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Tetrahedron: *Asymmetry* 18 (2007) 2125–2128

Approaches to (*R*)- and (*S*)-1′-(1-aminoethyl)ferrocene-1-carboxylic acid derivatives

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Received 10 July 2007; accepted 7 September 2007

Abstract—Lipase-catalyzed esterification of (±)-methyl 1′-(1-hydroxyethyl)ferrocene-1-carboxylate **4** afforded its (*R*)-acetate (−)-**5** (ee = 99%) and (*S*)-(+)-**4** (ee = 90%). Stereoretentive azidation/amination/acetylation of (*R*)-(−)-**5** gave (*R*)-(+)-methyl 1′-(1-acetamidoethyl)ferrocene-1-carboxylate (*R*)-**3** (ee = 98%). In a similar manner (*S*)-(+)-**4** was converted into (*S*)-(−)-**3** (ee = 84%). Both enantiomers of **3** were obtained in high chemical yields without a loss of enantiomeric purity. The title compounds can be coupled with natural amino acids and peptides on both C- and N-termini.

1. Introduction

Coupling of the appropriately protected ferrocene amino acid (**Fca**, **I**; X = OH, OMe; Y = H, Boc)[1] with natural amino acids using an EDC/HOBt procedure gave ferrocene-containing oligopeptides (**I**; X = $(AA)_m$OMe; Y = Boc$(AA)_n$). Their conformational and structural analysis confirms that a turn structure is induced by Fca and *antiparallel* orientation of the two peptide strands is stabilized by intramolecular hydrogen bonds, preponderantely giving *P*-helical conformation of the metallocene.[2] In our previous paper, the synthesis and properties of the 'homologous' ferrocene chiral amino acid (**Fcca**) derivatives (**II**; X = OH, OMe; Y = H, Boc, Ac) are described (Fig. 1).[3]

This ferrocene amino acid containing the stereogenic centre can be considered as a derivative of (1-**f**errocenyl**e**thyl)**a**mine (**Fea**). Ferrocenylalkylamine derivatives are highly efficient ligands in asymmetric catalysis[4] and appropriate chiral auxiliaries due to their high chiral induction ability.[5] In this context we demonstrated that EDC/HOBt-promoted coupling of racemic Fea with 0.5 equiv of Boc–AA–OH (AA = Ala, Phe) undergoes partial kinetic resolution giving diastereomeric Boc–AA–Fea's with a high de.[3] The applications of 1,1′-unsymmetrical ferrocene derivatives (P/P, P/S, P/O, oxazoline) in catalysis have been reported.[6] Although the other 1,1′-ferrocenes (N/C, P/N and P/C) have not been applied as chiral ligands for catalytical purpose, yet, one can expect their future application in this field. Herein, we report the chemoenzymatic preparation of (*R*)- and (*S*)-Fcca–OMe and their *N*-acetyl derivatives. These homochiral ferrocene amino acids are expected to (i) exert a certain induction ability, (ii) serve as bidentate ligands in asymmetric catalysis and (iii) be successfully used as templates (like Fca[2]) to nucleate and propagate certain conformations from its ordered region through an α-amino acid based part to form interesting turn structures.

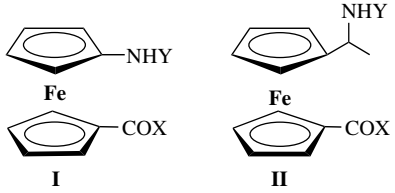

Figure 1. Types of heteroannularly substituted ferrocene amino acids (X = OH, Y = H) and the derived oligopeptides (X = $(AA)_m$OMe, Y = Boc$(AA)_n$).

2. Results and discussion

Racemic Fcca–OMe **2** was prepared in several steps via intermediate oxime **1**.[3] Our first attempt to obtain enantiomerically pure Fcca–OMe by asymmetric reduction of *O*-methyl oxime **1** with oxazaborolidine·BH_3[7] failed.

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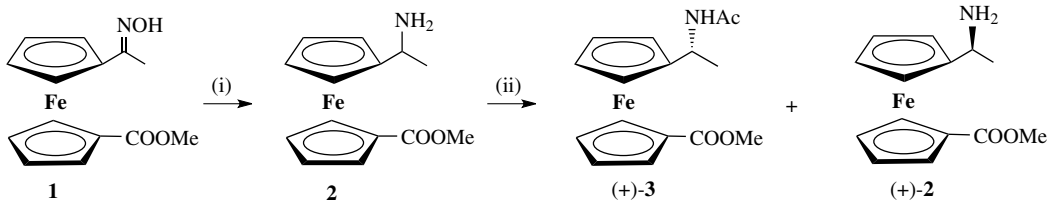
0957-4166/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2007.09.008



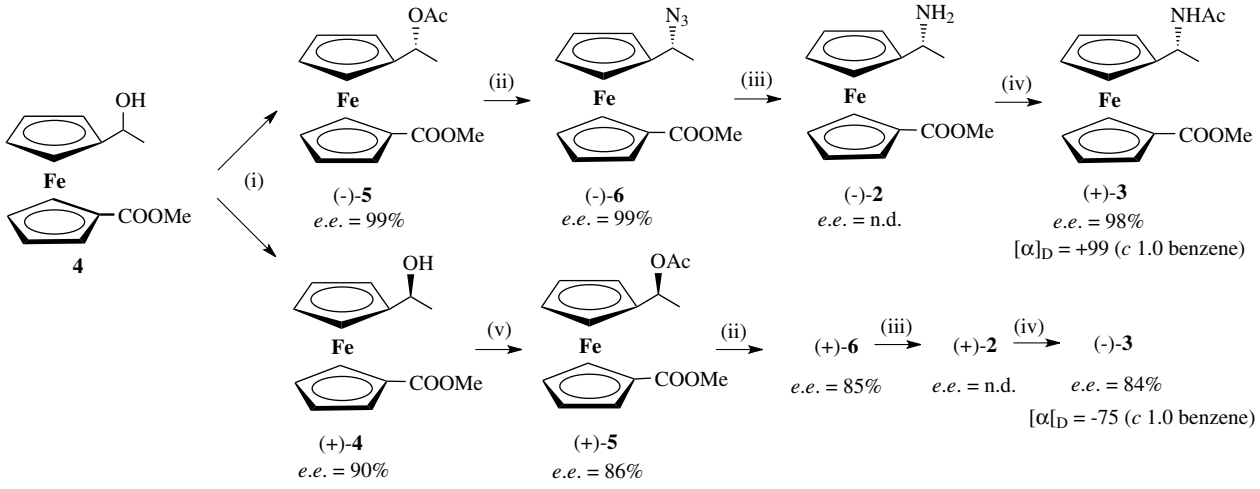
Scheme 1. Reagents: (i) H_2/Pd–C; (ii) CAL-B, ethyl acetate.

Bearing in mind the efficient biocatalytic resolution of racemic Fea[8] and related aralkylamines,[9] we applied this approach to ester **2** (Scheme 1). Its enzymatic acylation using *Candida antarctica* B lipase (CAL-B) was performed at 28 °C, 200 rpm, for 15 h in ethyl acetate as the acylation reagent and the solvent.[10] The enantiomeric excess of amine **2** and amide **3** was determined by chiral HPLC-analysis after their separation and transformation of the remaining **2** into its *N*-acetyl derivative. Acetylation of **2** yielded (+)-**3** in a good enantiomeric excess (ee = 85%) but with moderate conversion ($c = 20\%$). Monitoring of this biotransformation by Chiralcel-OD-H column was unsuccessful, while a prolonged reaction time caused decomposition of the substrate without any significant enhancement of the yield.

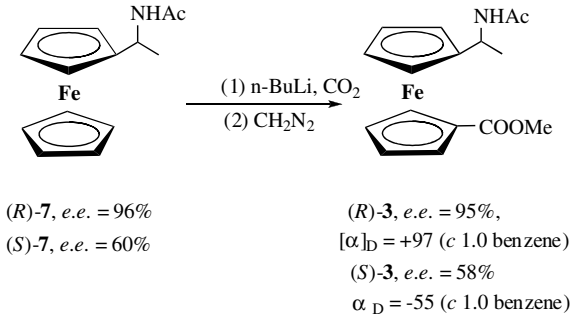
To optimize the ee and conversion, we applied another strategy (Scheme 2). It is known that lipases catalyze the esterification of numerous ferrocenylcarbinols,[11] which can be readily transformed into amines without the loss of enantiomeric purity.[11d,12] The substrate for our enzymatic resolution, methyl 1′-(1-hydroxyethyl)-ferrocene-1-carboxylate **4**, was prepared in a high yield by the reduction[13] of 1′-acetylferrocene-1-carboxylate.[3] Among the lipases tested, using vinyl acetate as an acyl-donor in hexane, only Novozym 435 showed the ability to perform its stereoselective acylation. *Pseudomonas fluorescens* and Lypozim were not suitable to promote the transesterification and even after prolonged reaction times only the unchanged substrate was isolated. It is worth mentioning the simplicity of monitoring the course of the resolution of **4** using a chiral-HPLC-column under the conditions which provide good separation of (+)-**4** and (−)-**5**.[14] In a typical experiment[15] Novozym 435 was filtered off after 32 h to afford alcohol (+)-**4** and acetate (−)-**5** in 48% conversion[16] and excellent ee values of 90% and 99%, respectively. The resolved alcohol (+)-**4** was transformed into the corresponding *O*-Ac-derivative (+)-**5** by acylation,[17] treated with NaN_3 to give azide (+)-**6**,[18] which was reduced with H_2/Pd–C[19] to afford amine (+)-**2**. The same reaction sequence was applied to acetate (−)-**5**. Both sequences proceeded in excellent chemical yields and with retention of configuration during nucleophilic displacement. Compounds (+)- and (−)-**3** were obtained with ee values 98% and 84%, respectively (Scheme 2).

The absolute configuration of the products was assigned by the correlation of the signs of their specific rotation[20] with that of (*R*)/(*S*)-**3** obtained by lithiation/carboxylation/esterification[3] of the resolved *N*-acetyl Fea's (*R*)- and (*S*)-**7**, for which the absolute configurations have been determined. The racemic Fea was prepared in four steps starting from ferrocene[3] and resolved by the action of CAL-B giving (*R*)- and (*S*)-**7** with a known absolute configuration (Scheme 3).[8] The results described show that CAL-B as a preference towards the (*R*)-enantiomer of ferrocene carbinol **4**, which is in accordance with Kazlauskas-rule.[21]

To demonstrate the chiral induction of Fcca and its turn character, analogously as done for Fea, EDC/HOBt-promoted coupling of the racemic Fcca derivatives with natural AA's was performed. Condensation of Fcca–OMe with



Scheme 2. Reagents: (i) Novozym 435, vinyl acetate/hexane; (ii) NaN_3, 1:1 MeOH/H_2O; (iii) 10% Pd/C, H_2, EtOAc; (iv) AcCl, Et_3N, CH_2Cl_2; (v) AcCl, Et_3N, toluene.



Scheme 3.

Boc–AlaOH afforded a mixture of diastereomeric dipeptides **II** (X = OMe; Y = BocAla). Hydrolysis of this mixture into the corresponding carboxylic acid and its condensation with Ala–OMe gave tripeptide (X = Ala-OMe; Y = BocAla). Analogously Ac–Fcca was coupled with AlaOMe to give **II** (X = AlaOMe; Y = Ac). In these coupling reactions moderate de's were found and in the oligopeptides prepared interchain hydrogen bonds were indicated on the basis of their ^{1}H NMR and IR spectra. These conjugates exhibit two distinct ν/cm^{-1} (NH) IR-bands assigned to hydrogen-bond-free and associated states: Boc–Ala–Fcca–OMe (3424, 3347), Boc–Ala–Fcca–Ala–OMe (3427, 3354), Ac–Fcca–Ala–OMe (3433, 3287). The following ^{1}H NMR-shifts for amide protons δ/ppm (in order from left to right in the formulas) were found: Boc–Ala–Fcca–OMe (5.4, 6.75), Boc–Ala–Fcca–Ala–OMe (5.47, 6.78, 7.44), Ac–Fcca–Ala–OMe (6.54, 7.47).

3. Conclusion

In conclusion, we have demonstrated a more efficient kinetic resolution of racemic ferrocene carbinol-ester **4** catalyzed by CAL-B in vinyl acetate affording its acetate (−)-**5** (ee = 99%) and (+)-**4** (ee = 90%), then of the corresponding amino ester **2**, which afforded (+)-**3** with 85% ee at 20% conversion. Transformation of (−)- and (+)-**5** into azides and amino esters was performed in a retentive manner as shown by the $[\alpha]_D$ values of the resulting amide-esters (*R*)- and (*S*)-**3**. Enantiomerically pure (*R*)- and (*S*)-**2** and (*R*)-/(*S*)-Ac–Fcca [obtained by the hydrolysis of (+)- and (−)-**3**] are appropriate materials for the coupling reactions with the natural amino acids and peptides on both C- and N-termini.

Acknowledgements

Financial support by the Ministry of Science, Education and Sports of Croatia (Program 0058023) is gratefully acknowledged. We are grateful to Professor V. Šunjić for helpful discussion. We would also like to thank Professor N. Metzler-Nolte and Dr. Katja Heinze for measuring of MS and HRMS spectra, and Professor Srđanka Tomić-Pisarović for polarimetric data. Novozym 435 was a gift from Dr. Zdenko Hameršak.

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10. Novozym 435 (10 mg) was added to a solution of racemic amino ester **2**[3] (54 mg) in ethyl acetate (3 ml). After 15 h, the enzyme was filtered off and the solution evaporated to dryness. Unreacted amine **2** was separated from amide **3** using standard DCM/10% citric acid workup and converted to its Ac-derivative.[3] The ee's of (*R*)-**3** and acylated (*S*)-**2** were determined as 85% and 21% by HPLC analysis (Chiralcel OD-H, *n*-hexane/2-propanol = 9/1) at 1 ml min^{-1} flow rate. (*S*)-**3** was eluted first (t_R = 7.9 min) followed by (*R*)-**3** (t_R = 9.02 min). IR, NMR and MS data are described in Ref. 3.
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13. *Procedure for the synthesis of methyl 1′-(1-hydroxyethyl)ferrocene-1-carboxylate* **4**: $NaBH_4$ (394.3 mg, 10.423 mmol) was added in small portions to a stirred solution of 1′-acetylferrocene-1-carboxylate[3] (426 mg, 1.489 mmol) in 1:1 Et_2O/EtOH (12 ml). After 4 h, TLC monitoring revealed no starting material; the mixture was poured into water and extracted three times with DCM. The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4 and evaporated in vacuo to dryness. The resulting dark-yellow oil was purified by TLC on silicagel with DCM/EtOAc (10:1) to give **4** (415 mg, 97%). IR (DCM) ν_{max}/cm^{-1}: 3011, 2953, 2878, 1712, 1466, 1143. ^{1}H NMR ($CDCl_3$) δ/ppm: 4.82 (s, 1H, H-2, Fn), 4.76 (s, 1H, H-5, Fn), 4.57 (m, 1H, CH), 4.43 (s, 2H, H-3, H-4, Fn), 4.21 (m, 4H, H-2′, H-5′, H-3′, H-4′, Fn), 3.83 (s, 3H, OCH_3), 2.64 (br s,

1H, OH), 1.38 (d, 3H, $J = 5.8$ Hz, CHCH_3). ^{13}C NMR, APT ($CDCl_3$) δ/ppm: 172.5 ($COOCH_3$), 96.42 (C-1′, Fn), 71.58 (C-2, Fn), 71.51 (C-5, Fn) 70.99 (C-1, Fn), 70.56 ($CHCH_3$), 70.09 (C-3′, Fn), 69 (C-4′, Fn), 68.93 (C-3, C-4, Fn), 67.35 (C-2′, Fn), 65.21 (C-5′, Fn), 51.76 (OCH_3), 24.4 (CHCH_3). HR-MS: calcd. for $C_{14}H_{16}O_3Fe$, 288.04489; found, 288.045. MS (EI): $m/z = 288$ (100) $[M]^+$, 270 (20) $[M^+-17]$, 196 (35), 166 (59), 145 (33), 121 (26), 92 (74), 56 (29).

14. Chiral-HPLC conditions: Chiralcel OD-H column, hexane/propan-2-ol = 9.5/0.5, 0.7 ml min^{-1}: $t_{R(S)} = 8.9$, $t_{R(R)} = 9.6$ min for **5**, $t_{R(S)} = 15.8$, $t_{R(R)} = 16.7$ min for **4**.
15. *Procedure for lipase-catalyzed transesterification of* **4**: Racemic carbinol **4** (500 mg) was dissolved in hexane (50 ml). Novozym 435 (70 mg) and vinyl acetate (5 ml) were added and the mixture was shaken at 210 rpm and 28 °C. The progress of the reaction was monitored by taking samples from the reaction mixture and analyzing them by chiral HPLC under conditions described in Ref. 14. After 32 h, the reaction was stopped by filtering off the enzyme near 50% conversion; the solution was evaporated and the resulting carbinol and acetate separated by column chromatography (aluminium oxide, DCM/petroleum ether = 8:2) gave (+)-**4** (238 mg) and (−)-**5** (235 mg). (+)-**4**, ee = 90%, $[\alpha]_D^{22} = +30.4$ (*c* 1.0, $CHCl_3$). (−)-**5**, ee = 99%, $[\alpha]_D^{22} = -46$ (*c* 0.79, $CHCl_3$). Spectral data for acetate **5**: IR (DCM) ν_{max}/cm^{-1}: 1730, 1712, 1466, 1372, 1143. ^{1}H NMR ($CDCl_3$) δ/ppm: 5.77 (q, 1H, CH), 4.77 (t, 2H, $J = 3.9$ Hz, H-2, H-5, Fn), 4.38 (t, 2H, $J = 3.9$ Hz, H-3, H-4, Fn), 4.28 (m, 1H, Fn), 4.20 (m, 3H, Fn), 3.80 (s, 3H, OCH_3), 2.05 (s, 3H, $OCCH_3$), 1.54 (s, 3H, CHCH_3). ^{13}C NMR, APT ($CDCl_3$) δ/ppm: 171.66 ($COOCH_3$), 170.40 ($OCCH_3$) 89.66 (C-1′, Fn), 71.93 (C-2, Fn), 71.91 (C-5, Fn) 71.82 (C-1, Fn), 70.85 (C-3′, Fn), 70.79 (C-4′, Fn), 70.09 ($CHCH_3$), 69.73 (C-3, Fn), 69.70 (C-4, Fn), 68.05 (C-2′, Fn), 67.52 (C-5′, Fn), 51.61 (OCH_3), 21.34 (CHCH_3), 19.86 ($OCCH_3$). HR-MS: calcd. for $C_{16}H_{18}O_4Fe$, 330.0555; found, 330.0582.
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17. To a cold solution (0 °C) of (+)-**4** (150 mg, 0.521 mmol) and Et_3N (436 μl, 3.124 mmol) in dry toluene (8 ml), acetyl chloride (148 μl, 2.084 mmol) was added. After stirring for 1 h at 0 °C, the reaction mixture was worked up similarly as described in Ref. 13 After column chromatography purification (aluminium oxide, DCM) (+)-**5** was obtained as an orange residue (140 mg, 81%) having the same spectral data as described above, ee = 86%, $[\alpha]_D^{22} = +40.8$ (*c* 1.0, $CHCl_3$).
18. NaN_3 (134.8 mg, 2.074 mmol) was added to a solution of (+)-**5** (60 mg, 0.182 mmol) in 1:1 H_2O/MeOH (10 ml). The reaction mixture was stirred for 2 h at 80 °C and worked up in the usual manner. Purification by TLC (silica gel, DCM) gave (+)-**6** as an orange oil (48 mg, 84%). The same procedure was applied for the conversion of (−)-**5** into (−)-**6**. (+)-**6**, ee = 85%, $[\alpha]_D^{22} = +64.4$ (*c* 1.0, $CHCl_3$). (−)-**6**, ee = 99%, $[\alpha]_D^{22} = -81.2$ (*c* 1.1, $CHCl_3$). Spectral data for azide **6**: IR (DCM) ν_{max}/cm^{-1}: 2100.9, 1712, 1466, 1142. ^{1}H NMR ($CDCl_3$) δ/ppm: 4.79 (t, 2H, $J = 3.8$ Hz, H-2, H-5, Fn), 4.41 (t, 2H, $J = 3.8$ Hz, H-3, H-4, Fn), 4.33 (q, 1H, CH), 4.24–4.20 (m, 4H, Fn), 3.80 (s, 3H, OCH_3), 1.53 (d, 3H, $CHCH_3$, $J = 6.7$ Hz). ^{13}C NMR, APT ($CDCl_3$) δ/ppm: 171.63 ($COOCH_3$), 90.31 (C-1′, Fn), 72.01 (C-2, Fn), 71.99 (C-5, Fn) 71.92 (C-1, Fn), 70.96 (C-3, Fn), 70.88 (C-4, Fn), 70.04 (C-3′, Fn), 69.76 (C-4′, Fn), 68.83 (C-2′, Fn), 67.32 (C-5′, Fn), 56.3 ($CHCH_3$), 51.62 (OCH_3), 19.81 (CHCH_3). HR-MS: calcd. for $C_{14}H_{15}O_2N_3Fe$, 313.0514; found, 313.0527.
19. Reduction of azides **6** using H_2 Pd/C in ethyl acetate over 3 h gave corresponding amines **2** in quantitative yields. (+)-**2**, ee = n.d., $[\alpha]_D^{22} = +7.75$ (*c* 0.5, $CHCl_3$). (−)-**2**, ee = n.d., $[\alpha]_D^{22} = -8.3$ (*c* 0.5, $CHCl_3$). IR, NMR and MS data are described in Ref. 3.
20. The absolute configuration of (*R*)-**3** was assigned by comparison of the value and sign of its specific rotation {$[\alpha]_D^{22} = +99$ (*c* 1.0, benzene) ee = 98%} with that of (*R*)-**3** {$[\alpha]_D^{22} = +97$ (*c* 1.0, benzene) ee = 95%} derived from (*R*)-**7** of the known absolute configuration. Analogously, configuration of (*S*)-**3** {$[\alpha]_D^{22} = -75.2$ (*c* 1.0, benzene) ee = 84%} was confirmed through the specific rotation of (*S*)-**3** {$[\alpha]_D^{22} = -55.2$ (*c* 1.0, benzene) ee = 58%} derived from (*S*)-**7**.
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