Tetrahedron: Asymmetry Vol. 4, No. 5, pp. 919-924, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

Separation of Stereoisomeric 1,1'-Bis(α-hydroxyethyl)ferrocenes by Lipase-Mediated Acetylation in Organic Solvent

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

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

Via del Santuario 110, 95028 Valverde CT, Italy

(*Received* 15 *February* 1993; *accepted* 25 *March* 1993)

Abstract - Acetylation of *meso,dl*-1,1'-bis(α-hydroxyethyl)ferrocene in dry acetone using vinyl acetate as acetyl donor and *Pseudomonas cepacia* lipase as catalyst allowed the diacetate of the (*R,R*)-enantiomer and the free (*S,S*)-diol to be obtained. A concurrent desymmetrization of the *meso*-diol was also obtained.

INTRODUCTION

The recent increase in demand for optically pure single enantiomers of possible use in different fields - for example pharmaceutical, agrochemical and optoelectronic - has aroused considerable interest in improved methods for the preparation of chiral organometallic compounds, among them ferrocenes, valuable in asymmetric catalysis and in asymmetric organic synthesis.[1] Of all the ferrocenes, those with a stereogenic α-carbon in a side chain are particularly attractive. This is primarily due to the possibility of carrying out on substrates of this type nucleophilic substitutions at the stereogenic center with complete retention of configuration.[2] Moreover, when an appropriate group is bound to the asymmetric center the introduction of a second substituent into the adjacent position of the same cyclopentadienyl ring can be carried out with high stereoselectivity, giving rise to compounds possessing planar in addition to central chirality.[3] These compounds, if available as single enantiomers, may be trasformed by classical chemical methods into a variety of optically active products.[4]

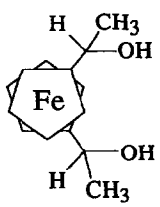
For the preparation of single enantiomers of ferrocenes with central chirality,

enzyme-mediated resolution of a racemic mixture, that in many cases compares favourably with alternative physico-chemical methods, can be taken into consideration.[5] In the present paper we wish to report the enzymatic separation of a mixture of (*R*,*R*)-, (*S*,*S*)- and (*R*,*S*)-isomers of a symmetrically 1,1'-disubstituted ferrocene derivative with central chirality, 1,1'-bis(α-hydroxyethyl)ferrocene. The metod chosen is similar to that used by Wallace *et al.*[6] for the separation of aromatic diol stereoisomers, but in the case in hand it is made more complicated by the possible interaction between the stereogenic centers.

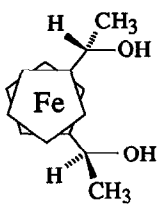
RESULTS AND DISCUSSION

Reduction of 1,1'-diacetylferrocene with litium aluminium hydride affords 1,1'-bis(α-hydroxyethyl)ferrocene **1** as an isomeric mixture from which *meso* and racemic forms, present in about equal amounts, can be separated by a combination of repeated recrystallizations from hexane and column chromatography.[7] Since this procedure is time-comsuming and may result in considerable losses of material, we decided to try to obtain the enantiomers directly from the whole isomeric mixture by irreversible transesterification using vinyl acetate as acylating agent in the presence of *Pseudomonas cepacia* (*fluorescens*) lipase, which is known to catalyze the esterification of the (*R*) configuration of secondary alchohols selectively.[8] Obviously this implies a reaction system more complicated than that without the *meso* compound, but we hoped to obtain, together with the resolution of the enantiomers, a desymmetrization of the *meso* form affording an additional optically active compound suitable for further manipulations to give potentially useful chiral compounds.

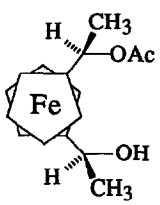
The isomeric mixture as obtained from reduction of 1,1'-diacetylferrocene was dissolved in dry acetone. The acetylating agent, vinyl acetate, was then added, followed by crude



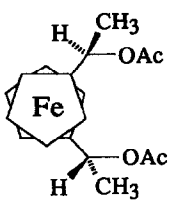
meso,dl-**1**



(*S*,*S*)-**1**



(*R*,*S*)-**2**

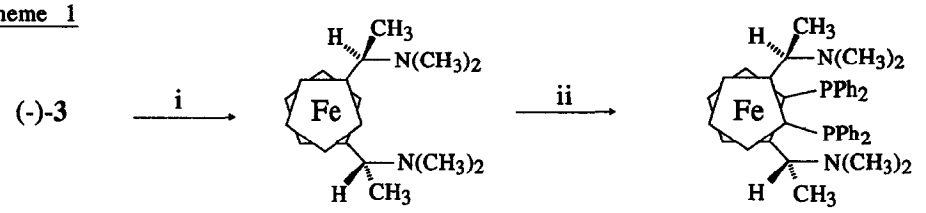


(*R*,*R*)-**3**

Pseudomonas cepacia lipase. The reaction was monitored by HPLC and quenched by filtering off the enzyme after 6 days, when the percentage of the diester approached the theoretical value (25%) calculated assuming that only the (*R*,*R*)-diol had been converted

into the corresponding diacetate. The reaction mixture was separated by column chromatography giving three main fractions. The less polar fraction was essentially (*R,R*)-diacetate **3** and no attempt was made to remove the (*R,S*)-diacetate impurity (ca. 4% as determined by ^{1}H-NMR analysis). The *R,R*-configuration, which could be anticipated by both the known stereochemical preference of the lipase used and the value of the optical rotatory power ($[\alpha]_D$ -48.5) which is almost twofold that of 1-ferrocenylethanol acetate[8] ($[\alpha]_D$ -28.5) was firmly established by chemical correlation with 2,2'-bis-[(*R*)-(α-*N,N*-dimethylamino)ethyl]-(*S*)-(*S*)-1,1'-bis(diphenylphosphino)ferrocene (-)-5,[9] a chiral catalyst of known absolute configuration, through 1,1'-bis[(*R*)-(α-*N,N*-dimethylamino)ethyl]ferrocene **4**, as summarized in Scheme 1.

Scheme 1



i) $NH(CH_3)_2/CH_3OH$; ii) *n*-BuLi, PPh_2Cl

The fraction of intermediate polarity was shown by ^{1}H-NMR spectroscopy also in the presence of a chiral shift reagent to consist of two diastereoisomeric monoacetates in a ratio of 6 to 1. Moreover, it was also evident that the more abundant diastereoisomer was in turn a mixture of two enantiomers in a ratio of 10 to 1. Since chemical acetylation of this fraction afforded a diester with a slightly positive optical rotation, it was inferred that the minor diastereoisomeric monoacetate was the (*S,S*)-isomer and the major one a mixture of the two enantiomeric monoacetates of the *meso*-diol, with a preponderance of the enantiomer bearing the acetoxy group at the *R* stereogenic center. The last assumption was based on the known stereopreference of the enzyme. Finally, NMR analysis of the more polar fraction from the column chromatography showed that it was a mixture of (*S,S*)- and (*R,S*)-diols in 3:1 ratio. This fraction was again subjected to lipase-mediated acetylation to give enantiomerically pure (*S,S*)-diol **1** and a less pure (*R,S*)-monoacetate **2**.

The results presented here show that from the *meso,dl*-mixture of the chiral diol **1** both *S,S*- and *R,R*-enantiomers, the last as the corresponding diacetate, can be obtained

in good optical purity by enzyme-mediated esterification. This reaction at the same time causes the desymmetrization of the *meso*-form giving the chiral *R,S*-monoacetate **2**, however of less satisfactory purity. The obtained compounds can be used as sources of chirality for the preparation of a variety of optically active ferrocenes.

EXPERIMENTAL

General methods

^{1}H- and ^{13}C-NMR spectra were recorded at 250.13 and 62.9 MHz respectively on a Bruker AC 250 spectrometer. Samples were dissolved in $CDCl_3$ containing TMS as internal reference. Optical rotations were measured on a Jasco DIP-370 polarimeter. IR spectra were recorded in $CHCl_3$ on a Perkin Elmer 1720X FT-IR spectrophotometer; data are given in frequency unit (ν, cm^{-1}). HPLC analyses were carried out on a Varian instrument fitted with an UV detector (λ 254 nm) using an Hypersil ODS column (150 x 4.6 mm) and mixtures of CH_3CN and water as eluent.

Materials

All reagents were analytical grade. 1,1'-Diacetylferrocene was from Aldrich. Lipase from *Pseudomonas cepacia* was obtained from Amano International Enzyme Co. and used as received. Acetone was dried overnight on 3 Å molecular sieves. Vinyl acetate was distilled prior to use. Column chromatography was performed on LiChroprep Diol 40-63 μm (Merck). Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] and (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's alcohol), used as chiral shift agents, were from Aldrich.

meso,dl-1,1'-*Bis(α-hydroxyethyl)ferrocene* ***1***

1,1'-Diacetylferrocene in THF was reduced with $LiAlH_4$ to afford *meso,dl*-**1** according to the procedure described by Yamakawa and Hisatome.[7] Separate resonances for *meso*- and *dl*-**1** are observed in proton[7] and carbon NMR spectra. ^{13}C-NMR: δ 25.20 (CH_3CH-, *meso*), 25.59 (CH_3CH-, *dl*), 65.48 (CH_3CH-, *meso*), 65.52 (CH_3CH-, *dl*), 65.19, 65.92, 66.50 and 67.34 (Cp, *meso*), 66.10, 67.49, 67.59 and 67.75 (Cp, *dl*), 95.15 (C-1 and C-1').

Conventional acetylation (Ac_2O/Py) of *meso,dl*-**1** gave *meso,dl*-**3**. ^{1}H-NMR: δ 1.52 (d, 3H, J=6.6 Hz, CH_3CH-, *meso*), 1.53 (d, 3H, J=6.6 Hz, CH_3CH-, *dl*), 2.03 (s, 6H, -OAc), 4.12 (m, 4H, Cp), 4.17 (m, 2H, Cp), 4.22 (m, 2H, Cp), 5.79 (bq, CH_3CH-). ^{13}C-NMR: δ 19.83 (CH_3CH-, *meso*), 20.04 (CH_3CH-, *dl*), 21.07 (-OAc), 66.35 (CH_3CH-, *meso*), 66.39 (CH_3CH-, *dl*), 68.21, 68.52, 68.65 and 68.89 (Cp), 88.37 (C-1, *meso*), 88.44 (C-1, *dl*), 170.01 (-OAc).

Lipase catalyzed acetylation of meso,dl-*1*.

To a solution of diol **1** (200 mg) in dry acetone (15 ml) were added vinyl acetate (0.15 ml) and *Pseudomonas cepacia* lipase (1.5 g). The mixture was continuously stirred (300 rpm) at 45 °C and the reaction progress was monitored by HPLC at regular time intervals. After 6 days, when the reaction mixture contained 25% of diacetates, the reaction was stopped filtering out the enzyme. Column chromatography on silica gel Diol (gradient of diethyl ether/petroleum ether as the eluent) of the mixture afforded three bands.

The first band was evaporated to dryness affording a yellow glassy solid (52 mg), $[\alpha]_D$ -48.4 (c=1, $CHCl_3$). IR ν_{max} 3020, 1724, 1373, 1254, which was shown by ^{1}H-NMR spectroscopy also in the presence of Eu(hfc)$_3$ to consist of (*R,R*)-**3** [(*R*)-1,1'-bis(α-acetoxyethyl)ferrocene] contaminated with a small amount (ca. 4%) of *R,S*-diacetate. Others stereoisomers were not detected by ^{1}H-NMR.

^{1}H-NMR data showed that the second band (82 mg), [α] +2.0 (c=1, $CHCl_3$), consisted of two diastereoisomeric monoacetates in a ratio of 6 to 1, the major one being (*R,S*)-**2** [(*R*)-1-(α-acetoxyethyl)-(*S*)-1'-(α-hydroxyethyl)ferrocene], with a 90% e.e. IR ν_{max} 3531, 3014, 1726, 1374, 1253, 1227. ^{1}H-NMR: δ 1.42 (d, 3H, J=6.4 Hz, *CH*$_3$CHOH-), 1.52 (d, 3H, J=6.4 Hz, *CH*$_3$CHOAc-), 2.07 (s, 3H, -OAc), 4.14 (m, 3H, Cp), 4.18 (m, 3H, Cp), 4.22 (m, 1H, Cp), 4.25 (m, 1H, Cp), 4.55 (q, 1H, J=6.4 Hz, CH$_3$*CH*OH-), 5.80 (q, 1H, J=6.4 Hz, CH$_3$*CH*OAc-). ^{13}C-NMR: δ 20.33 (*CH*$_3$CHOAc-), 21.32 (-OAc), 24.00 (*CH*$_3$CHOH-), 65.43 (CH$_3$*CH*OH-), 66.33, 66.47, 66.70 (CH$_3$*CH*OAc-), 66.83, 68.00, 68:14, 68.56, 88.85 (C-1), 95.27 (C-1'), 170.45 (-OAc).] Chemical acetylation (Ac_2O/Py) of an aliquot of this band gave a diester possessing $[\alpha]_D$ +6.0 (c=1, $CHCl_3$).

NMR spectral analysis of the third band (47 mg) indicated that the unreacted diol was a 3:1 mixture of (*S,S*)- and (*R,S*)-isomers. Recycling of this fraction through the enzyme-catalyzed esterification procedure afforded a mixture of (*R,S*)-monoacetate and (*S,S*)-diol, that was separated by column chromatography to give pure (*S,S*)-**1** [(*S*)-1,1'-bis(α-hydroxyethyl)ferrocene] (27 mg), $[\alpha]_D$ +42.0 (c=0.5, C_6H_6), 100% e.e. [evaluated from the ^{1}H-NMR spectrum run in the presence of Eu(hfc)$_3$]. In addition, a small fraction (9 mg) of monoacetates was obtained, with a composition similar to that the main monoacetate fraction.

Determination of the absolute configuration of (-)-3

Aqueous dimethylamine (33%, 0.5 mL) was added to a solution of (-)-**3** (100 mg) in methanol (2 mL) and the mixture was left at room temperature for 2 days. Subsequent work-up, similar to that described by Gokel[2] for the preparation of *N,N*-dimethyl-1-ferrocenylethylamine, afforded (+)-1,1'-bis[(α-*N,N*-dimethylamino)ethyl]ferrocene **4** (65 mg), $[\alpha]_D$ +26.8 (c=1.1, $CHCl_3$), e.e 100% (as determined by ^{1}H-NMR in the presence of Pirkle's alcohol), IR: ν_{max} 3094, 2976, 2940, 2864, 2828, 1474, 1457. ^{1}H-NMR: δ 1.43 (d, 6H, J=6.8 Hz, *CH*$_3$CH-), 2.06 (s, 12H, -N(CH$_3$)$_2$), 3.59 (m, 2H,

CH_3CH-), 4.06 (m, 8H, Cp). ^{13}C-NMR: δ 16.09 (CH_3CH-), 40.56 (-N(CH_3)$_2$), 58.48 (CH_3CH-), 67.09, 68.25, 68.49 and 70.32 (Cp), 87.06 (C-1).

An aliquot (50 mg) of (+)-**4** was reacted with *n*-BuLi followed by PPh_2Cl according to Hayashi *et al.*[9] to give 2,2'-bis-[(*R*)-α-(*N*,*N*-dimethylamino)ethyl]-(*S*)-(*S*)-1,1'-bis(diphenylphosphino)ferrocene (-)-**5**, $[\alpha]_D$ -435 (c=0.7, $CHCl_3$), lit.[9] $[\alpha]_D$ -457.

Acknowledgements - Authors are grateful to Amano International Enzyme Co. for kind supply of lipase. Thanks are due to CNR for financial support, under the scheme "Progetto Finalizzato per la Chimica Fine e Secondaria".

REFERENCES

1. a) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K. and Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772. b) Ojima, I; Clos, N. and Blastos, C. *Tetrahedron* **1989**, *45*, 6901. c) Blystone, S. L. *Chemical Rev.* **1989**, *89*, 1663. d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H. and Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.
2. Gokel, G. W.; Marquarding, D. and Ugi, I. K. *J. Org. Chem.* **1972**, *20*, 3052.
3. Marquading, D.; Klusacek, H.; Gokel, G.; Hoffmann, P. and Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.
4. Hayashi, T. and Yamazaki, A. *J. Organomet. Chem.* **1991**, *413*, 295.
5. a) Wang., Y-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E. and Womg, C-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200. b) Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061. c) Kim, M. J.; Cho, H. and Chol, Y. K. *J. Chem. Soc. Perkins Trans. 1* **1991**, 2270.
6. Wallace, J. S.; Baldwin, B. W. and Morrow, C. J. *J. Org. Chem.* **1992**, *57*, 5231.
7. Yamakawa, K. and Hisatome, M. *J. Organomet. Chem.* **1973**, *52*, 407.
8. Xie, Z-F. *Tetrahedron: Asymm.* **1991**, *2*, 733.
9. Hayashi, A.; Yamato, A.; Hojo, M.; Kishi, K.; Ito, Y.; Nishioka, E.; Miura, H. and Yanagi, K. *J. Organomet. Chem.* **1989**, *370*, 129.