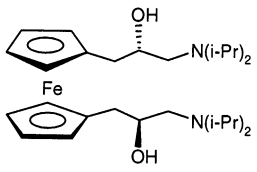
Tetraacetate (−)-**2** was enantiomerically and diastereoisomerically pure, as determined by ^{1}H NMR analysis in the presence of Eu(hfc)$_3$. The (*R*,*R*)-configuration of (−)-**2** could be assigned by comparison of its optical properties with those of an authentic sample prepared from ferrocene and (*R*)-benzylglycidyl ether.

Chemical acetylation of the diester (+)-**4** gave an optically active tetraacetate with the same, but opposite, $[\alpha]_D$ of (−)-**2**, so that the (*S*,*S*)-configuration of (+)-**4** and its single stereoform nature could be deduced. This data confirmed the *S*-stereo preference that lipase from *P. cepacia* had demonstrated in the resolution of (±)-**3**.

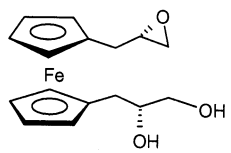
The tetraacetate derived from conventional acetylation of (−)-**5** showed a low positive optical rotation value compatible with its *meso* nature and the presence of about 8% of (*S*,*S*)-diastereoisomer. The enantiomeric excess of (−)-**5** was determined by ^{1}H NMR analysis with chiral shift reagent by comparison of its spectroscopic properties with those of a sample prepared from (±, *meso*)-**2** by controlled chemical hydrolysis in acidic medium. On the basis of the lipase stereo preference, the structure of 1-[((*S*)-2-acetoxy-3-hydroxy)propyl]-1′-[((*R*)-2,3-diacetoxy)propyl]ferrocene was assigned to (−)-**5**.

Alkaline hydrolysis of (−)-**2** afforded the corresponding tetrahydroxy derivative (*R*,*R*)-**1**; after treatment with 0.5 equiv. of TsCl and subsequent reaction with NaOMe the diepoxide (*R*,*R*)-**6** was obtained in 77% overall yield. The same reaction sequence was applied to compound (+)-**4** to give (*S*,*S*)-**6**.

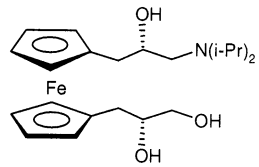
Enantiomers of **6** can be subjected to nucleophilic cleavage of the oxirane rings to give tetra substituted C_2-symmetrical ferrocenes suitable as ligands in asymmetric reactions: as a first example, the diaminodihydroxy derivative (+)-**7** was prepared by this route. Asymmetric monoepoxide (−)-**8** was also obtained from the triacetate (−)-**5** and reacted with NH(*i*-Pr)$_2$ to afford aminoalcohol (+)-**9**.



(+)-**7**



(−)-**8**



(+)-**9**

Another interesting application of diepoxide **6** could be envisaged in its reaction with bidentate nucleophiles to give chiral macrocyclic compounds containing a ferrocene unit and investigations in this direction are in progress.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated, at 250.13 and 62.9 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to TMS and all coupling constants (J) are in hertz. Optical rotations were measured on a DIP 370 JASCO instrument.

HPLC analyses were performed on a Cyclobond I 2000 column using CH_3CN/triethylammonium acetate mixtures. Europium tris[3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorate)], $Eu(hfc)_3$, was used as chiral shift reagent for the ^1H NMR determination of diastereoisomeric and enantiomeric composition of ferrocenylacetates.

Lipase from *Pseudomonas cepacia* (PSL) was obtained from Amano International Enzyme Co., column chromatography was performed on silica gel using specified eluants.

3.2. Synthesis of 1,1′-bis[(2,3-acetoxy)propyl]ferrocene, (±, meso)-**2**

To a solution of ferrocene (0.95 g, 5 mmol) in 25 ml of hexane, 6.7 ml of a 1.6 M solution of *n*-BuLi in hexane and 1.0 ml of TMEDA were added. The suspension was mantained at 60°C for 1 h then cooled at −40°C. After dilution with 10 ml of THF, a solution of benzyl glycidyl ether (1.6 ml, 10.5 mmol) in THF was added to the reaction mixture over 5 min. The cooling bath was then removed and the reaction was stirred for an additional 3 h at room temperature. The suspension was extracted with 1N HCl and the organic phase washed with sat. $NaHCO_3$ and brine. After evaporation of the solvent the residue was purified on a Si gel column (hexane/EtOAc 6:4) to give 1,1′-bis[(3-benzyloxy-2-hydroxy)propyl]ferrocene (1.15 g, 45% yield). This compound was dissolved in EtOH and reacted with H_2 (1 atm) in the presence of Pd/C at room temperature for 6 h. The suspension was filtered and the solution dried to give quantitatively (±, *meso*)-**1**, which was then subjected to conventional acetylation (Ac_2O/Py) to afford (±, *meso*)-**2**. ^1H NMR: δ 2.07 (6H, s), 2.09 (6H, s), 2.65 and 2.68 (AB system, each 2H, dd, $J=14.5$ and 6.5), 3.99 (2H, dd, $J=12.0$ and 6.5), 4.02 (2H, m), 4.07 (6H, m), 4.21 (2H, dd, $J=12.0$ and 3.5), 5.05 (2H, m); ^{13}C NMR: δ 20.7, 21.0, 31.1, 64.2, 68.6, 68.7, 69.6, 72.0, 82.4, 170.2, 170.6. *Anal.* calcd for $C_{24}H_{30}FeO_8$: C, 57.38; H, 6.02; Fe, 11.12. Found: C, 57.60; H, 6.05; Fe, 11.18.

3.3. Preparation of (RR,SS)/(RS,SR)-**5**

To a solution of 100 mg of (±, *meso*)-**2** in 5 ml of MeOH/H_2O 4:1 mixture, 30 mg of Dowex 50W X 8 (H^+) were added and the suspension maintained under stirring at 60°C overnight. The suspension was then filtered and the solution taken to dryness. The residue was then purified on a silica gel column (hexane/EtOAc 1:1) to give about 30% of the title compound.

3.4. Alcoholysis of (±, meso)-**2** with PSL

To a solution of (±, *meso*)-**2** (0.6 g, 1.2 mmol) in *t*-BME (60 ml), lipase (1.2 g) and *n*-BuOH (1.8 ml, 20 mmol) were added and the mixture was shaken at 45°C. The reaction course was monitored by TLC and HPLC and after 76 h the reaction was stopped by filtering off the enzyme. After evaporation of the solvent, the residue was purified on a silica gel column (from hexane/EtOAc, 7:3, to neat EtOAc as eluants) to give (−)-**2** (145 mg, 24% yield, 98% ee, 98% de, $[\alpha]_D$ −75.5 (*c* 0.60, $CHCl_3$), (−)-**5** (285 mg, 52% yield, 96% ee, 84% de) and (+)-**4** (110 mg, 22% yield, 97% ee, 96% de).

Alkaline hydrolysis (K_2CO_3/MeOH) of (−)-**2** afforded (*R*,*R*)-1,1′-bis[(2,3-dihydroxy)propyl]ferrocene, (*R*,*R*)-(+)-**1**, $[\alpha]_D$ +8.2 (*c* 0.50, H_2O); ^1H NMR (CD_3OD): δ 2.49 (2H, dd, $J=7.0$ and 14.2), 2.60 (2H, dd, $J=5.5$ and 14.2), 3.40 (2H, dd, $J=6.5$ and 11.0), 3.49 (2H, dd, $J=$, 4.3 and 11.0), 3.63 (2H, m), 4.06 (4H, bs), 4.10 (4H, bs); ^{13}C NMR (CD_3OD): δ 34.9,

66.5, 69.2, 69.3, 70.7, 71.1, 74.4, 86.0. *Anal.* calcd for $C_{16}H_{22}FeO_4$: C, 57.50; H, 6.64; Fe, 16.71. Found: C, 57.33; H, 6.60; Fe, 16.59.

*3.5. (S,S)-1,1′-Bis[(2-acetoxy-3-hydroxy)propyl]ferrocene, (+)-**4***

Data for (+)-**4**: $[\alpha]_D$ +67.0 (*c* 0.58, $CHCl_3$); ^1H NMR: δ 2.10 (6H, s), 2.69 (4H, d, $J=6.5$), 3.60 (2H, dd, $J=12.0$ and 5.7), 3.70 (2H, dd, $J=12.0$ and 3.5), 3.98 (2H, m), 4.07 (6H, m), 4.89 (2H, ddt, $J=6.5$, 5.7 and 3.5); ^{13}C NMR: δ 21.2, 30.8, 63.7, 67.8, 68.8, 69.8, 75.8, 83.1, 171.2. *Anal.* calcd for $C_{20}H_{26}FeO_6$: C, 57.43; H, 6.26; Fe, 13.35. Found: C, 57.54; H, 6.29; Fe, 13.41.

*3.6. 1-[((S)-2-Acetoxy-3-hydroxy)propyl]-1′-[((R)-2,3-diacetoxy)propyl]ferrocene, (−)-**5***

Data for (−)-**5**: $[\alpha]_D$ −6.2 (*c* 0.78, C_6H_6); ^1H NMR: δ 2.07 (3H, s), 2.09 (6H, s), 2.67 (4H, m), 3.60 (1H,dd, $J=12.0$ and 5.5), 3.70 (1H, dd, $J=12.0$ and 3.3), 3.98 (1H, dd, $J=11.8$ and 6.5), 4.06 (8H, m), 4.21 (1H, dd, $J=11.8$ and 3.5), 4.87 (1H, m), 5.05 (1H, m); ^{13}C NMR: δ 20.8, 21.1, 21.2, 30.8, 31.2, 63.7, 64.4, 68.7, 69.8, 72.1, 75.8, 82.5, 83.1, 170.4, 170.7, 171.0. Anal. calcd for $C_{22}H_{28}FeO_7$: C, 57.41; H, 6.13; Fe, 12.13. Found: C, 57.64; H, 6.17; Fe, 12.19.

*3.7. (R,R)-1,1′-Bis[(2,3-epoxy)propyl]ferrocene, (+)-**6** and 1-[((S)-2,3-epoxy)propyl]-1′-[((R)-2,3-dihydroxy)propyl]ferrocene, (−)-**8***

To a solution of (−)-**2** (200 mg, 0.6 mmol, 97% ee) in CH_2Cl_2 (5 ml) *p*-toluenesulfonyl chloride (250 mg, 0.55 equiv.) and pyridine (1 ml) were added. The solution was mantained at 0°C for 12 h, then diluted with cold water and extracted with ethyl acetate. After washing with dil. HCl the organic phase was dried over Na_2SO_4 and the solvent evaporated in vacuo. The crude residue was then dissolved in toluene and a 15% solution of sodium methoxide in MeOH was added dropwise. A white solid was formed immediately, which was removed by filtration and washed with toluene. The solution was taken to dryness and the residue purified on a silica gel column (hexane/EtOAc 8:2) to give diepoxide (+)-**6** (110 mg, 77% yield), $[\alpha]_D$ +13.7 (*c* 0.35, $CHCl_3$); ^1H NMR: δ 2.52 (2H, dd, $J=5.0$ and 2.8), 2.56 and 2.62 (AB system, each 2H, $J=15.0$ and 5.5), 2.79 (2H, t, $J=5.0$), 3.11 (2H, m), 4.11 (8H, bs); ^{13}C NMR: δ 32.6, 46.8, 52.1, 68.4, 69.1, 83.7. *Anal.* calcd for $C_{16}H_{18}FeO_2$: C, 64.45; H, 6.08; Fe, 18.73. Found: C, 64.26; H, 6.06; Fe, 18.60.

The reaction of (+)-**4** or (−)-**5** with 1 equiv. of TsCl according to the procedure described above afforded diepoxide (−)-**6** and monoepoxide (−)-**8**, respectively. Data for (−)-**8**: $[\alpha]_D$ −6.0 (*c* 0.40, EtOH); ^1H NMR (CD_3COCD_3): δ 2.47 (1H, m), 2.55 (4H, m), 2.70 (1H, dd, $J=4.0$ and 5.0), 3.06 (1H, m), 3.43 (2H, m), 3.61 (1H, m), 4.06 (4H, bs), 4.10 (2H, bs), 4.13 (2H, m); ^{13}C NMR (CD_3COCD_3): δ 32.3, 33.7, 45.8, 51.6, 65.6, 67.8, 68.8, 69.4, 69.6, 69.8, 72.9, 83.9, 85.4. *Anal.* calcd for $C_{16}H_{20}FeO_3$: C, 60.78; H, 6.37; Fe, 17.66. Found: C, 61.02; H, 6.33; Fe, 17.53.

*3.8. (S,S)-1,1′-Bis[(3-diisopropylamino-2-hydroxy)propyl]ferrocene, (+)-**7** and 1-[((S)-3-diisopropylamino-2-hydroxy)propyl]-1′-[((R)-2,3-dihydroxy)propyl]ferrocene, (+)-**9***

Epoxide (−)-**6** (50 mg) was dissolved in dioxane/H_2O (4:1, 5 ml) and reacted with NH(*i*-Pr)$_2$ (0.2 ml) at 60°C for 24 h. The solution was taken to dryness and the residue purified on silica gel (EtOAc/triethylamine 9:1) to give pure (+)-**7** (55 mg, 65% yield), $[\alpha]_D$ +40.9 (*c* 0.30, $CHCl_3$);

^{1}H NMR: δ 0.99 (12H, d, $J=6.8$), 1.27 (12H, d, $J=6.8$), 2.19 (2H, dd, $J=10.5$ and 13.2), 2.41 (2H, dd, $J=5.5$ and 14.2), 2.54 (2H, dd, $J=3.5$ and 13.2), 2.58 (2H, dd, $J=6.7$ and 14.2), 3.01 (4H, m), 3.51 (2H, m), 4.06 (6H, bs), 4.10 (2H, bs); ^{13}C NMR: δ 12.2, 23.0, 35.7, 48.0, 50.3, 67.8, 68.11, 68.3, 69.6, 69.8, 84.8. *Anal*. calcd for $C_{28}H_{48}FeN_2O_2$: C, 67.19; H, 9.66; Fe, 11.16; N, 5.60. Found: C, 67.41; H, 9.70; Fe, 11.23; N, 5.62.

The same procedure was applied to epoxide (−)-**8** to prepare aminoalcohol (+)-**9**, $[\alpha]_D$ +26.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (CD_3OD): δ 1.04 (6H, d, $J=6.5$), 1.06 (6H, d, $J=6.7$), 2.37 (1H, dd, $J=9.5$ and 13.2), 2.49 (3H, m), 2.61 (2H, dd, $J=5.7$ and 14.2), 3.13 (2H, m), 3.39 (1H, dd, $J=6.2$ and 11.0), 3.49 (1H, dd, $J=4.5$ and 11.0), 3.60 (2H, m), 4.07 (4H, m), 4.10 (4H, m); ^{13}C NMR (CD_3OD): δ 18.6, 20.5, 33.5, 35.02, 48.4, 50.1, 65.1, 67.7, 69.2, 69.5, 73.0, 84.5, 84.6. *Anal*. calcd for $C_{22}H_{35}FeNO_3$: C, 63.31; H, 8.45; Fe, 13.38; N, 3.35. Found: C, 63.45; H, 8.51; Fe, 13.46; N, 3.37.

Acknowledgements

Financial support from CNR Target Project on 'Biotechnology' is acknowledged. Thanks are also due to Amano Enzyme Europe Ltd for the generous gift of *P. cepacia* lipase.

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12. Quite surprisingly, no distinction in the ^{1}H and ^{13}C NMR resonances was observed for the diastereoisomeric forms of (±, *meso*)-**1** and (±, *meso*)-**2**. The diastereoisomeric ratio of (±, *meso*)-**2** was determined by ^{1}H NMR analysis in the presence of Eu(hfc)$_3$.