Pergamon

Tetrahedron Letters, Vol. 37, No. 1, pp. 127-130, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02090-X

Lipase-Mediated Resolution of Racemic 2-Hydroxymethyl-1-methylthioferrocene

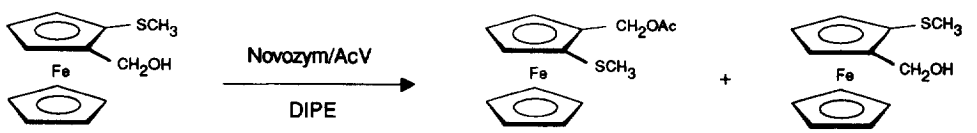
Daniela Lambusta, Giovanni Nicolosi,* Angela Patti and Mario Piattelli

Istituto CNR per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico
Via del Santuario 110, I-95028 Valverde CT, Italy

Abstract: Both enantiomers of 2-hydroxymethyl-1-methylthioferrocene have been obtained with high optical purity by lipase-catalysed resolution of the racemate.

Ferrocenyl derivatives with central or central/planar chirality have remarkable interest in organic asymmetric synthesis, since they can be used as catalysts in homogeneous phase.[1] In general, homochiral 1,2-disubstituted ferrocenes with both central and planar chirality can be obtained following a method developed by Ugi[2] and based on the use of chiral ferrocenylamino derivatives as starting material. These by treatment with butyl lithium undergo stereoselective *ortho*-lithiation, paving the way for the introduction of diverse substituents. As regards homochiral ferrocenes with only planar chirality, until now they have been obtained by either enzymatic synthesis[3] or resolution of racemates. In the application of the latter methodology, enantioselective lipase-catalysed reactions in non-aqueous media have been employed successfully to obtain homochiral hydroxymethylferrocenes.[4,5]

In the present paper we wish to report the enzymatic resolution of 2-hydroxymethyl-1-methylthioferrocene, **1**. The obtained enantiomers can be used as starting material for the synthesis of 1,2- and 1,2,3-substituted ferrocenes with predetermined planar chirality.



(±)-**1** (+)-**2** (+)-**1**

Initial attempts at esterification of racemic 2-hydroxymethyl-1-methylthioferrocene, (±)-**1**,[6] with vinyl acetate in toluene in the presence of different enzymes evidenced that lipases from *Aspergillus niger*, *Rhizophus javanicus* and *Mucor javanicus* are inactive, while lipases from *Mucor miehei* (immobilised, Lipozyme® IM), *Candida antarctica* (immobilised, Novozym® 435), *C. cylindracea* and *Pseudomonas cepacia* gave ester **2**, however with low enantiomeric excess. Better results were obtained replacing toluene with *tert*-butyl methyl

ether (*t*-BME) or diisopropyl ether (DIPE). In this last solvent the value of E was 20 and 30 with Lipozyme® IM and Novozym® 435, respectively (Table 1). The enantioselectivity of lipase from *Pseudomonas cepacia*, whose stereopreference is opposite, is very low (E = 2).

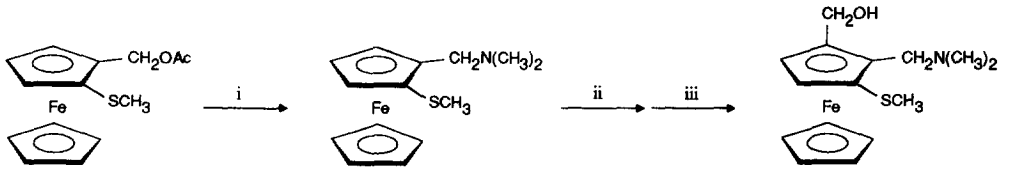
Table 1. Acetylation of 2-Hydroxymethyl-1-methylthioferrocene Promoted by different Lipases

Lipase from	Time, min.	Conv., %	e.e. ester[a]	E	Stereopreference	e.e. alcool
Mucor miehei (Lipozyme® IM)	25	46	81	20	1*R*	69
Candida antarctica (Novozym® 435)	55	32	90	30	1*R*	48
Candida cylindracea	20	36	76	11	1*R*	42
Pseudomonas cepacia	300	20	33	2	1*S*	22

Experimental conditions: diisopropyl ether as solvent; substrate 10 mg/mL; lipase 20 mg/mL; vinyl acetate 10 μL/mL (10 eqv).
[a]Determined after reductive deacylation with $LiAlH_4$ by ^1H NMR in the presence of $Eu(hfc)_3$.

A preparative esterification[7] of (±)-**1** catalysed by Novozym® 435 in DIPE furnished (+)-**2** in good chemical (47%) and optical (e.e. 84%) yields. From (+)-**2** the corresponding alcohol, (–)-**1**, was obtained by cleavage with $LiAlH_4$. If the enzyme-mediated esterification of (±)-**1** is allowed to proceed up to a conversion value of 60%, the e.e. value of the unreacted alcohol (+)-**1** reaches 95%.

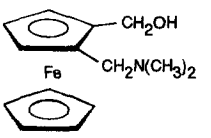
The absolute configuration of (–)-**1** was determined by chemical correlation with the known aminoalcohol (–)-**5**. To this end, ester (+)-**2** was reacted with dimethylamine in aqueous methanol to give compound (–)-**3**, which was converted into the 1,2,3-ferrocenyl derivative (–)-**4**,[8] taking advantage of the *ortho*-orientating effect of the amino group of (–)-**3**. The reductive removal (Raney nickel) of the methythio group afforded (–)-**5**,[5] thus allowing to assign the absolute configuration to (–)-**1** as 1*R*,2*S*.[9]



(+)-**2** (-)-**3** (-)-**4**

iv

i $NH(CH_3)_2$/ MeOH
ii *n*-BuLi
iii $C_3H_6O_3$
iv Raney Ni



(-)-**5**

Alternatively, (–)-**1** can be prepared from racemic ester (±)-**2** by alcoholysis with *n*-butanol in DIPE or *t*-BME in the presence of Novozym® 435. In the latter solvent (–)-**1** was obtained with 40% chemical yield and very good e.e. (90%). However, alcoholysis of the ester requires a much longer reaction time than direct esterification of the free alcohol.

Compounds (–)-**1**, (–)-**3**, (–)-**4** and some of their derivatives are under investigation in our laboratory for possible catalytic activity towards the alkylation of aldehydes with diethylzinc.

In brief, both enantiomers of 2-hydroxymethyl-1-methylthioferrocene can be obtained with high optical purity by enzyme-catalysed acetylation of the racemic (±)-**1** or transesterification of the corresponding acetate (±)-**2**.

Acknowledgements. Thanks are due to National Council of Research (Roma) "Progetto Strategico Tecnologie Chimiche Innovative" for financial support. We also thank Novo Nordisk for a gift of Lipozyme® IM and Novozym® 435.

REFERENCES AND NOTES

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis;* John Wiley & Sons Inc., New York, 1993, pp. 255-297. Sawamura, M; Ito, Y. *Chem. Rev.* **1992**, *92*, 857-871 and references therein.

2. Marquading, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389-5393.

3. Izumi, T.; Hiro, T.; Kasahara, A. *J. Chem. Tech. Biotechnol.* **1991**, *50*, 571-573. Izumi, T.; Murakami, S.; Kasahara, A. *Chem. & Ind.*, **1990**, 79-80. Yamazaki, Y.; Hosono, K. *Agr. Biol. Chem.* **1990**, *54*, 2183-2186. Yamazaki,Y.; Uebayasi, M.; Hosono, K. *Eur. J. Biochem.* **1989**, *184*, 671-680. Yamazaki,Y.; Hosono, K. *Biotechnol. Lett.* **1989**, *10*, 679-684.

4. Nicolosi, G.; Patti, A.; Piattelli, M. *J. Org. Chem.* , **1994**, *59*, 251-254. Lambusta, D.; Nicolosi, G.; Patti, A.; Piattelli , M. *Tetrahedron: Asymmetry*, **1993**, *4*, 919-924. Izumi, T.; Aratani, S. *J. Chem. Tech. Biotechnol.* **1993**, *57*, 33-36. Izumi, T.; Hiino, T.; Ishihara, A. J. *Chem. Tech. Biotechnol.* **1993**, *56*, 45-49. Izumi, T.; Tamura, F.; Sasaki, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2784-2788. Izumi, T.; Hino, T. J. *Chem. Tech. Biotechnol.* **1992**, *55*, 325-331.

5. Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron Asymmetry* **1994**, *5*, 1275-1280.

6. Compound (±)-**1** was prepared from dimethylaminomethylferrocene, by metalation with *n*-BuLi and subsequent reaction with dimethyldisulfide to give (±)-**3**, that was then treated with CH_3I. The resultant quaternary ammonium derivative was dissolved in a mixture of THF-H_2O (1:1 v/v) and the solution refluxed for 12 h to afford (±)-**1** in 55% yield. ^1H NMR δ 1.88 (1H, dd, J=4.1 and 7.1 Hz, -OH), 2.24 (3H, s, CH_3S-), 4.17 (6H, bs, C'p and Cp), 4.35 (2H, m, Cp), 4.45 (1H, dd, J=12 and 4.1 Hz,

-CH_aOH), 4.58 (1H, dd, J=12 and 7.1 Hz, -CH_bOH). ^{13}C NMR δ 21.06 (-SCH_3), 59.54 (-CH_2OH), 67.77, 69.29, 69.68, 73.22, 81.93 (C-1), 89.63 (C-2).

7. In a typical experiment Novozym® 435 (1.8 g) and vinyl acetate (3.3 mL) were added to a solution of (±)-**1** (900 mg, 3.4 mmol) in DIPE (83 mL) and the mixture was shaken (300 rpm) at 45 °C. After 2 h, when the conversion of the substrate had reached about 50%, the enzyme was filtered off and the filtrate was taken to dryness in vacuo. Column chromatography of the residue afforded 2(*S*)-acetoxymethyl-1(*R*)-methylthioferrocene (+)-**2** (490 mg, 47% yield, e.e. 84%), $[\alpha]_D$ +6 (*c* 0.2, $CHCl_3$). ^1H NMR δ 2.03 (3H, s, CH_3CO-), 2.21 (3H, s -SCH_3), 4.15 (5H, s, C'p). 4.22 (1H, m, Cp), 4.39 (2H, m, Cp), 5.06 (2H, s, -CH_2OAc), and (+)-**1** (420 mg, 47% yield, e.e. 83%). In a parallel experiment, in which the reaction was allowed to proceed up to a conversion of 60% (ca. 4 h), the unconverted (+)-**1** was recovered with 95% e.e., $[\alpha]_D$ +80 (*c* 0.35, $CHCl_3$).

8. This compound was obtained in 18% yield of the starting aminoderivative (–)-**3** and characterised by its spectoscopic properties. ^1H NMR δ 2.19 [6H, s, -$N(CH_3)_2$], 2.20 (3H, s, -SCH_3), 3.25 and 3.80 [AB system, each 1H, d, J=12.7 Hz, -$CH_2N(CH_3)_2$], 4.04 (5H, s, C'p), 4.10 and 4.74 (AB system, each 1H, d, J=12.3 Hz, -CH_2OH), 4.25 (2H, m, Cp). ^{13}C NMR δ 20.57 (-SCH_3), 44.53 [-$N(CH_3)_2$], 55.73 (-CH_2N-), 60.38 (-CH_2OH), 69.14 (Cp), 69.91 (C'p), 70.37 (Cp), 83.5 (C-1), 86.26 (C-2), 88.42 (C-3). $[\alpha]_D$ –91 (*c* 0.15, $CHCl_3$).

9. The Schlögl-Cahn-Prelog system (Schlögl, K. *Top. Stereochem.* **1967**, 39) is used in this paper.

(*Received in UK* 13 *October* 1995; *accepted* 3 *November* 1995)