Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3073–3080

TETRAHEDRON: *ASYMMETRY*

# Lipase-mediated resolution of 2-hydroxymethyl-1-iodoferrocene: synthesis of ferrocenes and biferrocenes with planar chirality

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Received 15 July 1998; accepted 31 July 1998

**Abstract**

Racemic 2-hydroxymethyl-1-iodoferrocene (±)-**1** was subjected to esterification in the presence of lipase from *Candida antarctica* (Novozym® 435) to afford (1*S*,2*S*)-2-acetoxymethyl-1-iodoferrocene (−)-**2** having 89% ee and unreacted (1*R*,2*R*)-2-hydroxymethyl-1-iodoferrocene (+)-**1** in enantiopure form. A single enantiomer of 2-hydroxymethyl-1-iodoferrocene gave easy access to new ferrocenes and biferrocenes possessing only planar chirality. 

## 1. Introduction

The importance of ferrocene derivatives in synthetic chemistry and in the preparation of catalysts in the homogeneous phase cannot be overlooked.[1] Of particular interest are the 1,2-heterodisubstituted ferrocenes since they possess planar chirality and in principle can be obtained in enantiomerically pure form. Enantiopure 1,2-disubstituted ferrocenes with both planar and central chirality can be obtained according to the procedure described by Ugi et al.,[2] consisting of diastereoselective *ortho*-lithiation with *n*-BuLi of homochiral (α-dimethylamino)ethylferrocene followed by reaction with a suitable electrophile. More recently, a chiral acetal of ferrocenecarboxaldehyde has been proposed as a substrate for the *ortho*-lithiation. Electrophilic quenching of the metallated compound and subsequent removal of the chiral moiety affords enantiopure *ortho*-substituted ferrocenecarboxaldehydes with only planar chirality.[3]

Enzymatic resolution of *ortho*-substituted hydroxymethylferrocenes is a different approach for the preparation of enantiopure 1,2-disubstituted ferrocenyl compounds to be used as starting materials in the

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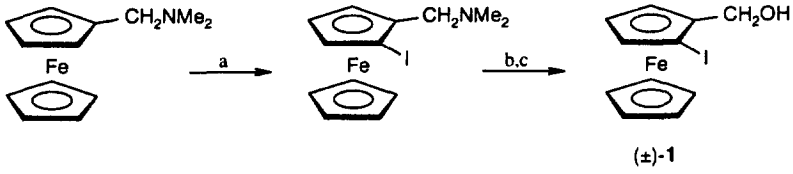
0957-4166/98/$ - see front matter 
*PII:* S0957-4166(98)00311-5

synthesis of different types of enantiopure ferrocenes of established planar chirality. A hydroxymethylferrocene bearing a halogen atom in the *ortho*-position appears to be a particularly attractive substrate, due to the large number of different groups which can be introduced by substitution after the enantiomeric resolution.

Although lipases from different sources have been found to catalyse the kinetic resolution of various *ortho*-substituted hydroxymethylferrocenes,[4] a single case is reported in the literature in which the substituent is a halogen atom, namely 2-bromo-1-hydroxymethylferrocene. This compound, by enantioselective esterification catalysed by *Mucor miehei* lipase (Lipozyme) in benzene–hexane gave (1*S*,2*R*)-1-hydroxymethyl-2-bromoferrocene, however with low enantiomeric excess (ee 25%).[4a]

In the present paper we wish to describe the efficient resolution of 2-hydroxymethyl-1-iodoferrocene (±)-**1**, easily obtained by *ortho*-metalation of prochiral (dimethylaminomethyl)ferrocene followed by reaction with $I_2$.[5]




(±)-**1**

a: *tert*-BuLi in THF, $I_2$; b: $Ac_2O$, reflux; c: $K_2CO_3$ in MeOH

## 2. Results and discussion

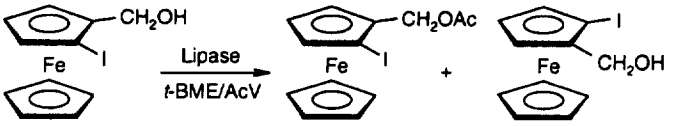
The iodoferrocene (±)-**1** was subjected to transesterification with vinyl acetate in *tert*-butyl methyl ether (*t*-BME) in the presence of a lipase (from *Pseudomonas cepacia*, *Mucor miehei*, *Candida cylindracea*, *Candida antarctica* or porcine pancreas) which in previous work had shown acceptance for 2-dimethylaminomethyl-, 2-alkylthio- and 2-phenylthio-1-(hydroxymethyl)ferrocene.[4c–e] No esterification was observed with *P. cepacia* lipase or porcine pancreas lipase, while lipases from *M. miehei* and *C. cylindracea* were found to catalyse formation of ester (−)-**2** with acceptable rate but moderate enantioselectivity. Under the same conditions, lipase from *C. antarctica* (immobilised on matrix, Novozym® 435) promotes a slower but more enantioselective (E=15)[6] reaction.

In order to enhance this result, the reaction was carried out in di-*iso*-propyl ether (DIPE) and $CH_2Cl_2$. Enantioselectivity of *C. antarctica* lipase in DIPE is almost doubled (E=28) and in $CH_2Cl_2$ reaches satisfying levels for preparative uses (E=67).[7] After quenching the reaction at 25% conversion, ester (−)-**2** was isolated with a 96% ee (see Table 1).

A multigram reaction was carried out in $CH_2Cl_2$ until substrate conversion reached 52% to afford unreacted alcohol (+)-**1** with 96% ee and ester (−)-**2** with 89% ee. The stereostructure of the latter compound was assessed as (1*S*,2*S*)-2-acetoxymethyl-1-iodoferrocene by conversion into the known aldehyde (+)-**3**.[3] Hydrolysis of (−)-**2** and recrystallisation of the corresponding alcohol from hexane gave enantiopure (−)-**1** (80% overall yield and ee >98%).

The 2*S*-stereopreference of *C. antarctica* lipase observed in the present instance agrees with what had been previously observed for other ferrocenes possessing only planar chirality,[4c–e] and it seems a general rule that this enzyme preferentially recognises, possibly for steric reasons, the enantiomer in which the hydroxymethyl is flanked in a clockwise direction by the second group. Consequently, a preferred enantiomer model, in terms of size of substituents *ortho* to the $CH_2OH$ group, can be assumed,

Table 1
Esterification of ferrocenylalcohol (±)-**1**, in the presence of different lipases[a]

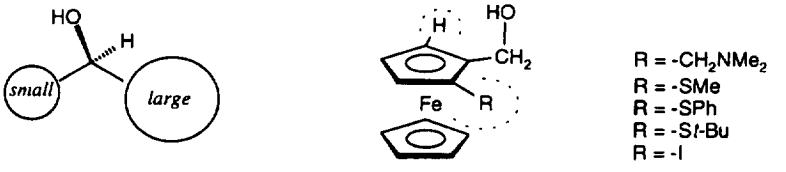



(±)-**1** (−)-**2** (+)-**1**

| Lipase source | Solvent | Time (h) | Conv. (%)[b] | ee Ester[c] | E[d] | ee Alcohol[e] |
|---|---|---|---|---|---|---|
| *Pseudomonas cepacia* | *t*-BME | 12 | 0 | - | - | - |
| Porcine pancreas | *t*-BME | 12 | 0 | - | - | - |
| *Mucor miehei* | *t*-BME | 0.3 | 37 | 65 | 7 | 38 |
| *Candida cylindracea* | *t*-BME | 0.5 | 25 | 70 | 7 | 28 |
| *Candida antarctica* | *t*-BME | 2 | 30 | 81 | 15 | 41 |
| *Candida antarctica* | DIPE | 2.5 | 45 | 86 | 28 | 70 |
| *Candida antarctica* | $CH_2Cl_2$ | 6 | 25 | 96 | 67 | 32 |

[a]Experimental conditions: lipase (10 mg/ml), substrate (5 mg/ml) vinyl acetate (15 μl/ml), 40 °C, 300 rpm.
[b]Determined by hplc analysis
[c]Determined by chiral hplc analysis after hydrolysis to the corresponding alcohol
[d]Calculated according to the ref. 6.
[e]Determined by chiral hplc analysis

similar to that proposed by Kazlauskas for the stereopreference of lipases in the recognition of secondary alcohols.[8]

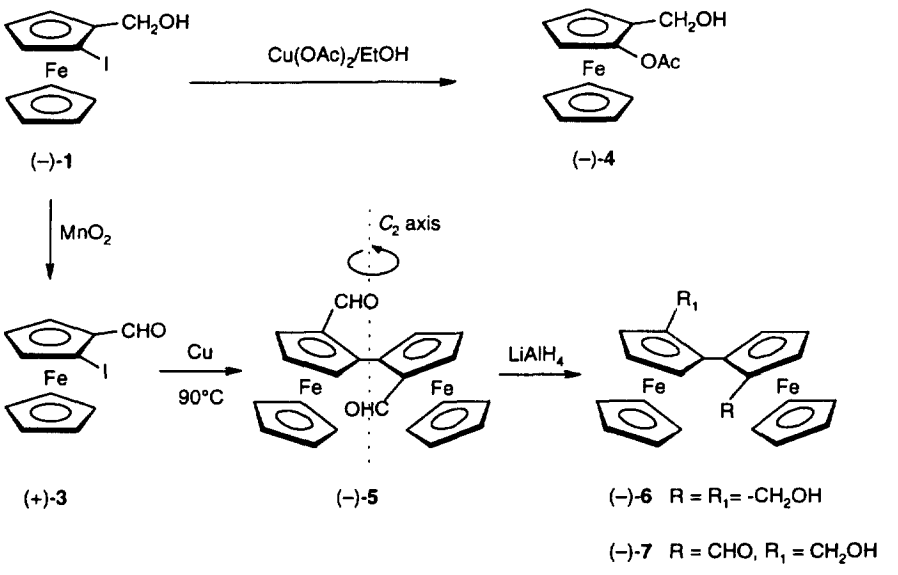



*Preferred enantiomer*

The enantiomers of 2-hydroxymethyl-1-iodoferrocene can be subjected to copper-assisted substitution reactions[9] to give new enantiopure 1,2-disubstituted ferrocenes, as well as to coupling[10] to afford 2,2′-disubstituted-1,1′-biferrocenes.

As an example of nucleophilic substitution of the iodine atom we report here the reaction of (−)-**1** with $Cu(OAc)_2$ in ethanol, which yielded 70% of (1*R*,2*S*)-1-acetoxy-2-(hydroxymethyl)ferrocene (−)-**4** (Scheme 1). By the same route (−)-**1** can be transformed into chiral hydroxymethylferrocenes with nitrogen or sulfur containing groups having the heteroatom directly connected to the cyclopentadienyl ring.

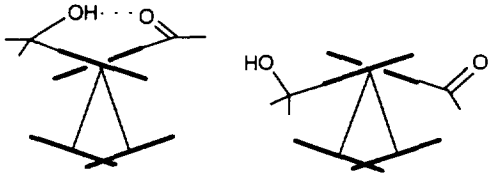
Alcohol (−)-**1** also allowed the synthesis of enantiopure biferrocenyl derivatives with $C_2$-symmetry. To this end, (−)-**1** was converted into the more suitable aldehyde[11] (+)-**3** by $MnO_2$ oxidation followed by coupling in the presence of activated Cu-bronze to give dialdehyde (−)-**5** in 68% isolated yield, whose reduction with $LiAlH_4$ afforded diol (−)-**6**. Due to the highly symmetrical structure of these biferrocenyls




Scheme 1.

their dimeric nature was confirmed by NMR analysis of the corresponding hydroxyaldehyde (−)-**7**, prepared by controlled $MnO_2$ oxidation of (−)-**6** (Scheme 1).

The proton NMR spectrum of (−)-**7** showed two distinct singlets for the unsubstituted cyclopentadienyl rings and well defined resonances for protons on formyl- and hydroxymethylsubstituted rings, assigned by homonuclear correlation.




*A* *B*

A broad triplet for the alcoholic proton was also present indicating an intramolecular hydrogen bond, compatible with the favoured conformation A with respect to B, as deduced from molecular modelling of (−)-**7**.

Chiral biferrocenes (−)-**5** to (−)-**7**, due to their possible conversion into complexes with different metals, have great potential use in the field of catalysis in the homogenous phase.[12]

## 3. Conclusion

Lipase from *C. antarctica* (Novozym® 435) catalysed the esterification of 2-hydroxymethyl-1-iodoferrocene (±)-**1**, showing 2*S*-stereopreference and high enantioselectivity. Due to the easy substitution of the iodine atom, the obtained enantioforms of this haloferrocene contribute to broaden the scant number of starting materials useful to synthesise further enantiopure ferrocenes and biferrocenes possessing only planar chirality. By this route the new (1*R*,2*S*)-1-acetoxyl-2-(hydroxymethyl)ferrocene (−)-**4** and (1*R*,1′*R*)-2,2′-bis-hydroxymethyl-1,1′-biferrocene, (−)-**6** were prepared.

## 4. Experimental

$^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution, unless otherwise stated, at 250.13 and 62.9 MHz respectively. Chemical shifts ($\delta$) are reported in ppm relative to TMS; all coupling constants ($J$) are in hertz. Optical rotations were measured on a DIP 135 JASCO instrument. Melting points were determined on a MELT-TEMP II device and are uncorrected.

Lipases from *Candida cylindracea* and *Pseudomonas cepacia* were obtained from Amano International Enzyme Co. Porcine pancreas lipase was from Sigma. Lipozyme® IM (immobilised lipase from *Mucor miehei)* and Novozym® 435 (immobilised lipase from *Candida antarctica*) are registered marks from Novo Nordisk.

Column chromatography was performed on silica gel (230–400 mesh); analytical TLC was carried out on Merck silica gel 60-$F_{254}$ precoated glass plates and compounds were visualised by spraying with molybdophosphoric acid.

Chiral HPLC analyses were carried out on a Varian instrument fitted with a UV detector ($\lambda$=250 nm) using a Ciclobond I 2000 column. Elution of compounds was performed in isocratic conditions with a MeCN:MeOH (92:8) mixture containing 0.25% triethylamine and 0.3% acetic acid (flow 0.5 mL/min).

*N,N*-Dimethylaminomethylferrocene was commercially available from Aldrich. All reagents were analytical grade and have been used without further purification. Solvents were dried according to standard procedures.

### 4.1. Synthesis of 2-hydroxymethyl-1-iodoferrocene, (±)-1

A solution of *tert*-BuLi in hexane (10 mL, 1.7 M, 17 mmol), was added dropwise to a stirred solution of *N,N*-dimethylaminomethylferrocene (4 g, 16.4 mL) in dry THF (11 mL) at 0°C. After 30 min, a solution of $I_2$ (4.2 g, 33 mmol) in THF (4 mL) was added and the mixture left at room temperature for 3 h. The reaction mixture was then partitioned between EtOAc and aqueous $Na_2S_2O_3$. The organic layer was dried over $Na_2SO_4$ and the solvent evaporated at reduced pressure. The residue was purified on a silica gel column (MeOH:THF=9:1) to give 2-(*N,N*-dimethylaminomethyl)-1-iodoferrocene (2.7 g, 44% yield) whose protonic resonances were in agreement with the reported values.[13] The obtained aminoiodoferrocene was dissolved in THF (20 mL) and treated with $Ac_2O$ (10 mL) under reflux for 1 h. The mixture was then taken to dryness and the residue dissolved in MeOH (20 mL) containing $K_2CO_3$ (1 g). The suspension was maintained stirring at room temperature and the progress of the reaction monitored by TLC. After extraction with $H_2O$/*t*-BME the organic phase was taken to dryness to give 2-hydroxymethyl-1-iodoferrocene, (±)-**1**, recrystallised from hexane (1.5 g), $^1H$ NMR ($C_6D_6$): $\delta$ 1.65 (1H, bs, –OH), 3.93 (1H, t, $J$=2.25, Cp), 4.13 (5H, C′p), 4.16 (1H, m, Cp), 4.32 (1H, m, Cp), 4.32 and 4.37 (AB system, each 1H, $J$=12.2, $-CH_2OH$); $^{13}C$ NMR ($C_6D_6$): $\delta$ 44.1, 61.2, 67.8, 69.0, 71.6, 75.0, 88.9.

### 4.2. General procedure for small-scale esterification of (±)-1

Lipase (10 mg/mL) was added to a solution of (±)-**1** (5 mg/mL) in *t*-BME containing vinyl acetate (15 μl/mL) and the suspension was shaken at 40°C. The progress of the reaction and the ee of the unreacted alcohol were monitored by HPLC analysis of aliquots. At time intervals (Table 1) the reaction was stopped by filtering off the enzyme. After work-up of the reaction mixture and chromatography on a silica gel column (hexane:EtOAc=3:1 as eluant) the enantiomeric excess of acetate **2** was determined

by chiral HPLC after hydrolysis with $K_2CO_3$:MeOH. According to the same procedure, reactions in different solvents in the presence of Novozym® 435 using vinyl acetate or propionate were carried out.

### 4.3. Kinetic resolution of (±)-1

Alcohol (±)-**1** (2.0 g, 5.8 mmol) was dissolved in $CH_2Cl_2$ (400 mL) and to this solution Novozym® 435 (4.0 g) and vinyl acetate (6.0 mL) were added. The suspension was maintained at 45°C under continuous shaking (300 rpm) for 68 h, when conversion of substrate reached 52%. The enzyme was then filtered off and the solution taken to dryness. Chromatographic purification of the residue (silica gel, hexane:EtOAc=3:1 as eluant) afforded (−)-**2** (1.2 g, 50% yield, 89% ee) and unreacted (+)-**1** (0.9 g, 46% yield, 96% ee), $[\alpha]_D$ +23.4 (*c* 0.45, $CHCl_3$).

### 4.4. (1S,2S)-2-Acetoxymethyl-1-iodoferrocene, (−)-2

$[\alpha]_D$ −3.1 (*c* 0.75, $CHCl_3$); $^1$H NMR: δ 2.06 (3H, s, $CH_3CO$–), 4.17 (5H, s, C′p), 4.27 (1H, t, *J*=2.5, Cp), 4.36 (1H, m, Cp), 4.48 (1H, m, Cp), 4.89 and 5.01 (AB system, each 1H, d, *J*=12.5, –$CH_2OAc$); $^{13}$C NMR: δ 20.8, 44.6, 62.8, 69.0, 69.5, 71.4, 75.4, 82.5, 170.6.

### 4.5. (1S,2S)-2-Hydroxymethyl-1-iodoferrocene, (−)-1

Alcohol (−)-**1** with ee >98% was obtained from (−)-**2** by alkaline hydrolysis ($K_2CO_3$ in MeOH) and subsequent recrystallisation from hexane in 80% overall yield, $[\alpha]_D$ −24.1 (*c* 0.50, $CHCl_3$).

### 4.6. (1S,2S)-2-Formyl-1-iodoferrocene, (+)-3

Compound (−)-**2** (50 mg, 0.13 mmol, 89% ee) was treated with $K_2CO_3$ in MeOH for 1 h at room temperature. After extraction with $H_2O$/*t*-BME the organic phase was taken to dryness and the residue was dissolved in $CH_2Cl_2$ (5 mL). Active $MnO_2$ (100 mg) was added to this solution and the suspension stirred at room temperature until complete conversion of the substrate. After removal of $MnO_2$ by centrifugation the solution was taken to dryness to give a residue of (+)-**3**, $[\alpha]_D$ +484.5 (*c* 0.2, $CHCl_3$), [lit.[3] $[\alpha]_D$ +542 (*c* 0.36, $CHCl_3$)].

### 4.7. (1R,2S)-1-Acetoxyl-2-(hydroxymethyl)ferrocene, (−)-4

To a solution of (−)-**1** (100 mg, 0.29 mmol, >98% ee) in 10 mL of 50% EtOH, $Cu(OAc)_2 \cdot H_2O$ (300 mg, 1.5 mmol) was added and the mixture left under reflux for 1 h. After extraction with EtOAc the organic phase was dried and the solvent removed to give a residue that was subjected to silica gel chromatography (hexane:EtOAc=7:3). Compound (−)-**4** was recovered in a 70% yield (56 mg), $[\alpha]_D$ −17.1 (*c* 0.2, $C_6H_6$); $^1$H NMR: δ 2.20 (1H, bs, –OH), 2.26 (3H, s, $CH_3CO$–), 4.02 (1H, t, *J*=2.7, Cp), 4.15 (1H, m, Cp), 4.24 (5H, s, C′p), 4.39 (1H, m, Cp), 4.41 and 4.45 (AB system, each 1H, d, *J*=10.0, –$CH_2OH$); $^{13}$C NMR: δ 21.0, 58.2, 61.5, 63.0, 64.6, 69.7, 79.1, 87.5, 170.9.

### 4.8. (1R,1′R)-2,2′-Bis-formyl-1,1′-biferrocene, (−)-5

Activated copper powder[14] (1.2 g) was added to a solution in $CH_2Cl_2$ (3 mL) of aldehyde (+)-**3** (200 mg, >98% ee) obtained by oxidation of alcohol (−)-**1** as above. The solvent was then removed by a

stream of $N_2$ and the remaining mixture was heated under argon at 90°C for 3 h. After cooling at room temperature $CH_2Cl_2$ was added and the insoluble material removed by filtration. The solution was taken to dryness to give a residue that was chromatographed on silica gel ($CH_2Cl_2$:EtOAc=9:1) to afford (−)-**5** (85 mg, 68% yield), $[\alpha]_D$ −60.5 (*c* 0.07, $C_6H_6$); $^1$H NMR δ 4.30 (5H, s, C′p), 4.73 (1H, t, *J*=2.7, Cp), 4.94 (2H, m, Cp), 9.93 (1H, s, CHO); $^{13}$C NMR δ 68.8, 71.0, 71.9, 76.7, 78.6, 85.4, 192.2.

### *4.9. (1R,1′R)-2,2′-Bis-hydroxymethyl-1,1′-biferrocene, (−)-6*

A solution of (−)-**5** (50 mg, 0.12 mmol) in $Et_2O$ was treated with $LiAlH_4$ and the suspension stirred for 30 min at room temperature. The reaction mixture was then partitioned between $H_2O$ and EtOAc and the organic layer dried over $Na_2SO_4$. The solvent was removed *in vacuo* to afford (−)-**6** (48 mg, 95% yield), mp 116–118°C, $[\alpha]_D$ −752.0 (*c* 0.08, $CHCl_3$); $^1$H NMR δ 4.20 (2H, bs, $-CH_2OH$), 4.22 (5H, s, C′p), 4.23 (1H, m, Cp), 4.31 (1H, dd, *J*=2.3 and 1.5, Cp), 4.46 (1H, dd, *J*=2.3 and 1.5, Cp); $^{13}$C NMR δ 59.1, 67.1, 69.1, 69.3, 72.9, 83.7, 87.4.

### *4.10. (1R,1′R)-2-Formyl-2′-hydroxymethyl-1,1′-biferrocene, (−)-7*

Compound (−)-**6** (50 mg, 0.12 mmol) was dissolved in $CH_2Cl_2$ and to this solution a suspension of $MnO_2$ in $CH_2Cl_2$ was added dropwise. The resulting mixture was stirred at room temperature and the reaction course was monitored by TLC ($CH_2Cl_2$:EtOAc=9:1). Complete conversion of substrate with the concomitant formation of (−)-**7** along with minor amounts of (−)-**5** was obtained within 2 h. After filtration of $MnO_2$ and removal of the solvent *in vacuo*, the residue was subjected to silica gel chromatography ($CH_2Cl_2$:EtOAc=9:1) to afford (−)-**7** (32 mg, 65% yield), mp 135–137°C, $[\alpha]_D$ −421.0 (*c* 0.11, $CHCl_3$); $^1$H NMR δ 1.91 (1H, bt, –OH), 4.21 (5H, s, C′p), 4.29 (3H, m, $CH_2OH$ and Cp), 4.33 (5H, s, C′p), 4.39 (1H, dd, *J*=2.5 and 1.5, Cp), 4.55 (1H, dd, *J*=2.5 and 1.5, Cp), 4.69 (1H, t, *J*=2.5, Cp), 4.87 (1H, dd, *J*=2.5 and 1.5, Cp), 4.90 (1H, dd, *J*=2.5 and 1.5, Cp), 9.95 (1H, s, CHO); $^{13}$C NMR δ 59.2, 67.4, 68.8, 68.9, 69.6, 70.8, 71.8, 72.5, 77.0, 78.1, 81.9, 88.1, 94.6, 193.5.

## Acknowledgements

Financial support from the CNR Target Project on 'Biotechnology' is gratefully acknowledged. Thanks are also due to Novo Nordisk for kindly providing lipases from *Candida antarctica* and *Mucor miehei*.

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