Tetrahedron: Asymmetry Vol. 3, No. 6, pp. 753-758, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Lipase Mediated Desymmetrization of 1,2-Bis(hydroxymethyl)ferrocene in Organic Medium: Production of Both Enantiomers of 2-Acetoxymethyl-1-hydroxymethylferrocene

Giovanni Nicolosi*, Raffaele Morrone, 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

(*Received* 29 *April* 1992)

Abstract - Both enantiomers of 2-acetoxymethyl-1-hydroxymethylferrocene have been obtained *via* enantiotoposelective irreversible acylation in organic medium of 1,2-bis(hydroxymethyl)ferrocene using vinyl acetate as acyl donor and a lipase as catalyst.

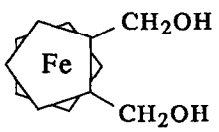
INTRODUCTION

In the last decades chemistry of metallocenes has become the object of an ever increasing attention, at least in part due to the peculiarities of their stereochemistry ('metallocene chirality'), and hundreds of optically active compounds of this class have been obtained so far. The use of biocatalysis in the preparation of chiral metallocenes, for long time hampered by the generally low solubility of organometallic compounds in water, has now become very attractive in consequence of the recent finding that enzymes can be used successfully in nonaqueous media.[1]

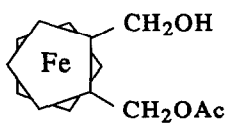
While 1,2-symmetrically substituted ferrocenes are *meso* forms, those 1,2-unsymmetrically substituted possess planar chirality and therefore can exist in two enantiomeric forms. In this paper we would like to report the desymmetrization of a *meso* compound, 1,2-bis(hydroxymethyl)ferrocene **1**, by the aid of biocatalyzed acyl-transfer reaction in organic medium.

RESULTS AND DISCUSSION

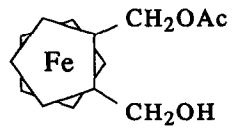
At the onset of this work we observed that *Pseudomonas cepacea* lipase (Amano PS) in benzene catalyzes the acetylation of **1** with vinyl acetate[2] as acetyl donor to give (–)-2-acetoxymethyl-1-hydroxymethylferrocene (**2a**) of good enantiomeric purity (Table, entry 6). Further experiments with this same



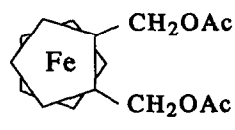
1



2a

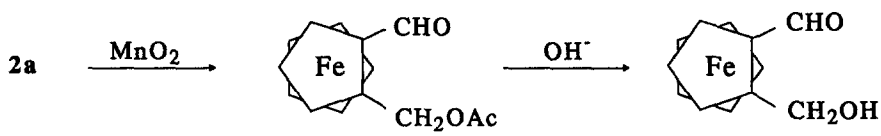


2b



3

enzyme immobilized on Hyflo Super Cel gave still better results and **2a** could be obtained with good chemical yield and extremely high optical purity (entry 14). Its absolute configuration was established by the sequence of reactions outlined in the following scheme:



4 **5**

Oxidation of **2a** with activated MnO_2 gave (–)-2-acetoxymethyl-1-formylferrocene (**4**), which on alkaline hydrolysis yielded (1*S*)-(–)-1-formyl-2-hydroxymethylferrocene (**5**) with known absolute configuration.[3] At this point we tried to obtain the antipodal (1*R*)-(+)-2-acetoxymethyl-1-hydroxymethylferrocene (**2b**) following an approch successfully used with prochiral aliphatic diols.[4] The rationale of this approach is that an enzyme which catalyzes the acetylation of a substrate of this type to afford a chiral monoacyl derivative should give the enantiomer by enzymatic hydrolysis of the corresponding diacyl derivative, provided that in both instances the enantioselectivity of the enzyme remains the same. In our hands, attempts to obtain **2b** by hydrolysis of

diacetate **3** met with little success, if any, and this also applies to the efforts to achieve the desired result *via* alcoholysis of **3** in organic medium using *n*-butanol. Therefore, we decided to reconsider the direct acetylation of **1**, testing a series of commercially available hydrolytic enzymes potentially effective in an acyl-transfer reaction in organic media (lipases, esterases and proteases)[1] in the hope to find at least one of them possessing opposite stereopreference to that of *P. cepacea* lipase.

The data on chemical and optical yield for these experiments are shown in the Table.

The three proteases tested (entries 11-13) and also porcine liver esterase (entry 10) were completely inactive under the condition adopted, as well as lipases from *Rhizopus arrhizus*, *Rhizopus javanicus* and wheat germ (entry 7-9). Among the other lipases screened, in addition to that from *P. cepacea*, which gave an essentially perfect enantiotopic discrimination, only *Mucor javanicus* lipase gave the *S* isomer, however of definitely lower optical purity, while lipases from *Candida cylindracea* and *Chromobacterium viscosum* (entries 2 and 3) proved to be reasonably active and gave the *R* isomer. The latter enzyme, in view of its less tendency to form the diacetate as compared to *C. cylindracea* lipase, was chosen as catalyst in the preparation of **2b** and experiments were undertaken to optimize chemical and optical yields. Immobilized *C. viscosum* lipase, much more active than the crude enzyme, was used and at various intervals (entries 15-17), the chemical yield and enantiomeric excess of **2b** were determined. With increase of the incubation time, the enantiomeric purity of **2b** increased steadily, 100% e.e. being reached at the time of the disappearance of the starting diol. This behaviour is due to the fact that during the acyl-transfer reaction kinetic amplification of the enantiomeric excess is operative and the optical purity of the monoester fraction enhanced at the expense of the chemical yield, owing to the preferential removal of the minor enantiomer in the second acylation step[5] (enantiotoposelective transesterification followed by kinetic resolution). Although this implies a moderate chemical yield, it is to be noted that the diacetate formed can be recovered, hydrolyzed and the diol recycled.

In conclusion, 1,2-bis(hydroxymethyl)ferrocene by acetylation with vinyl acetate in benzene affords (1*S*)-(–)-2-acetoxymethyl-1-hydroxymethylferrocene **2a** or the antipode **2b**, as optically pure compounds, using as catalyst immobilized *P. cepacea* or *C. viscosum* lipase, respectively.

Table. Enzymatically mediated esterification of 1,2-bis(hydroxymethyl)ferrocene[a]

Entry	Enzyme	Yield of 2(%)[b]	Stereopreference	e.e. (%)[c]	Yield of 3(%)[b]	Unreacted 1(%)[b]
	Lipases from					
1	*Aspergillus niger*	43	none	0	6	51
2	*Candida cylindracea*	54	*R*	75	46	–
3	*Chromobacterium viscosum*	20	*R*	15	–	80
4	*Mucor javanicus*	30	*S*	50	–	70
5	Porcine pancreas	<5	n.d.	n.d.	–	> 95
6	*Pseudomonas cepacea*	27	*S*	94	–	73
7	*Rhizopus arrhizus*	no reaction				
8	*Rhizopus javanicus*	no reaction				
9	Wheat germ	no reaction				
	Esterase from					
10	Porcine liver	no reaction				
	Proteases from					
11	*Bacillus licheniformis*	no reaction				
12	Papaya	no reaction				
13	*Aspergillus oryzae*	no reaction				
	Immobilized lipases					
14	*Pseudomonas cepacea* (12h)	80	*S*	100	–	20
15	*Chromobacterium viscosum* (12h)	61	*R*	46	5	34
16	*Chromobacterium viscosum* (18h)	73	*R*	62	19	8
17	*Chromobacterium viscosum* (30h)	57	*R*	100	43	–

[a]n.d. = not determined; – indicates absence. Experimental conditions: substrate 20 mg in 4 mL of benzene, vinyl acetate (5 molar equivalent), enzyme 80 mg (raw, entries 1-13) or 40 mg (immobilized on Hyflo Super Cel, entries 14-17); incubation time: entries 1-13, 48 h, others as indicated; 40 °C, 300 rpm. [b]Determined by ^{1}H-NMR of the crude mixture. [c]Determined from chiral shift experiments using Pirkle's alcohol [(*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol].

EXPERIMENTAL

General Methods

Melting point is uncorrected and was determined with a Kofler instrument. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. ^{13}C- and ^{1}H-NMR spectra were recorded at 62.9 and 250 MHz, respectively, in $CDCl_3$ using a Bruker AC250 spectrometer. Chemical shifts are reported as ppm (δ) from TMS.

Materials

All chemicals used were of analytical grade. Benzene was dried overnight on 3Å molecular sieves. 1,2-Bis(hydroxymethyl)ferrocene (**1**) was prepared as previously reported from C. Moise *et al.*[6] Lipases from *Aspergillus niger* (AP6), *Mucor javanicus* (M-10), *Pseudomonas cepacea* (PS), *Rhizopus javanicus* (FAP-15) and esterase from porcine liver were from Amano International Enzyme Co. Lipases from *Candida cylindracea*, *Rhizopus arrhizus*, wheat germ, porcine pancreas and proteases from *Aspergillus oryzae*, papaya and *Bacillus licheniformis* were obtained from Sigma Chemical Co. Lipase from *Chromobacterium viscosum* was from FinnSugar Biochemicals. Crude enzymes were used in most of the experiments. *C. viscosum* and *P. cepacea* lipases immobilized on Hyflo Super Cel were prepared as reported previously.[7]

General procedure for enzyme catalyzed esterification of 1

1,2-Bis(hydroxymethyl)ferrocene (20 mg) was dissolved in dry benzene (4 mL). A known amount of enzyme (80 mg for raw and 40 mg for immobilized enzymes, respectively) and vinyl acetate (5 molar equivalents) were added. The suspension was kept at 40 °C under continuous stirring (300 rpm). After the reaction time (see Table) the catalyst was removed by filtration and the solvent was evaporated at reduced pressure. The residue was analyzed (^{1}H-NMR) for quantification of the products and the unreacted diol, and the e.e. determined after addition of Pirkle's chiral shift reagent [(*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol].

Determination of the absolute configuration of 2a

The reaction mixture obtained from a larger scale acetylation of **1** (400 mg) using immobilized *P. cepacea* lipase was purified on Si gel with a gradient of ether in hexane to give 355 mg of (1*S*)-(–)-2-acetoxymethyl-1-hydroxymethylferrocene (**2a**), orange oil, $[\alpha]_D^{25}$ –28.3 (*c* 0.12, EtOH); ^{1}H-NMR δ 4.32 (bs; H-3 and H-5), 4.21 (bs; H-4), 4.31 and 4.57 (AB

system, J=11 Hz ; CH_2OH), 4.81 and 5.15 (AB system, J=12 Hz; CH_2OAc), 4.14 (s, H-1'–H-5'), 2.01 (s, $COCH_3$); ^{13}C-NMR δ 171.3, 87.1, 80.1, 70.9, 70.0, 68.8 (5C), 68.1, 61.3, 59.0, 21.0. An aliquot (300 mg) of the obtained product was dissolved in CH_2Cl_2 (10 mL) and activated MnO_2 (1.5 g) was added. The suspension was kept at room temperature for 24 h under continuous stirring. The catalyst was filtered off and the solvent evaporated in vacuo. The residue was purified by column chromatography on Si gel (gradient of ether in hexane) to give 270 mg of 2-acetoxymethyl-1-formylferrocene (**4**), m.p. 79 °C (from hexane), $[\alpha]_D^{25}$ –34.2 (*c* 0.1, EtOH), ^{1}H-NMR δ 4.69 (dd, J=1.5, 2.5 Hz, H-3), 4.57 (t, J=2.5 Hz; H-4), 4.79 (dd, J = 1.5, 2.5 Hz; H-5), 5.16 and 5.21 (AB system, J=11 Hz, CH_2-OAc), 2.01 (s, $COCH_3$), 10.06 (s, CHO); ^{13}C-NMR δ 193.2, 170.7, 83.4, 77.6, 75.4, 72.3, 71.6, 70.2 (5C), 60.6, 20.9. To a solution of **4** (100 mg) in EtOH (5 mL) a 0.5N aqueous solution of NaOH was added and the mixture left at room temperature for 2 h. Extraction with benzene and chromatographic purification of the crude product afforded 70 mg of **5**, whose ^{1}H-NMR spectrum and $[\alpha]_D$ were identical to those reported for (1*S*)-(–)-1-formyl-2-hydroxymethylferrocene.[3]

Aknowledgments - We are grateful to Dr. D. Bianchi (Istituto G. Donegani, Novara) for helpful discussion upon ferrocene chirality. We are also indebted to Amano International Enzyme Co. for kind supply of lipases. Thanks are due to CNR for financial assistence, under the scheme "Progetto Finalizzato per la Chimica Fine e Secondaria".

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