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Original Scientific Paper

Synthesis of the First Heteroannularly Substituted Ferrocene Amino Acid and Isomeric Carbamic Acid Derivatives Containing Chiral Centres

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Syntheses of *N*- and *C*-protected derivatives of 1'-(1-aminoethyl)ferrocene-1-carboxylic acid (Fcca) and isomeric carbamic acid are reported. The first attempt to prepare *N*-Ac-Fcca (**8**) by cleavage of 1-[1-(acetamido)ethyl]-1'-(*o*-chlorobenzoyl)ferrocene (**7**) with *t*-BuOK/H_2O/GLYME failed. Friedel-Crafts reactions of *N*-substituted (1-**f**errocenyl**e**thyl)**a**mines [Boc-Fea (**5**) and Ac-Fea (**6**)] with $ClCOSMe/AlCl_3$ gave the corresponding heteroannularly substituted thioesters **9/10**, which were hydrolyzed into Boc-Fcca/Ac-Fcca and esterified into Boc-Fcca-OMe (**11**)/ Ac-Fcca-OMe (**12**). In a multi-step sequence, bromoferrocene was transformed into 1'-brominated Fea (**15**), Boc-Fea (**16**) and Ac-Fea (**17**). Lithiation/ethoxycarbonylation of these bromine compounds gave the corresponding carbamic esters **18** and **19**, instead of the expected Fcca esters. By lithiation/carboxylation and subsequent esterification, **5**, **6**, **16** and **17** were converted into the desired **11** and **12**. 1'-Acetylferrocene-1-carboxylic acid (**21**) was transformed into oxime **22** and oxime-ester **23**. Hydrogenation of this intermediate resulted in formation of Fcca-OMe (**24**) in very good yield. The structure of the compounds prepared was confirmed by HRMS and spectroscopic analyses.

Keywords
ferrocene chiral amino acid
ferrocene chiral carbamic acid
oxime reduction
lithiation
carboxylation

INTRODUCTION

During our studies of ferrocene-containing oligoamides **I** (m = 0–3, n = 4–6) we prepared the corresponding monomers – heteroannularly substituted amino amido acids **I** (m = 2 and 3, n = 1) – by reactions of 1,1-(1,1'-ferrocenylene)bis(ethylamine) with either succinic or glutaric anhydride in toluene. The spectral properties and solubility of these compounds indicated their zwitterionic character (Figure 1).[1]

Two types of similar amino acids with inserted ferrocene units are homo- **II** and heteroannularly substituted compounds **III** presented in Figure 2. *N,N*-Dimethyl derivative of **II** (m = 0, n = 1) was prepared by regioselective lithiation and carboxylation of *N,N*-dimethyl(ferrocenylmethyl)amine.[2] Hydrogenation of (*R*)- and (*S*)-methyl 2-nitroferrocene-1-carboxylate gave the corresponding amino ester, but the attempt to obtain the parent amino acid **II** (m, n = 0) by its hydrolysis resulted in decomposition.[3]

Butler and Quayle reported the synthesis and characterization of the first »homologue« of series **III** (n = m = 0; Fca = **F**erro**c**ene **a**mino acid). They prepared this compound by lithiation of 1'-amino-1-bromoferrocene

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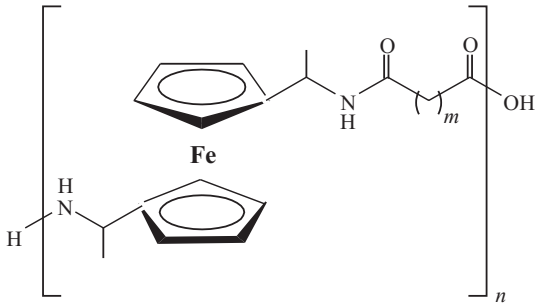
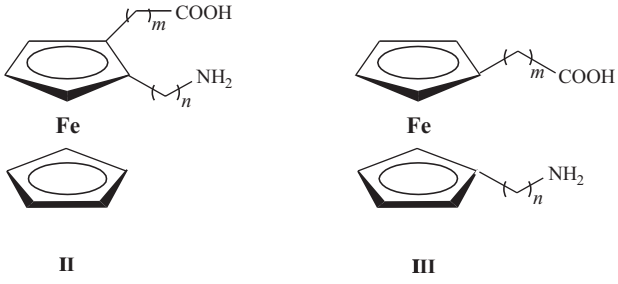


I, m = 0-3; n = 1-6

Fig.1. Ferrocene-containing oligoamides



II **III**

Fig. 2. Homo-(**II**) and heteroannularly substituted ferrocene amino acids (**III**)

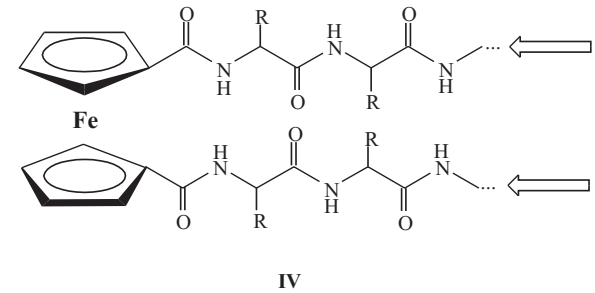
and quenching with solid carbon dioxide, but its isolation was not entirely successful. The treatment of the reaction mixture with methanolic hydrogen chloride resulted in formation of methyl 1'-aminoferrocene-1-carboxylate contaminated with some byproducts.[4] Nakamura's group prepared *N*-Boc- and *N*-Ac-Fca (in rather low yields) starting from *N*-acetylaminoferrocene *via* its heteroannularly substituted *o,o'*-dichlorobenzoyl derivate, aiming to synthesize the corresponding amide-linked dimer Ac-Fca-Fca-NHMe as the lowest of the ferrocene-based oligomers ferrolons – X-(Fca)$_n$-Y[5]. A similar synthesis of Fca-hydrochloride was performed recently by Heinze and Schlenker.[6] We have described a convenient preparation of zwitterionic Fca, as well as of its *C*-protected (ester) and *N*-protected stable derivatives and precursors (*N*-Ac-, *N*-Boc-, *N*-Cbz-Fca). In all of these preparations, the crucial intermediate was methyl-1'-azidocarbonylferrocene-1-carboxylate and the products were obtained in good yields as analytically pure samples.[7–9] Using a similar method (*via* the corresponding intermediate ferrocene ester-azides), we have prepared *N*- and *C*-protected higher homologues of Fca (**III**; m, n = 0, 3, 4), showing in this way the general character of this procedure.[10]

Since the separation between cyclopentadiene rings in ferrocene of about 3.3 Å is close to the NH···O distance in β-sheets, this ordered conformation is a mimic for this structural element. This aspect was first been realized by Herrick and coworkers, who proposed the use of ferrocene-1,1'-dicarboxylic acid as a turn mimetic.[11] Subsequently, structural work has been carried out by several groups, in particular those of Hirao and Kraatz.[12–17]

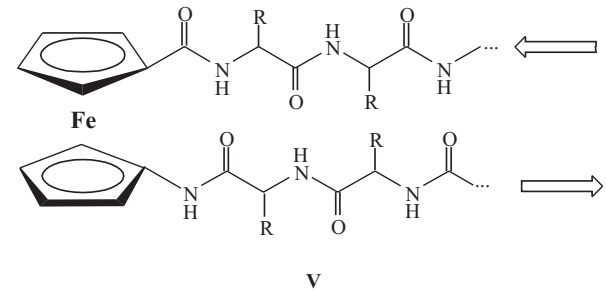
An important consequence of the symmetrical nature of complexes **IV** derived from ferrocene-1,1'-dicarboxylic acid is that only *parallel* peptide strands can be formed. Natural peptide turns, however, will always result in *anti-parallel* peptide strands. This feature can be realized in type **V** compounds, which incorporate Fca coupled with natural amino acids (Figure 3).

The first synthesis of conjugates **V** containing Fca and 1–4 L-alanine units using DCC/ HOBt was reported by us at the 1st ISBOMC.[18] In collaboration with Metzler-Nolte's group, we published the preparation and structure determination of one of these compounds – tetrapeptide Boc-Ala-Fca-Ala-Ala-OMe. The solid state structure of this tetrapeptide confirms that (*i*) a turn structure is induced by Fca, (*ii*) an *anti-parallel* orientation of the two peptide strands persists, which is (*iii*) stabilized by two intramolecular hydrogen bonds, giving in this way *P*-helical conformation of the metallocene.[19] The higher homologues of Fca – **III** (m, n = 0, 3, 4) should prove to be flexible building blocks incorporated into the natural peptide chain.[10]

Having in mind the mentioned interesting properties of oligopeptides **V** (strong intramolecular hydrogen bonds, helical chirality, *etc*.), which are unlike all previous metallocene turn structures also truly organometallic turn mimetics, we decided to extend our studies to ferrocene amino acids of type **VI** (Figure 4) containing the chiral center. In this paper, we report the synthetic routes to ob-

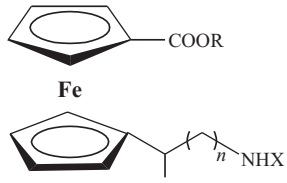


IV



V

Fig. 3. Ferrocene bioconjugate with parallel (**IV**) and anti-parallel peptide strands (**V**)



VI

Fig. 4. C- and N-protected heteroannularly substituted ferrocene amino acids containing chiral centre

taining the first homologue of this series (**VI**, $n = 0$; Fcca = **F**erro**c**ene **c**hiral **a**mino acid), aiming to incorporate it into the peptide chains composed of natural amino acids.

One should emphasize that Fcca can be considered a derivative of the chiral (1-**f**errocenyl**e**thyl)**a**mine (Fea, **2**). It is well known that α-ferrocenylalkylamines turned out to be the only ferrocene compounds that were chosen as appropriate chiral auxiliaries, because (*i*) they had very high induction ability, and (*ii*) they could be readily cleaved from the generated chiral compounds.[20] *E.g.*, these amines transmitted chiral information in a »cascade way» to a carbonyl compound, an acid, and an isocyanide leading, in the so-called *four component condensation*, to a single product containing four chiral centers.[21] Similar applications of Fea are either an asymmetric synthesis of alanine by enantioselective reduction of the corresponding intermediate imine[22] or diastereoselective addition of a racemic cyclic anhydride to a Schiff base derived from Fea and piperonal.[23]

Considering compound **2** as an analogue of phenethylamine (or of other similar aralkylamines), one could imagine its biocatalyzed stereoselective transformations to the corresponding amides, as well as the reactions of Fcca with natural amino acids giving peptides. There are numerous examples of lipase-catalyzed dynamic resolution of primary amines, ArCHR-NH_2, *via* ester aminolysis. The »Kazlauskas-rule« predicts a faster reacting enantiomer: (*R*)-amines are preferentially acylated if the sequence rule order of substituents is Ar > R (*i.e.*, Large > Medium).[24] Lipases CAL-B, PCL, and PAL often show high enantioselectivity in such biotransformations (E > 100).[25–27]

EXPERIMENTAL

The majority of syntheses were carried out under argon. CH_2Cl_2 used for syntheses and FT-IR were dried (P_2O_5), distilled over CaH_2 and stored over molecular sieves (4 Å). THF was dried and freshly distilled prior to use. All the syntheses and manipulations of air- and moisture-sensitive materials were carried out in flame-dried glassware and using syringes. Hydrogenation was performed in a Paar reactor under 600 psi pressure. EDC, HOBt (Aldrich), Phe and Ala (Merck) were used as received. Products were purified by preparative thin layer chromatography on silica gel (Merck, Kieselgel 60 HF_{254}) using a mixture of CH_2Cl_2/EtOAc and CH_2Cl_2/diethyl ether. Melting points were determined with a Buechi apparatus. The IR spectra were recorded as CH_2Cl_2 solutions with a Bomem MB 100 mid FTIR spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 or Bruker Avance 600 MHz spectrometer in $CDCl_3$ solution with Me_4Si as internal standard. Mass spectra (MS) were run on MAT 8200 (EI, FAB), Hewelett--Packard HP 5989 (ESI) or VG Analytical 70/20 (EI, HR--MS) instruments. HPLC analysis was carried out on a Chiralcel OD-H column (Knauer model K-2501 pump and K-501 detector) in *n*-hexane/*i*-propanol or *n*-hexane/*t*-BuOH 10:1 mixtures at a 0.7–1.0 ml/min flow rate. 4-Ferrocenyl-3-thiapentanoic acid (**1**) was prepared in high yields using the standard procedures:[1, 38] acetylation of ferrocene gave acetylferrocene, which was reduced by $NaBH_4$ in methanol into 1-ferrocenylethanol and converted into thiaacid (**1**) by the action of thioglycolic acid in the presence of TFA.

AA = amino acid, Fca = 1'-aminoferrocene-1-carboxylic acid, Fcca = 1'-(1-aminoethyl)ferrocene-1-carboxylic acid, Fea = (1-ferrocenylethyl)amine, Fc = ferrocenyl, Fn = 1,1'-ferrocenylene, EDC = *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimyde-hydrochloride, HOBt = 1-hydroxybenzotriazole-hydrate.

*(1-Ferrocenylethyl)amine (**2**)*

To a cold solution (0 °C) of thiaacid (**1**) (470 mg, 1.55 mmol) in 25 % NH_4OH (25 ml), NH_4Cl (124 mg, 2.32 mmol) and $HgCl_2$ (630 mg, 2.32 mmol) were added. The mixture was stirred for 1 hour at 0 °C, poured into excess of ice water and extracted with dichloromethane. The organic layer was acidified with 10 % HCl to give a yellow aqueous phase, in which 1 mol dm^{-3} aqueous solution of NaOH was added, and the product was extracted with CH_2Cl_2 as yellow oil (262 mg, 74 %).[1] IR (KBr) ν_{max}/cm^{-1}: 3376 m (N-H).

*BocAlaNHCHMeFc (**3a/ 4a**)*

To a suspension of L-Boc-Ala-OH (95 mg, 0.5 mmol) in dichloromethane (3 ml), EDC (115 mg, 0.6 mmol) and HOBt (81 mg, 0.6 mmol) were added. After stirring for 15 minutes at r.t., the mixture was cooled to 0 °C and racemic amine **2** (100 mg, 0.44 mmol) was added. The mixture was stirred for 1 hour at r.t., washed thrice with saturated solution of $NaHCO_3$, 10 % aqueous solution of citric acid and H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. TLC-purification of the crude product with CH_2Cl_2/EtOAc (10:1) gave a mixture of diastereomers **3a/4a** in the form of orange resin (124 mg, 71 %). Coupling of racemic Fea **2** with 0.5 equivalent of AA gave a mixture of diastereomers **3a/4a** in 1:2 ratio (based on HPLC and NMR).

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3420 m (N-H free), 3308 w (N-H assoc.), 1709 s (C=O, COO*t*-Bu), 1674 s (CONH). ^{1}H-NMR ($CDCl_3$) δ/ppm: 6.54 (s br, 1H, NHAla), 5.30/5.28 (each s, 1H, NHFc), 5.17/4.83 (each t, 1H, CHFc, $^3J_1 = 14.6$ Hz, $^3J_2 = 14.3$ Hz), 4.19/4.18 (each s, 5H, $Cp_{unsubst}$), 4.16–4.10 (m, 5H, 4H Fc + 1H CHAla), 1.46/1.45 (each s, 9H, $C(CH_3)_3$), 1.42 (m, 3H, CH_3Fc), 1.38 (m, 3H, CH_3Ala). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 171.53 (COAla), 155.30

(COO*t*Bu), 95.57 (C-1, Fc), 78.17 (*C*(CH_3)$_3$), 70.24/ 70.18 ($Cp_{unsubst.}$), 69.61 (C-3, Fc), 69.41 (C-4, Fc), 68.79 (C-2, Fc), 67.41/ 67.40 (C-5, Fc), 50.41(CHAla), 45.23/45.11 (C*H*CH_3), 30.01 (C(*C*H_3)$_3$), 22.58 (CH*C*H_3), 18.03 (CH_3Ala). HR-MS: calc. for $C_{20}H_{28}N_2O_3Fe$ = 400.29, found: 400.3067.

*BocPheNHCHMeFc (**3b/ 4b**)*

L-Boc-Phe-OH (131 mg, 0.5 mmol) was activated as described for L-Boc-Ala-OH and coupled with racemic amine **2** (100 mg, 0.44 mmol). After 1 hour, the mixture was worked up and purified using the same procedure as for compounds **3a/4a** to give 171 mg (80 %) of diastereomeric product. Coupling of racemic Fea **2** with 0.5 equivalent of AA gave a mixture of **3a/4a** in approximately 1:4 diastereomeric ratio (based on HPLC and NMR).

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3418 m (N-H), 1713 s (C=O, COO*t*-Bu), 1671 s (CONH). ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.25 (m, 5H, Ph), 6.25/ 6.03 (each d, 1H, NHPhe, $^3J_{1,2}$ = 8.04 Hz), 5.2/5.08 (each d, 1H, NHFc, $^3J_1$ = 7.0 Hz, $^3J_2$ = 7.3 Hz), 4.75/4.33 (each t, 1H, CHFc, $^3J_1$ = 7.0 Hz, $^3J_2$ = 6.8 Hz), 4.08/4.03 (each s, 5H, $Cp_{unsubst}$), 4.11–3.87 (m, 5H, 4H Fc + 1H CHAla), 3.16–3.01 (m, 2H, CH_2), 1.40 (s, 9H, C(CH_3)$_3$), 1.32–1.17 (m, 3H, CH_3). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 169.86/ 169.70 (COPhe), 155.33 (COO*t*Bu), 136.87/ 136.59 (C-1, Ph), 129.42 (C-3, C-5, Ph), 128.76/128.75 (C-2, C-6, Ph), 127 (C-4, Ph), 91.00 (C-1, Fc), 80.34/80.21 (*C*(CH_3)$_3$), 68.42/68.40 ($Cp_{unsubst.}$), 67.79 (C-3, Fc), 67.77/ 67.74 (C-4, Fc), 67.29/67.11 (C-2, Fc), 65.67/65.53 (C-5, Fc), 56.16/56.0 (CHPhe), 43.55/43.46 (C*H*CH_3), 38.77/38.28 (CH_2), 28.44 (C(*C*H_3)$_3$), 20.53/20.36 (CH*C*H_3). HR-MS: calc. for $C_{26}H_{32}N_2O_3Fe$ = 476.382, found: 476.1770. MS (EI): *m/z* = 476 (50) [M]$^+$, 402 (100) [M$^+$– *t*BuOH], 337 (25) [COPheNHMeCHCpFe], 213 (27) [Cp_2FeCHMe], 147 (18) [COCH(CH_2Ph)NH], 120 (20) [CpFe], 91 (13) [CpCHMe].

N-*(*tert-*Butoxycarbonyl)-(1-ferrocenylethyl)amine (**5**)*

Amine **2** (200 mg, 0.87 mmol) was dissolved in dioxane/ water (2:1) and 1 mol dm^{-3} aqueous solution of NaOH (0.5 ml) was added. After cooling to 0 °C, Boc_2O (210 mg, 0.96 mmol) was added and the reaction mixture was stirred for 30 minutes, poured into water and extracted thrice with dichloromethane. The organic extracts were combined, washed with water, saturated solution of NaCl, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The resulting orange oil was purified by TLC on silicagel with CH_2Cl_2/ EtOAc (10:1) to give *N*-Boc derivative **5** (300 mg, 91 %) as orange crystals.[59]

M.p.: 79.5–82.3 °C. IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3439 m (N-H), 1707 s (C=O, COO*t*-Bu). ^{1}H-NMR ($CDCl_3$) δ/ppm: 4.71 (bs, 1H, NH), 4.57 (bs, 1H, CH), 4.19 (s, 5H, $Cp_{unsubst}$), 4.15 (s, 4H, Fc-H), 1.49 (s, 9H, C(CH_3)$_3$), 1.44 (d, 3H, CH_3, ^3J = 6.6 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 154.90 (*C*OO*t*Bu), 95.57 (C-1, Fc), 79.04 (*C*(CH_3)$_3$), 68.49 ($Cp_{unsubst.}$), 67.84 (C-3, Fc), 67.50 (C-4, Fc), 66.88 (C-2, Fc), 65.81 (C-5, Fc), 44.84 (*C*HCH_3), 28.32 (C(*C*H_3)$_3$), 21.39 (CH*C*H_3). HR-MS: calc. for $C_{17}H_{23}NO_2Fe$ = 329.212, found: 329.1080. MS (EI): *m/z* = 329 (65) [M]$^+$, 273 (100) [M$^+$ – Fe], 213 (25) [Cp_2FeCHMe], 186 (12) [Cp_2Fe], 120 (16) [CpFe], 91 (12) [CpCHMe].

N-*Acetyl-(1-ferrocenylethyl)amine (**6**)*

Acetyl chloride (0.1 ml, 1.3 mmol) was added dropwise to a cold solution (0 °C) of amine **2** (100 mg, 0.32 mmol) and NEt_3 (0.27 ml, 1.95 mmol) in dry CH_2Cl_2 (10 ml). After 20 minutes of stirring and cooling, the reaction mixture was worked up similarly as described for the *N*-Boc derivative. TLC-purification of the row product with CH_2Cl_2/EtOAc (10:1) gave 73 mg (84 %) of *N*-Ac derivative **6** in the form of orange crystals. IR, NMR and MS are described in Ref. 60.

*1-[1-(Acetamido)ethyl]-1'-(*o*-chlorobenzoyl) ferrocene (**7**)*

To a cold solution (0 °C) of acetamide **6** (150 mg, 0.554 mmol) in CH_2Cl_2 (10 ml), *o*-chlorobenzoyl chloride (70.3 µl, 0.554 mmol) and $AlCl_3$ (103 mg, 0.776 mmol) were added. After stirring for two hours at 0 °C, the reaction mixture was worked up similarly as described for compound **6**. After TLC-purification with CH_2Cl_2/EtOAc (10:1), the product was obtained as red oil (86 mg, 38 %).

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3434 m (N-H), 1663 s (C=O, $COCH_3$), 1606 s (C=O, COAr). ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.49–7.34 (m, 4H, Ph), 6.69 (d, 1H, NH, ^3J = 7.62 Hz), 5.05 (s, 1H, H-2', Fn), 4.86 (s, 1H, CH), 4.7 (s, 1H, H-5', Fn), 4.61 (s, 1H, H-3', Fn), 4.46 (s, 1H, H-4', Fn), 4.33 (s, 1H, H-2, Fn), 4.29 (s, 1H, H-5, Fn), 4.11 (s, 2H, H-3, H-4, Fn), 2.23 (s, 3H, $COCH_3$), 1.49 (d, 3H, CHC*H*$_3$, ^3J = 6.57 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 170.2 (*C*OCH_3), 143.70 (C-1, Ph), 138.42 (C-2, Ph), 131.43 (C-4 Ph), 130.61 (C-6, Ph), 129.22 (C-3, Ph), 126.33 (C-5, Ph), 94.07 (C-1, Fn), 76.60 (C-1', Fn), 73.63 (C-3', Fn), 73.18 (C-4', Fn), 71.82 (C-2', Fn), 71.51 (C-5', Fn), 69.60 (C-3, Fn), 69.40 (C-4, Fn), 69.12 (C-2, Fn), 68.14 (C-5, Fn), 42.50 (*C*HCH$_3$), 23.19 (CO*C*H$_3$), 21.01 (CH*C*H$_3$). HR-MS: calc. for $C_{21}H_{20}NO_2FeCl$ = 409.685, found: 409.0531. MS (EI): *m/z* = 409 (100) [M]$^+$, 317 (20) [M$^+$ – CpCHMe], 240 (12), 206 (55) [M$^+$– CpCOPhCl], 177 (23) [CpFe + NHAc], 147 (25) [CpFeCHMe].

*Attempted Preparation of 1'-[1-(acetamido)ethyl]ferrocene-1-carboxylic acid (**8**)*

Solution of **7** (62 mg, 0.14 mmol) in 1,2-dimetoxyethane (GLYME) (3 ml) was added dropwise to a suspension of *t*-BuOK (67 mg, 0.59 mmol) and water (10 µl). The reaction mixture was refluxed for 2 hours and TLC-monitored, but formation of the desired product was not observed.

S-*Methyl 1'-[1-(*tert-*butoxycarbonylamino)ethyl]ferrocene-1-thiocarboxylate (**9**)*

Perrier's complex [prepared by addition of ClC(=O)SMe (78 µl, 0.92 mmol) to a suspension of aluminium chloride (123 mg, 0.92 mmol) in dry dichloroethane (3 ml)] was added dropwise to a solution of **5** (150 mg, 0.46 mmol) in 1,2-dichloroethane. After refluxing for 1.5 h, the reaction mixture was poured into water, extracted with dichlorometha-

ne, washed with 5 % aqueous KOH, saturated solution of NaCl in water, dried and evaporated to dryness. TLC-purification with dichlorometane/ethyl acetate (10:1) gave 86 mg (46.5 %) of **9** as orange resin and 25 mg of **9a**.

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3433 m (N-H), 1667 s (C=O, COOC(CH_3) and C=O, COSCH_3). ^{1}H-NMR ($CDCl_3$) δ/ppm: 6.51 (d, 1H, NH, ^3J = 6.0 Hz), 4.72 (m, 1H, CH), 4.70 (s, 2H, H-2, H-5, Fn), 4.51 (s, H-3, H-4, Fn), 4.40–4.1 (m, 4H, H-3', H-4', H-2', H-5', Fn), 2.50 (s, 3H, SCH_3), 1.49 (s, 9H, C(CH_3)$_3$), 1.42 (d, 3H, CHC*H*$_3$, ^3J = 6.2 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 194 (*C*OS), 155.11 (*C*O*O*t*Bu), 95.04 (C-1', Fn), 79.61 (*C*(CH$_3$)$_3$), 78.92 (C-1, Fn), 73.22 (C-3, Fn), 73.62 (C-4, Fn), 71.02 (C-2, Fn), 70.19 (C-5, Fn), 69.56 (C-3', Fn), 69.48 (C-4', Fn), 69.03 (C-2', Fn), 68.41 (C-5', Fn), 44.06 (*C*HCH$_3$), 27.98 (C(*C*H$_3$)$_3$) 21.55 (CH*C*H$_3$), 12.73 (SCH$_3$). HR-MS: calc. for $C_{19}H_{25}NO_3FeS$ = 403.314, found: 403.1124.

S-*Methyl 1'-[1-(acetamido)ethyl]ferrocene-1-thiocarboxylate (**10**)*

10 was prepared in a similar way as described for compound **9**. Suspension of $AlCl_3$ (98 mg, 0.738 mmol) and *S*-methyl-chlorothioformiate (63 µl, 0.738 mmol) in dichloroethane (9 ml) was heated to the boiling point and a solution of **6** (200 mg, 0.738 mmol) in 1,2-dichloroethane was added dropwise. Reaction mixture was refluxed for 30 minutes and worked up as previously described. TLC-purification with dichlorometane/ethyl acetate (10:1) gave 25 mg of **6**, orange resinous **10** (107 mg, 48 %, calculated on the basis of converted **6**) and 17 mg of yellow crystalline **10a**.

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3433 m (N-H), 1677 s (C=O, COOC(CH_3) and C=O, COSCH_3). ^{1}H-NMR ($CDCl_3$) δ/ppm: 6.43 (d, 1H, NH, ^3J = 5.76 Hz), 4.90–4.83 (m, 3H, CH + H-2, H-5, Fn), 4.51 (s, 1H, H-3, Fn), 4.30 (s, 1H, H-4, Fn), 4.21–3.97 (m, 4H, H-3', H-4', H-2', H-5', Fn), 2.42 (s, 3H, SCH_3), 2.12 (s, 3H, $COCH_3$), 1.44 (d, 3H, CHC*H*$_3$, ^3J = 6.54 Hz). 13C-NMR, APT (CDCl3) δ/ppm: 196 (*C*OS), 169.8 (*C*OCH3), 94.1 (C-1', Fn), 79.54 (C-1, Fn), 72.18 (C-3, Fn), 72.09 (C-4, Fn), 71.20 (C-2, Fn), 69.9 (C-5, Fn), 69.71 (C-3', Fn), 69.59 (C-4', Fn), 68.73 (C-2', Fn), 68.23 (C-5', Fn), 42.60 (*C*HCH$_3$), 23.13 (CO*C*H$_3$), 20.81 (CH*C*H$_3$), 11.35 (SCH$_3$). HR-MS: calc. for $C_{16}H_{19}NO_2FeS$ = 345.236, found: 345.0492. MS (EI): *m/z* = 345 (90) [M]$^+$, 280 (10) [M$^+$ – Cp], 253 (55) [M$^+$ – CpCHMe], 206 (100) [M$^+$ – CpCOSCH$_3$], 147 (30) [CpFeCHMe], 119 (57) [CpFe], 91 (24) [CpCHMe].

*Methyl 1'-[1-(*tert*-butoxycarbonylamino)ethyl]ferrocene-1-carboxylate (**11**)*

Thiaester **9** (100 mg, 0.25 mmol) was added to a solution of KOH (268 mg, 4.78 mmol) in ethanol/water = 1:1 (5 ml). Reaction mixture was stirred for 30 minutes at 50 °C, cooled and extracted with dichloromethane. Aqueous layer was acidified, extracted with dichloromethane, washed with saturated aqueous solution of NaCl, dried and evaporated to dryness. The resulting crude carboxylic acid was treated with excess of CH_2N_2 and TLC-purified with dichloromethane/ethyl acetate (10:1) to afford aminoester **11**, yellow resin (76 mg, 78 %).

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3439 m (N-H free), 3408 w (N-H assoc.), 1710 (C=O, $COOCH_3$ and CO*O*t-Bu). ^{1}H-NMR ($CDCl_3$) δ/ppm: 5.01 (d, 1H, NH, ^3J = 7.71 Hz), 4.81 (s, 2H, H-2, H-5, Fn), 4.54 (t, 1H, CH, J = 4.0 Hz), 4.41 (d, 2H, H-3, H-4, Fn, ^3J = 1.56), 4.21 (s, 1H, H-3', Fn), 4.14 (d, 2H, H-2', H-5', Fn, ^3J = 6.78), 4.09 (s, 1H, H-4', Fn), 3.86 (s, 3H, OCH_3), 1.49 (s, 9H, C(CH_3)$_3$), 1.43 (d, 3H, CH_3, ^3J = 6 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 172 (*C*O*O*CH$_3$), 155.2 (*C*O*O*t*Bu), 93.8 (C-1', Fn), 79.17 (*C*(CH$_3$)$_3$), 71.73 (C-2, C-5, Fn), 71.31 (C-1, Fn), 70.69 (C-3, Fn), 70.28 (C-4, Fn), 69.43 (C-3', Fn), 69.23 (C-4', Fn), 68.07 (C-2', Fn), 67.92 (C-5', Fn), 51.66 (OCH$_3$), 44.2 (*C*HCH$_3$), 28.4 (C(*C*H$_3$)$_3$), 21.15 (CH*C*H$_3$). HR-MS: calc. for $C_{19}H_{25}NO_4Fe$ = 387.248, found: 387.2955.

*Methyl 1'-[1-(acetamido)ethyl]ferrocene-1-carboxylate (**12**)*

Ester **12** was prepared in a similar way as described for compound **11**. Thiaester **10** (96 mg, 0.28 mmol) was added to a solution of KOH (300 mg, 5.36 mmol) in ethanol/water = 1:1 (5 ml). Reaction mixture was stirred for 30 minutes at 50 °C and worked up in the manner described above. The resulting crude carboxylic acid was treated with excess of CH_2N_2 and TLC-purified with dichlorometane/ethyl acetate (10:1) to afford aminoester **8**, yellow resin (66 mg, 76 %).

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3434 m (N-H free), 3359 m, (N-H assoc.), 1708 s (C=O, $COOCH_3$), 1664 s (C=O, $COCH_3$). ^{1}H-NMR ($CDCl_3$) δ/ppm: 6.56 (d, 1H, NH, ^3J = 7.32 Hz), 4.84 (s, 2H, H-2, H-5, Fn), 4.76 (s, 1H, CH), 4.44 (s, 2H, H-3, H-4, Fn), 4.26 (s, 1H, H-3', Fn), 4.16 (s, 1H, H-4' Fn), 4.11 (s, 1H, H-2', Fn), 3.98 (s, 1H, H-5', Fn), 3.82 (s, 3H, OCH_3), 2.01 (s, 3H, $COCH_3$), 1.44 (d, 3H, CHC*H*$_3$, ^3J = 6.6 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 173 (*C*O*O*CH$_3$), 169.4 (*C*O*C*H$_3$), 93.4 (C-1', Fn), 71.66 (C-2, Fn), 70.97 (C-1, Fn), 70.83 (C-5, Fn), 70.34 (C-3, Fn), 69.9 (C-4, Fn), 69.05 (C-3', Fn), 68.99 (C-4', Fn), 68.34 (C-2', Fn), 67.97 (C-5', Fn), 51.70 (OCH$_3$), 43.39 (*C*HCH$_3$), 22.96 (CO*C*H$_3$), 20.57 (CH*C*H$_3$). HR-MS: calc. for $C_{16}H_{19}NO_3Fe$ = 329.17, found: 329.0706. MS (EI): *m/z* = 329 (100) [M]$^+$, 206 (55) [M$^+$ – CpCOOMe], 177 (16) [CpFe + NHAc], 119 (10) [CpFe].

N-*(*tert*-Butoxycarbonyl)-[1-(1'-bromoferrocenyl)ethyl]amine (**16**) and* N-*acetyl-[1-(1'-bromo-ferrocenyl)ethyl]amine (**17**)*

The starting bromoferrocene was obtained in a multi-step synthesis from chloromercuryferrocene.[53] It was acetylated in 69 % yield,[54] and reduced to 92 % of carbinol **13**,[55] which reacted with $HSCH_2COOH$/ TFA giving 91 % of bromothiaacid **14**. [1-(1'-Bromoferrocenyl)ethyl]amine (**15**) was prepared (using a similar procedure to that described for compound **2**) from 380 mg (0.99 mmol) of thiaacid (**14**): 212 mg (76 %) of unstable **15** in the form of yellow oil]. IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3377 m (N-H)] was transformed without further purification into *N*-Boc- (**16**) and *N*-Ac-derivative (**17**) by the procedures applied to preparation of compounds **5** and **6**.

16: orange oil, yield: 398 mg (98 %). IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3438 m (N-H), 1708 s (C=O, COO*t*-Bu). ^{1}H-NMR ($CDCl_3$) δ/ppm: 4.77 (bs, 1H, NH), 4.64 (bs, 1H, CH), 4.40 (t, 2H, H-2', H-5', Fn, ^3J = 3.6 Hz), 4.19 (m, 4H, H-3, H-4, H-3', H-4', Fn), 4.11 (m, 2H, H-2, H-5, Fn), 1.47 (s, 9H, $C(CH_3)_3$), 1.44 (d, 3H, CH_3, ^3J = 1.2 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 154.96 (*C*OO*t*Bu), 93.72 (C-1, Fn), 79 ($C(CH_3)_3$), 77.64 (C-1', Fn), 71.18 (C-2', Fn), 71.13 (C-5', Fn), 70.65 (C-3', Fn), 70.50 (C-4', Fn), 70.21 (C-3, Fn), 69.12 (C-4, Fn), 68.62 (C-2, Fn), 67.55 (C-5, Fn), 44.57 (*C*HCH$_3$), 28.36 (C(*C*H$_3$)$_3$) 21.64 (CH*C*H$_3$). HR-MS: calc. for $C_{17}H_{22}NO_2FeBr$ = 408.12, found: 408.1845. MS (ESI): *m/z* = 407.9 (15) [M]$^+$, 406.8 (70) [M$^+$– H], 292 (75) [M$^+$– NHBoc], 290.8 (85).

17: orange oil, yield: 94 mg (84 %). IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3433 m (N-H), 1669 s (C=O, $COCH_3$). ^{1}H-NMR ($CDCl_3$) δ/ppm: 6.02 (s, 1H, NH), 4.98 (s, 1H, CH), 4.41 (s, 2H, H-2', H-5', Fn), 4.18 (m, 6H, H-3, H-4, H-3', H-4', H-2, H-5, Fn), 2.02 (s, 3H, $COCH_3$), 1.5 (s, 3H, CH_3). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 168.2 (*C*OCH_3), 92.96 (C-1, Fn), 77.51 (C-1', Fn), 71.10 (C-2', Fn), 70.50 (C-5', Fn), 70.41 (C-3', Fn), 70.15 (C-4', Fn), 69.96 (C-3, Fn), 69.29 (C-4, Fn), 69.0 (C-2, Fn), 67.53 (C-5, Fn), 43.02 (*C*HCH$_3$), 23.74 (CO*C*H$_3$), 21.01 (CH*C*H$_3$). HR-MS: calc. for $C_{14}H_{16}NOBrFe$ = 348.97647, found: 348.97660. MS (EI): *m/z* = 349 (15) [M]$^+$, 271 (15) [M$^+$ – Br], 206 (100) [M$^+$ – CpBr], 177 (16) [CpFe + NHAc], 147 (53) [CpFeCHMe], 120 (24) [CpFe], 91 (28) [CpCHMe], 56 (16) [Fe].

*Lithiation and Ethoxycarbonylation of Bromoferrocenes **15** and **16** into* N,N-*diethoxycarbonyl-(1-ferrocenylethyl)amine (**18**) and* N-*(*tert-*butoxycarbonyl)*-N-*ethoxycarbonyl-(1-ferrocenylethyl)amine (**19**)*

n-BuLi (1.6 mol dm^{-3} in hexane, 2 eq.) was added to a cold (–25 °C) solution of **15** (0.3 mmol) or **16** (0.5 mmol) in dry THF (5 ml) and stirred at –25 °C for 2 hours. After that, ClCOOEt (0.6 mmol) was added and the mixture was stirred for an additional hour at the same temperature, poured into water, extracted with CH_2Cl_2, washed with saturated aqueous solution of NaCl, dried and evaporated. TLC-purification of crude products with CH_2Cl_2/diethyl ether (15:1) gave yellow products **18** and **19**.

18: yellow resin, yield: 71 mg (63 %). IR (CH_2Cl_2) ν_{max}/cm^{-1}: 1739 s (COOEt), 1711 s (COOEt). ^{1}H-NMR ($CDCl_3$) δ/ppm: 5.38 (q, 1H, CH), 4.15 (m, 13 H, 9H Fn + 4H CH_2), 1.62 (d, 3H, CHC*H*$_3$, ^3J = 7.2 Hz) 1.22 (t, 6H, 2 × CH_2CH_3, ^3J = 7.5 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 153.2 (2 × *C*OOEt), 87.60 (C-1, Fc), 68.30 ($Cp_{unsubst.}$), 67.80 (C-3, Fc), 67.71 (C-4, Fc), 67.37 (C-2, Fc), 67.17 (C-5, Fc), 62.36 (2 × *C*H$_2$CH$_3$), 52.09 (*C*HCH$_3$), 17.84 (CH*C*H$_3$), 13.89 (2 × CH_2CH_3). HR-MS: calc. for $C_{18}H_{23}NO_4Fe$ = 373.222, found: 373.3032.

19: yellow resin, yield: 113 mg (66 %). M.p.: 49.8–53.6 °C. IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3437 m (N-H), 1737 (C=O, COOEt), 1706 (C=O, COO*t*-Bu). ^{1}H-NMR ($CDCl_3$) δ/ppm: 5.5 (q, 1H, CH), 4.28 (s, 2H, H-2, H-5, Fc), 4.14 (m, 9H, $Cp_{unsubst.}$ + H-3, H-4 Fc + CH_2), 1.65 (d, 3H, CHC*H*$_3$, ^3J = 7.2 Hz), 1.39 (s, 9H, C(CH$_3$)$_3$), 1.27 (t, 3H, CH$_2$C*H*$_3$, ^3J = 7.0 Hz). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 153.4 (*C*OO*t*Bu), 151.7 (*C*OOEt), 87.85 (C-1, Fc), 81.75 (*C*(CH$_3$)$_3$), 68.55 ($Cp_{unsubst.}$), 68.19 (C-3, Fc), 67.73 (C-4, Fc), 67.61 (C-2, Fc), 65.81 (C-5, Fc), 62.03 (*C*H$_2$), 51.61 (*C*HCH$_3$), 27.34 (C(*C*H$_3$)$_3$), 17.73 (CH*C*H$_3$), 13.90 (CH$_2$*C*H$_3$). HR-MS: calc. for $C_{20}H_{27}NO_4Fe$ = 401.12894, found: 401.12880. MS (EI): *m/z* = 401 (20) [M]$^+$, 329 (19) [M$^+$ – COOEt], 301 (100) [M$^+$– COOC(CH$_3$)$_3$], 273 (21) [M$^+$ – COOEt – Fe], 213 (24) [Cp$_2$FeCHMe], 147 (14) [CpFeCHMe], 120 (19) [CpFe], 91 (14) [CpCHMe], 56 (39) [Fe].

Lithiation, Carboxylation and Esterification of N-*protected Amines **5**, **6**, **16** and **17** into* N-*Boc- (**11**) and* N-*Ac-amino ester (**12**)*

n-BuLi (1.6 mol dm^{-3} in hexane, 2.5 eq.) was added to a cold (–50 °C) solution of **5** or **6** (0.3 mmol), **16** or **17** (0.5 mmol) in dry THF (5 ml). Reaction mixture was stirred at –50 °C for 2 hours, cooled to –78 °C, treated with gaseous CO_2 for 20 minutes and allowed to warm up to room temperature. After standard workup with diethyl ether and aqueous NH_4Cl solution, the resulting carboxylic acids were treated with excess of CH_2N_2 in Et_2O and methanol and TLC-purified with dichloromethane/ethyl acetate (10:1) to afford amino esters **11** and **12**.

11: yellow oil, yield: 52 mg (27 %) from **5**, 58 mg (30%) from **16**.

12: yellow oil, yield: 82 mg (50 %) from **6**, 78 mg (48 %) from **17**.

Spectral data for the compounds obtained are identical to those described in the above text.

*1'-Acetyl-*N,N-*diphenylferrocene-1-carboxamide (**20**)*

Acetyl chloride (0.84 g, 10.5 mmol) was added dropwise to a cold (–30 °C) suspension of *N,N*-diphenylferrocenecarboxamide (4g, 10.5 mmol) and $AlCl_3$ (2.8 g, 21mmol) in dry dichloroethane. Reaction mixture was stirred for one hour at the same temperature, poured into water, extracted with dichloromethane, washed thrice with 5 % aqueous KOH, saturated solution of NaCl in water, dried and evaporated giving a dark red oil (3.52 g, 80 %).[57]

*1'-Acetylferrocene-1-carboxylic acid (**21**)*

Ketone-amide **20** (1 g, 2.36 mmol) was dissolved in 10 % KOH in EtOH (17.5 ml) and refluxed for 20 hours. Reaction mixture was concentrated and dissolved in 5 % aqueous KOH. The solution obtained was neutralized with 1:1 HCl/H_2O and extracted with CH_2Cl_2. TLC-purification of crude product with CH_2Cl_2/EtOAc (10:1) gave red crystals (450 mg, 70 %).[58]

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3093–2869 m (OH), 1658 s (C=O, COOH and $COCH_3$).

*Methyl 1'-[1-(hydroxyimino)ethyl]ferrocene-1-carboxylate (**23**)*

A solution of keto-acid **21** (950 mg, 3.5 mmol), $NH_2OH \cdot HCl$ (728 mg, 10.5 mmol) and KOH (1.18 g, 21 mmol) in

EtOH (25 ml) was refluxed for one hour and worked up as described for compound **21,** giving orange crystals (803 mg, 80 %) of 1'-[1-(hydroxyimino)ethyl]ferrocene-1-carboxylic acid (**22**). [IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3600 m (OH free, NOH), 3180 bm (OH assoc., COOH), 1681 s (C=O, COOH)]. This acid (800 mg, 2.8 mmol) was dissolved in absolute MeOH (150 ml), treated with an excess of CH_2N_2 in Et_2O and MeOH and TLC-purified with dichlorometane/ethyl acetate (10:1) to afford oxime-ester **23**. Orange crystals, 716 mg, 85 %, M.p.: 99.6–104 °C.

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3574 m (OH free, NOH), 1712 s (C=O, $COOCH_3$), 1609 m (C=N). ^{1}H-NMR ($CDCl_3$) δ/ppm: 8.9 (s, 1H, NOH), 4.83 (s, 2H, H-2, H-5, Fn), 4.59 (s, 2H, H-3, H-4, Fn), 4.46 (s, 2H, H-2', H-5', Fn), 4.35 (s, 2H, H-3', H-4', Fn), 3.82 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 171.2 (*C*$OOCH_3$), 154.6 (C=N), 82.9 (C-1', Fn), 72.4 (C-1, Fn), 72.12 (C-2, C-5, Fn), 71.02 (C-3, C-4, Fn), 70.93 (C-3', C-4', Fn), 67.75 (C-2', C-5', Fn), 51.64 (OCH_3), 12.40 (CH_3). HR-MS: calc. for $C_{14}H_{15}NO_3Fe$ = 301.118, found: 301.0395. MS (EI): *m/z* = 301 (100) $[M]^+$, 177 (12) [FeCpCOOMe], 105 (20) [CpMeC=N].

*Methyl 1'-(1-aminoethyl)ferrocene-1-carboxylate (**24**)*

A solution of **23** (390 mg) in MeOH (30 ml) was hydrogenated in a Paar reactor under H_2 pressure (40 atm, 50 °C) for 24 hours. The reaction mixture was filtered and evaporated. The product was dissolved in CH_2Cl_2, extracted with 10 % citric acid, neutralized, extracted with dichloromethane, dried and evaporated to leave a yellow resin (320 mg, 86 %).

IR (CH_2Cl_2) ν_{max}/cm^{-1}: 3412 w (NH_2), 1713 (C=O, $COOCH_3$). ^{1}H-NMR ($CDCl_3$) δ/ppm: 4.79 (s, 1H, H-2, Fn), 4.76 (s, 1H, H-5, Fn), 4.40 (s, 2H, H-3, H-4, Fn), 4.19–4.15 (m, 5H, CH + H-2', H-3', H-4', H-5', CH Fn), 3.81 (s, 3H, OCH_3), 1.32 (d, 3H, CH_3, ^3J = 12 Hz), 1.25 (s, 2H, NH_2). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 172 (*C*$OOCH_3$), 97.8 (C-1', Fn), 71.54 (C-2, Fn), 71.51 (C-5, Fn), 71.42 (C-1, Fn), 70.60 (C-3, Fn), 70.33 (C-4, Fn), 69.23 (C-3', Fn), 68.96 (C-4', Fn), 67.37 (C-2', Fn), 67.31 (C-5', Fn), 51.61 (OCH_3), 45.56 (*C*HCH_3), 24.98 (CH*C*H_3). The structure of amino ester **24** was additionally confirmed by its transformation into Boc-amino ester **11** (95 %) using the same procedure as applied for preparation of **5**.

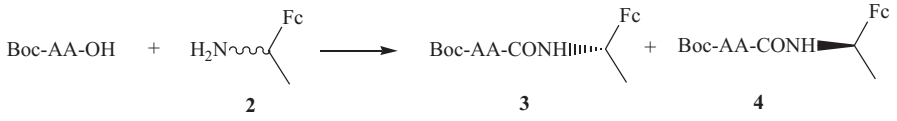
RESULTS AND DISCUSSION

Proteases (subtilisins, thermolysin B, *etc*.) are also appropriate and effective biocatalysts for resolution of primary amines, but they exerted an opposite enantiopreference for lipases. *E.g*., subtilisins (Carlsberg or BPN') favored acylation of (*S*)-aralkylamines with E ranging from 19 to > 50. In this way, lipases and subtilisins are a pair of complementary enantioselective reagents for organic synthesis.[24,25]

Successful resolutions of ethyl 2-aminocycloalkane-1-carboxylates (which may be considered as Fcca analogues) by acetates or chloroacetates in the presence of PCL or CAL-B are described.[25] In stunning examples of selectivity, CLECs of proteases have been used to catalyze either the ligation of natural amino acids to give peptides or in amidation of amino acids.[28–31] In this context, Margolin's group published coupling of amino acid derivatives or peptides (to 30 amino acids peptides) using thermolysin-CLEC.[32] Subtilisin-CLEC has been reported to be an efficient catalyst in the synthesis of optically active alkylamides of amino acids and peptides. The high enantioselectivity of this catalyst toward L-amino acids and (*S*)-amines (*e.g*., α-(1-naphthyl)ethylamine) resulted in formation of (*S,S*)-alkylamide regardless of the optical purity of substrates (Scheme 1). These diastereomers were obtained with *e.e.* > 98 % even when both amines and amino acids were used in racemic form![33]

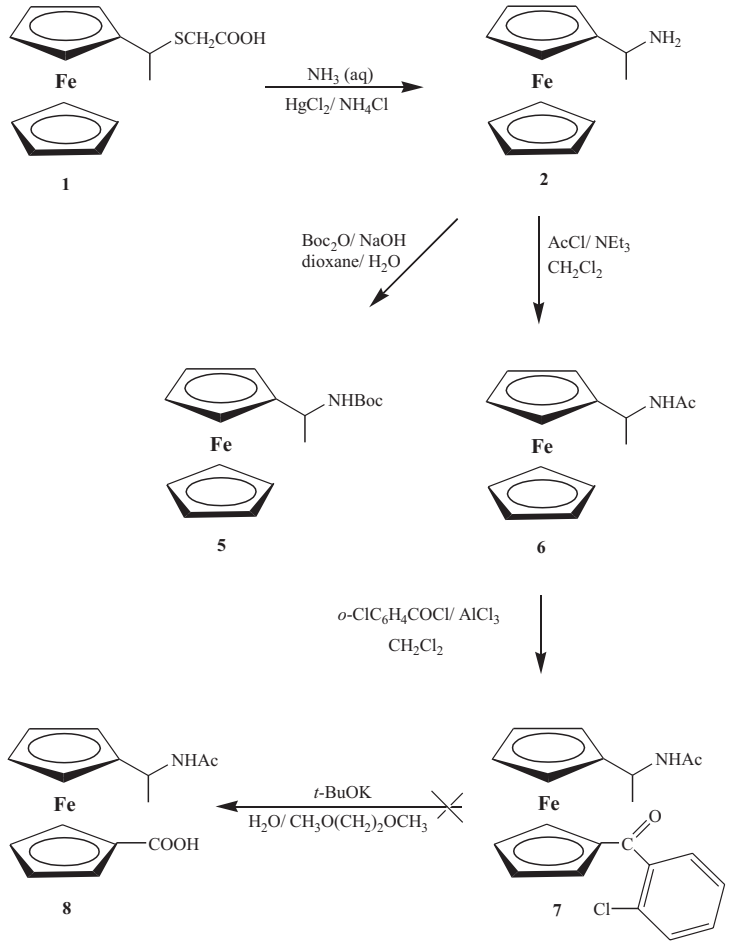
Having in mind the above described (*i*) properties of FcCHR-NH_2 as chiral auxiliaries, and (*ii*) the possibility of successful biocatalyzed dynamic resolution of the analogous ArCHR-NH_2, we decided to find out a ratio-

Scheme 1.



a; L-Ala
b; L-Phe

Scheme 2.



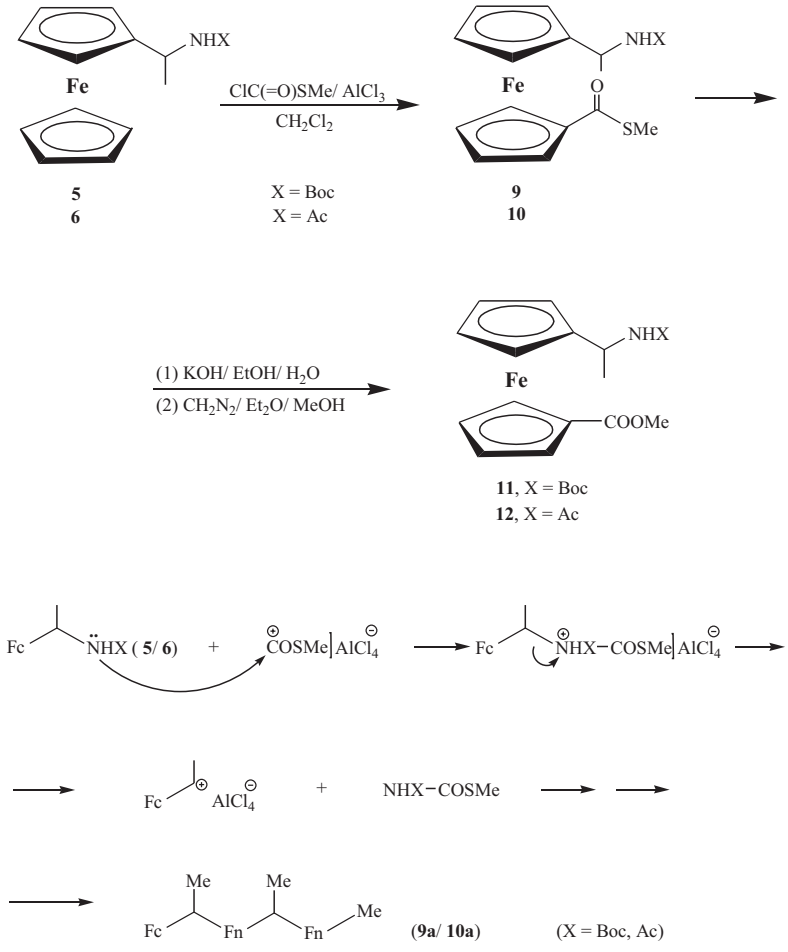
Scheme 3.

nal synthesis of the related Fcca. We estimated that the optically pure Fcca would exert a high induction ability and that it could be successfully used as a template (like Fca)[7–9] to nucleate and propagate certain conformations from its ordered region through a disordered region (α-amino acid based part) to form turn structures.[34,35] On the other side, we expected that the reactions of racemic Fcca with natural amino acids (or peptides) would proceed in a diastereoselective manner.

In preliminary experiments, we investigated whether a chiral induction occurs in the coupling reaction of Fea (**2**, a model substance for Fcca) with natural amino acids. To this end, starting from **2** and an excess of Boc-AA (AA = **a**, L-alanine; **b**, L-Phe), we prepared mixtures of diastereomers **3/4** using the EDC/HOBt-protocol and characterized them spectroscopically and by HPLC. Then, a 0.5 equivalent of Boc-AA-OH was activated by HOBt and EDC and added to racemic **2**. Experiments were carried out at r.t. in CH_2Cl_2 and samples were HPLC-monitored every 10 min over a period of 1 hour (Scheme 2).

In such a way, we showed that in the reaction of racemic Fea with L-Boc-Ala-OH one of the two possible diastereomers, **3a** and **4a**, was formed in an excess of about 64 %, which did not change appreciably with time. In the case of Fea coupling with L-Boc-Phe-OH, the corresponding diastereomers **3b/4b** were formed in a 22:78 ratio, obviously because of the bulkier amino acid residue. These HPLC findings were confirmed by careful integration of characteristic ^{1}H NMR signals of the mixtures of enriched diastereomers.

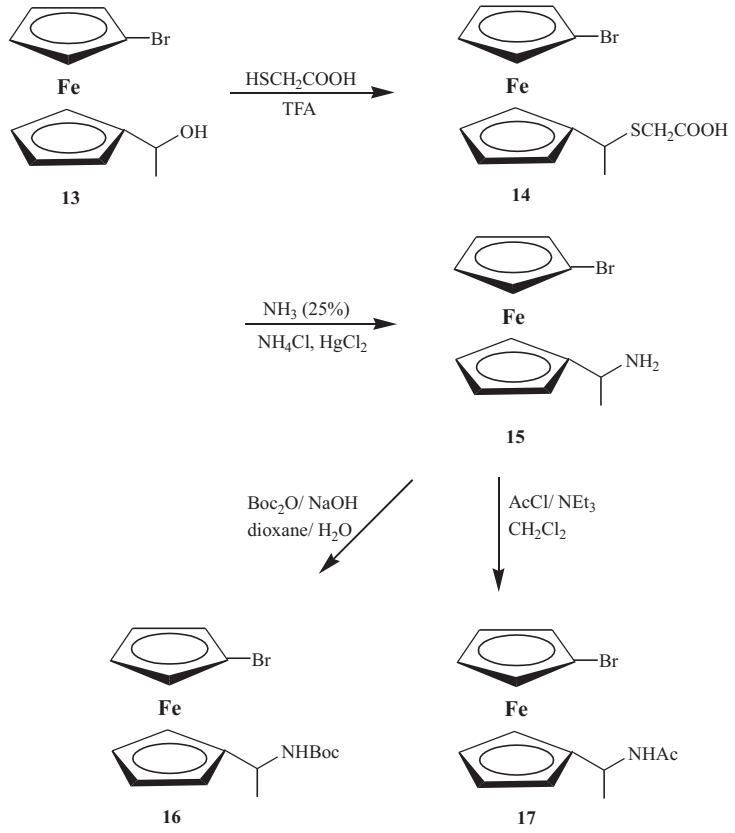
Prompted by these results, we researched the possibilities of Fcca preparation. In the first attempt, we prepared *N*-acetylamino derivative **7,** aiming to cleave its aroyl substituent to carboxylic group by the Haller-Bauer reaction[36] (Scheme 3). Here, we started with α-ferrocenylethanol, which was converted by thioglycolic acid in the presence of TFA in 93 % of thiaacid **1**,[37] subsequently cleaved into 74 % of Fea **2**.[38] Using standard methods, it was transformed to 91 % of *N*-Boc- **5** and 84 % of *N*-Ac- derivative **6**. *N*-Monosubstitution, *i.e.*, the presence of NHCO groups in these compounds is evident from IR-bands at 3439 m/ 3433 m and 1707/ 1668 s cm^{-1}, indicating ν (N–H) free and ν (C=O) frequencies. These data are corroborated by chemical shifts at 4.71/ 5.28 ppm (s, 1H, NH free), as well as by the corresponding ^{1}H- and ^{13}C- signals of *tert*-butyl and acetyl groups. The key intermediate **7** was obtained in 38 % yield by



Scheme 4.

the Friedel-Crafts aroylation of acetamide **6**. [It is worth mentioning that analogous acetylation proceeded with an 85 % yield, so that the conversion **6** → **7** had to be inhibited by steric interaction of the bulky reactant and ferrocene substituent.] Unfortunately, the planned scission of ketone **7** to *N*-Ac-Fcca **8** by means of *t*-BuOK/ H_2O in refluxing GLYME solution did not succeed. [To prove the validity of our experiments and the quality of reagents, we conducted a successful cleavage of *o*-chloroaroylferrocene into 87 % of ferrocene-carboxylic acid.] In our previous publication,[39] we showed that 1'-substituted *o*,*o*-dichloroaroylferrocenes (R' = *o*,*o*-$Cl_2C_6H_4$–, C_6H_5, CH_3) can be converted into 85–95 % of the corresponding ferrocenecarboxylic acids. It is obvious that the voluminous sp^3-hybridized 1'-substituent in **7** inhibited addition of the hydroxylic nucleophile to the carbonyl group, as well as deprotonation of the possibly formed tetrahedral intermediate by the bulky *t*-butoxyde base.[36,40] Cleavage **7** → **8** could not be effected by the use of alcoholic solutions of other bases (OH^-, MeO^-) either.[41,42]

In the second trial, we planned to prepare *N*-Boc- (**11**) and *N*-Ac-Fcca-ester **12** by hydrolysis and methylation of the corresponding thiolesters **9** and **10** as shown in Scheme 4. In this connection, we kept in mind the above mentioned successful heteroacetylation of acetamide **6**, as well as the described preparation of *S*-methyl 1'-acetylferrocene-1-thiocarboxylate (53 %; by the Friedel-Crafts reaction of acetylferrocene with an equimolar amount of *S*-methyl chlorothioformate in refluxing dichloromethane) and its hydrolysis to 95 % of 1'-acetylferrocene-1-carboxylic acid.[43] Under similar conditions, *N*-Boc- (**5**) or *N*-Ac-derivative (**6**) reacted with *S*-methyl chlorothioformate giving the corresponding red chlorothioformates **9** (46.5 %) and **10** (48 %), accompanied with yellow materials **9a** and **10a**. By changing the experimental conditions (temperature, solvents – CH_2Cl_2, $ClCH_2CH_2Cl$ –, excess of reagent, *etc*.), we obtained practically the same results. One can see heteroannular methylthiocarbonylation (without *N*-substitution) in reactions **5/6** → **9/10** from the absence of peaks at ≈1100 and 1000 cm^{-1} and from the signals at 3433/ 3432 w (NH) and 1667/ 1777 s (C=O) cm^{-1}. High frequencies belonging to ν (N–H) indicated that there are no intramolecular hydrogen bonds in these compounds. The by-products of these reactions, **9a** and **10a,** are characterized by very similar spectra, appreciably higher R_f-values than **9** and **10**, and by the equal highest *m/z* = 623 (EI-MS). Although they could not be obtained



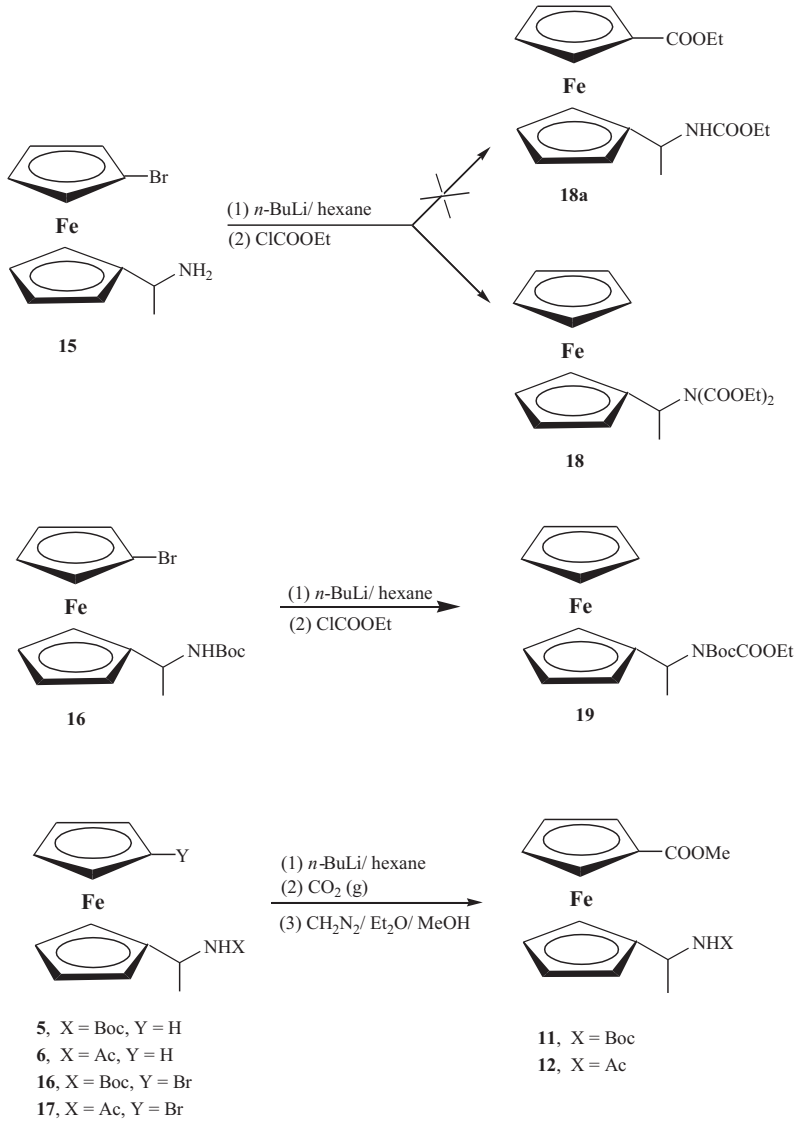
Scheme 5.

in the pure form from IR- and ^{1}H-NMR-spectra, the absence of any functionalities is evident; the ratio of the present ferrocene (≈4) to alkyl protons (≈1.5 ppm) is about 3:1, and the dominant IR-signals are found at 3100, 1605 (Fc) and 2930 cm^{-1} (Me). One can assume formation of this product by initial *N*-methylthiocarbonylation of the starting products **5/6** and by the subsequent cleavage of this intermediate under generation of very stable α-ferrocenylethylcarbenium ions.[44] These species could then combine together and with methyl carbocation (formed from ClCOSMe)[43] give a »trimer» of molecular weight 623 (Scheme 4). Hydrolysis of esters **9** and **10** by aqueous ethanolic solution of potassium hydroxide, followed by the action of ethereal solution of diazomethane on the intermediate amino acids, gave the desired esters **11** (78 %) and **12** (76 %).

Further, we decided to research the introduction of carboxylic or ethoxycarbonyl groups *via* the corresponding lithium intermediates. It is known that lithioferrocene is usually prepared by (*i*) direct abstraction of proton from ferrocene by alkyllithium – *e.g.*, reaction of ferrocene with an excess of *n*-BuLi in Et_2O giving 25 % of FcLi,[45] (*ii*) transmetallation between FcHgCl and RLi,[46,47] (*iii*) metal-halogen exchange between bromoferrocene and *n*-BuLi, which proceeded with excellent yields;[48] (*iv*) a special case is the regioselective (and diastereoselective) lithiation in α-position of various FcCHRXR$_n$ derivatives (X = N, S, O) by coordination of the metal with heteroatoms of the substituents.[49–51] All the resulting organolithiums may be trapped with various electrophils *inter alia* with CO_2 and ClCOOR. Inspired with the successful monolithiation of 1,1'-dibromoferrocene and successive conversion of lithium intermediate into ethyl 1'-bromoferrocenecarboxylate,[52] as well as with the above mentioned lithiation and carboxylation of 1'-amino-1-bromoferrocene,[4] we decided to apply method (*iii*) for preparation of the desired Fcca derivatives.

To this end, we first prepared bromo-amides **15**–**17**. The tedious synthesis of the starting bromoferrocene was performed in a multi-step sequence starting from chloromercuryferrocene.[53] This intermediate was acetylated (69 %),[54] and reduced to 92 % of carbinol **13**.[55] Analogously to reactions **1** → **2** → **5** (**6**), compound **13** was converted to 91 % of bromo-thiaacid **14**, which was cleaved to bromo-amine **15** in 67 % yield. Thereafter, *N*-Boc- (**16**) and *N*-Ac-bromo-amine **17** were obtained in high yields using the standard methods (Scheme 5).

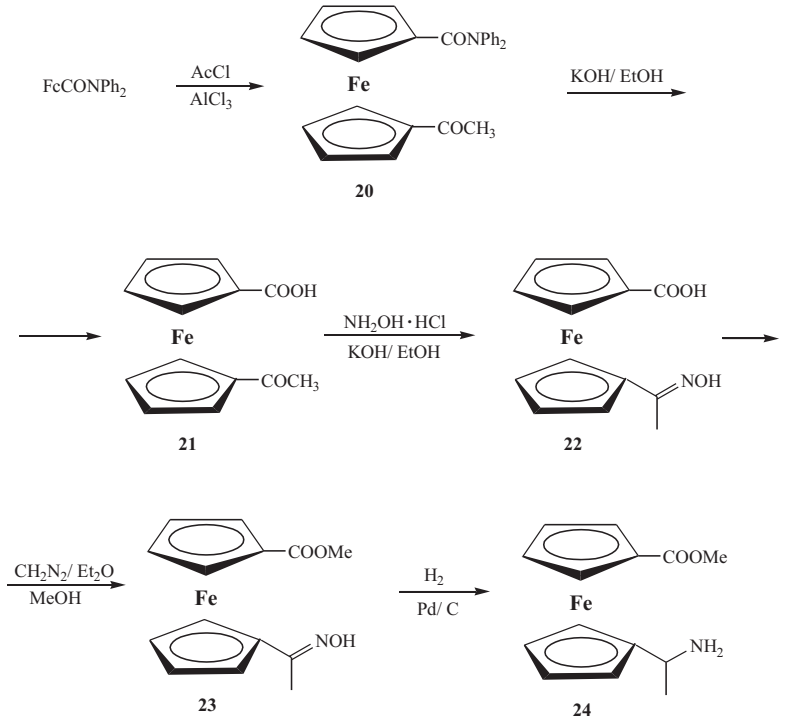
The first experiment of lithiation/ethoxycarbonylation of compound **15** was accomplished under similar conditions as in a procedure described in:[52] 2 equivalents of *n*-BuLi in hexane followed by ClCOOEt at –25 ^{O}C were added to a solution of substrate in THF. Instead of the desired heteroannularly substituted diester **18a**, as the trapping product of the corresponding dianion, we isolated



Scheme 6.

63 % of *N*,*N*-diethoxycarbonylated amine **18**. The same unique product (with lower conversion) was obtained by the reaction with equimolar quantities of *n*-BuLi and ClCOOEt. Ethoxycarbonylation of *N*-Boc- (**16**) was performed under similar conditions. Unfortunately, here we obtained similar results as well: 66 % of ester **19** was isolated (Scheme 6). Obviously, *N*-ethoxycarbonylation was the predominant reaction in all the described experiments. *N*,*N*-Disubstitution in formation of compounds **18** and **19** is evident from spectroscopic data: IR-bands at ≈1000 and 1100, as well as the absence of NH signals indicate ferrocenes substituted by the –CHMeN(COOEt)Boc group.

Further trials to prepare Fcca derivatives **11** and **12** were made under the circumstances described in Butler's synthesis of Fca:[4] lithiation of **16** and **17** in THF was carried out using 2.5 equivalents of *n*-BuLi at –78 °C. Bubbling with a stream of dry gaseous carbon dioxide as a quenching reagent at –50 °C, followed by esterification with diazomethane, resulted in formation of 30 % of **11** and 48 % of **12**. In the meantime, a publication of J. M. Chong and L. S. Hegedus[56] appeared, dealing with the reaction of *N*-Boc derivative **5** with 2 equivalents of *n*-BuLi aimed at obtaining 2-metalated product according to procedure (*iv*) (*vide ultra*). Unexpectedly, *N*,1'-dimetalation occurred and trapping with various electrophils resulted in formation of the corresponding 1'-substituted derivatives in 71–96 % yields with no evidence of other isomers. This result is very surprising because one could expect *N*-derivatization similar to that in our transformations **16** → **19** and **17** → **20**. By applying this method to derivatives **5** and **6**, after quenching with CO_2 and action of CH_2N_2 on the intermediate, we were able to isolate only 27 % of *N*-Boc (**11**) and 50 % of *N*-Ac-amino ester **12** (Scheme 6). [To examine the validity of our experiments and the quality of *n*-BuLi, we performed succes-



Scheme 7.

sful lithiation/carboxylation of bromoferrocene in yields similar to those in literature procedures.[48]]

One can see that metalation-carboxylation-esterification of *N*-Boc substrates **5** and **16** gave product **11** in practically equal yields (27 and 30 %). *N*-Ac compounds **6** and **17** reacted in a similar way giving 50 and 48 % of ester **12**. In contrast to the findings in Ref. 48, in this case substitution by bromine did not »activate« ferrocene to lithiation. The results presented in Scheme 6 could be rationalized in the following manner: Metalation of all substrates gave dark precipitates of *N*- and/or *N*,1'-lithium salts. Formation of *N*-anion is thereby more favourable than that of C(1')-anion because of higher acidity of the NH function. In this way, ethoxycarbonylation of **15** and **16** occurred regioselectively on the nitrogen atom. The formed bulky *N*-diacylated group inhibited heteroannular reaction and products **18** and **19** were generated in high yields. It is obvious that smaller molecule of CO_2 was able to react with both positions of the intermediate bident nucleophile. The work-up of lithium dicarboxylates formed with H_2O/HCl resulted in decarboxylation of the carbamic part of the molecule and after esterification compounds **11** and **12** were isolated as unique products.

Finally, we prepared Fcca-OMe **24** by hydrogenation of the intermediate oxime-ester **23**: acetylation of *N*,*N*-diphenylferrocenecarboxamide afforded 80 % of ketone-amide **20,**[57] which was hydrolized to ketone-acid **21** in 72 % yield;[58] its oxime **22** was esterified with diazomethane to 90 % of oxime-ester **23,** which was hydrogenated over Pd-C in methanol under the pressure of 600 psi, giving after work-up 86 % of the stable ester **24**. IR-spectra of oxime **23** and amine **24** are characterized by the presence of ν O–H at 3574 and ν N–H at 3412 cm^{-1}. The corresponding ^{1}H NMR-signals are found at 8.9 and at 1.25 ppm. On the basis of these data, one can conclude that no intramolecular hydrogen bonds exist in these compounds (like in amido-esters **11** and **12**).

CONCLUSIONS

It was demonstrated that racemic (1-ferrocenylethyl)amine (Fea, **2**) showed appreciable chiral induction in coupling reactions with (0.5 equivalent) of L-Ala and L-Phe, resulting in formation of the corresponding diastereomers in 64:36 and 78:22 ratios, respectively. These results prompted us to plan similar reactions of suitable *N*- or *C*-protected 1'-(1-aminoethyl)ferrocene-1-carboxylic acid (Fcca) with natural amino acids. Here, we had in mind the interesting results obtained in the coupling of 1'-aminoferrocene-1-carboxylic acid with L- and D-Ala.[18, 19] To this end, we synthesized *N*-Boc-Fcca and *N*-Ac-Fcca in good yields by ethylthiocarbonylation/hydrolysis or lithiation/carbonylation of Boc- and Ac-Fea, as well as of their 1'-brominated derivatives. By the action of CH_2N_2 these acids were esterified into Boc-Fcca-OMe (**11**) and Ac-Fcca-OMe (**12**). Further, 1'-acetylferrocene-1-carboxylic acid **21** was transformed into oxime **22** and oxime-ester **23**; hydrogenation of this intermediate resulted in formation of racemic Fcca-OMe (**24**) in very good yield. In this way, we obtained *N*- and *C*-protected Fcca suitable for *C*- or *N*-coupling with natural amino acids, aiming to obtain the corresponding oligopeptides. In prelimi-

nary experiments, the reaction of the racemic ester **24** with 0.5 equivalent of Boc-Ala-OH, following the EDC/HOBt protocol, gave the corresponding diastereomeric dipeptides with a high *d.e*. Aiming to prepare enantiomerically pure amino-ester **24,** we performed kinetic resolution of its racemic form by enzymatic aminolysis using *Candida antarctica* B lipase (Novozym 435) and ethyl acetate as acylation donor/solvent. In our initial experiments, we obtained *N*-acylated chiral product **12** with *e.e.* ≈ 85 %, $c \approx 50$ %. One should emphasize that this enantiomeric enriched *N*-acetylamine and the remaining antipodean amine are the substrates of choice for the planned coupling with natural amino acids (and oligopeptides). Another possibility of obtaining optically pure **24** is the stereoselective reduction of oxime **22** using oxazaborolidine·BH_3. Experiments of refinement of enzymatic resolution and this reduction are in progress in our Laboratory.

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REFERENCES

1. Z. Zorić, V. Rapić, S. Lisac, and M. Jukić, *J. Polym. Sci*., *Part A: Polym. Chem.* **37** (1999) 25–36.
2. P. Reich-Rohrwig and K. Schlögl, *Monatsh. Chem.* **99** (1968) 1752–1763.
3. R. Salter, T. E. Pickett, and C. J. Richards, *Tetrahedron: Asymetry* **9** (1998) 4239–4247.
4. I. R. Butler and S. C. Quayle, *J. Organomet. Chem.* **552** (1998) 63–68.
5. T. Okamura, K. Sakauye, N. Ueyama, and A. Nakamura, *Inorg. Chem.* **37** (1998) 6731–6736.
6. K. Heinze and M. Schlenker, *Eur. J. Inorg. Chem.* (2004) 2974–2988.
7. L. Barišić, V. Rapić, and V. Kovač, *Croat. Chem. Acta* **75** (2002) 199–210.
8. G. Pavlović, L. Barišić, V. Rapić, and I. Leban, *Acta Crystallogr., Sect. E* **58** (2002) m 13–15.
9. G. Pavlović, L. Barišić, V. Rapić, and V. Kovač, *Acta Crystallogr., Sect. C* **59** (2003) m 55–57.
10. L. Barišić, V. Rapić, H. Pritzkow, G. Pavlović, and I. Nemet, *J. Organomet. Chem.* **682** (2003) 131–142.
11. R. S. Herrick, R. M. Jarett, T. P. Curran, D. R. Dragoli, M. B. Flaherty, S. E. Lindyberg, R. A. Slate, and L. C. Thorton, *Tetrahedron Lett.* **37** (1996) 5289–5292.
12. A. Nomoto, T. Moriuchi, S. Yamazaki, A. Ogawa, and T. Hirao, *Chem. Commun.* (1998) 1963–1964.
13. T. Moriuchi, A. Nomoto, K. Yoshida, and T. Hirao, *J. Organomet. Chem.* **589** (1999) 50–58.
14. T. Moriuchi, A. Nomoto, K. Yoshida, and T. Hirao, *Organometallics* **20** (2001) 1008–1013.
15. T. Moriuchi, A. Nomoto, K. Yoshida, A. Ogawa, and T. Hirao, *J. Am. Chem. Soc.* **123** (2001) 68–75.
16. Y. Xu, P. Saweczko and H.-B. Kraatz, *J. Organomet. Chem.* **637** (2001) 335–342.
17. H.-B. Kraatz and M. Galka, *Metal Ions Biol. Syst.* **38** (2001) 385–409.
18. (a) V. Rapić, L. Barišić, and M. Dropučić, First International Symposium on Bioorganometallic Chemistry (ISBOMC'02), Paris, France, 18–20 July 2002, PA 24.
(b) L. Barišić, M. Čakić, K. A. Mahmoud, Y. Liu, H.-B. Kraatz, H. Pritzkow, S. I. Kirin, N. Metzler-Nolte, and V. Rapić, *Chem. Eur. J.* **12** (2006) 4965–4980.
19. L. Barišić, M. Dropučić, V. Rapić, H. Pritzkow, S. I. Kirin, and N. Metzler-Nolte, *Chem. Commun.* (**2004**) 2004–2005.
20. G. Wagner and R. Herrmann, in: *Ferrocenes,* A. Togni and T. Hayashi (Eds.), VCH, Weinheim, 1995, Chap. 4, p. 208.
21. G. Gokel, P. Hoffmann, H. Kleimann, H. Klusacek, G. Lüdke, D. Marquarding, and I. Ugi, in: I. Ugi (Ed.), *Isonitrile Chemistry,* Academic Press, New York, 1971, Chap. 9.
22. A. Ratajczak and A. Czech, *Bull. Acad. Pol., Ser. Sci. Chim.* **27** (1979) 661–664.
23. M. Cushman and J.-K. Chen, *J. Org. Chem.* **52** (1987) 1517–1521.
24. K. Faber, *Biotransformations in Organic Chemistry*, Springer, Berlin, 2004, p. 369.
25. R. J. Kazlauskas and A. N. E. Weissfloch, *J. Mol. Catal. B: Enzym.* **3** (1997) 65–72.
26. M. Roje and V. Šunjić, *Chirality* **14** (2002) 625–631.
27. B. G. Davis and V. Boyer, *Nat. Prod. Rep.* **18** (2001) 618–640.
28. N. L. St. Clair and M. A. Navia, *J. Am. Chem. Soc.* **114** (1992) 7314–7316.
29. N. Khalaf, C. P. Govardhan, J. J. Lalonde, R. A. Persichetti, J.-F. Wang, and A. L. Margolin, *J. Am. Chem. Soc.* **118** (1996) 5494–5495.
30. K. Vogel, J. Cook, and K. Chmielewski, *Chem. Biol.* **3** (1996) 295–299.
31. W. J. Moore, P. Sears, K. Kawashiro, K. Witte, and C. H. Wong, *J. Am. Chem. Soc.* **119** (1997) 3942–3947.
32. R. A. Persichetti, N. L. St. Clair, J. P. Griffith, M. A. Navia, and A. L. Margolin, *J. Am. Chem. Soc.* **117** (1995) 2732–2737.
33. Y.-F. Wang, K. Yakovlevsky, and A. L. Margolin, *Tetrahedron Lett.* **37** (1996) 5317–5320.
34. J. P. Schneider and J. W. Kelly, *Chem. Rev.* **95** (1995) 2169–2187.
35. J. S. Nowick, *Acc. Chem. Res.* **32** (1999) 287–296.
36. G. Mehta and R. V. Venkateswaran, *Tetrahedron* **56** (2000) 1399–1422.
37. S. Lisac and V. Rapić, *J. Organomet. Chem.* **507** (1996) 215–220 and references cited therein.
38. R. Urban, *Tetrahedron* **35** (1979) 1841–1843.
39. V. Rapić, K. Schlögl, and B. Steinitz, *J. Organomet. Chem.* **94** (1975) 87–98.
40. D. G. Davies, M. Derenberg, and P. Hodge, *J. Chem. Soc.* C (**1971**) 455–460.
41. J. J. Beereboom, *J. Org. Chem.* **30** (1965) 4230–4234.
42. T. R. Potts and R. E. Harmon, *J. Org. Chem.* **34** (1969) 2792–2793.
43. D. E. Bublitz and G. H. Harris, *J. Organomet. Chem.* **4** (1965) 404–408.
44. G. Wagner and R. Herrmann, in: A. Togni and T. Hayashi (Eds.), *Ferrocenes*, VCH, Weinheim, 1995, Chap. 4, p. 175.
45. D. W. Slocum, T. R. Engelmann, C. Ernst, C. A. Jennings, W. Jones, B. Koonsvitsky, J. Lewis, and P. Shenkin, *J. Chem. Educ.* **66** (1969) 144–150.

46. M. D. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.* **22** (1957) 900–903.
47. D. Seyferth, H. P. Huffman, R. Burton, and J. F. Helling, *Inorg. Chem.* **1** (1962) 227–231.
48. F. L. Hedberg and H. Rosenberg, *Tetrahedron Lett.* **10** (1969) 4011–4012.
49. D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, and I. Ugi, *J. Am. Chem. Soc.* **92** (1980) 5389–5393.
50. T. Sammakia, H. A. Latham, and D. R. Schaad, *J. Org. Chem.* **60** (1995) 10–11.
51. O. Riant, G. Argouarch, D. Guillaneux, O. Samuel, and H. Kagan, *J. Org. Chem.* **63** (1998) 3511–3514.
52. T.-Y. Dong and L.-L. Lai, *J. Organomet. Chem.* **509** (1996) 131–134.
53. R. W. Fish and M. Rosenblum, *J. Org. Chem.* **30** (1965) 1253–1254.
54. D. W. Hall and J. H. Richards, *J. Org. Chem.* **28** (1963) 1549–1554.
55. D. W. Hall, E. A. Hill, and J. H. Richards, *J. Am. Chem. Soc.* **90** (1968) 4972–4976.
56. J. M. Chong and L. S. Hegedus, *Organometallics* **23** (2004) 1010–1014.
57. W. F. Little and R. Eisenthal, *J. Am. Chem. Soc.* **82** (1960) 1577–1580.
58. A. N. Nesmeyanov and O. A. Reutov, *Dokl. Akad. Nauk SSSR* **115** (1957) 518–521.
59. G. W. Gokel, D. Marquarding, and I. K. Ugi, *J. Org. Chem.* **37** (1972) 3052–3058.
60. M. Čakić Semenčić, M. Dropučić, L. Barišić, K. Molčanov, and V. Rapić, *Struct. Chem.* (submitted).

SAŽETAK

Priprava derivatâ prve heteroanularno supstituirane ferocenske aminokiseline i izomerne karbaminske kiseline s kiralnim centrima

Mojca Čakić Semenčić, Maja Dropučić, Lidija Barišić i Vladimir Rapić

Opisane su sinteze *N*- i *C*-zaštićenih derivata 1'-(1-aminoetil)ferocen-1-karboksilne kiseline (Fcca) i izomerne karbaminske kiseline. Prvi je pokušaj priprave *N*-Ac-Fcca (**8**) hidrolizom 1-[1-(acetamido)etil]-1'-(*o*-klorobenzoil)ferocena (**7**) s *t*-BuOK/ H_2O/ GLYME bio neuspješan. Friedel-Craftsovim reakcijama *N*-supstituiranih (1-**f**eroceni**l**etil)**a**minâ [Boc-Fea (**5**) i Ac-Fea (**6**)] s ClCOSMe/ $AlCl_3$ pripravljeni su odgovarajući heteroanularno supstituirani tioesteri **9/10**, koji su hidrolizirani u Boc-Fcca/Ac-Fcca i esterificirani u Boc-Fcca-OMe (**11**)/ Ac-Fcca-OMe (**12**). Višestupanjskim reakcijama pretvoren je bromferocen u 1'-bromiranu Fea (**15**), Boc-Fea (**16**) i Ac-Fea (**17**). Litiranjem/etoksikarboniliranjem rečenih bromidâ pripravljeni su odgovarajući karbaminski esteri **18** and **19** umjesto očekivanih Fcca esterâ. Litiranjem/karboksiliranjem te naknadnom esterifikacijom **5**, **6**, **16** i **17** prevedeni su u željene spojeve **11** i **12**. 1'-Acetilferocen-1-karboksilna kiselina **21** pretvorena je u oksim **22** i oksim-ester **23**. Hidrogeniranje tih intermedijara rezultiralo je tvorbom Fcca-OMe (**24**) u visokom iskorištenju. Strukture pripravljenih spojeva potvrđene su HRMS i spektroskopskim analizama.