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Novel access to chiral 1,1′-disubstituted ferrocene derivatives via double stereoselective cyanohydrin synthesis exploiting the hydroxynitrile lyase from *Hevea brasiliensis*

Richard F. G. Fröhlich, Antonina A. Zabelinskaja-Mackova, Martin H. Fechter and Herfried Griengl*

Institute of Organic Chemistry, Graz University of Technology, Stremayrgasse 16, A-8010 Graz, Austria; SFB Biokatalyse Projekt Nr. F0113

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Abstract—A novel route to chiral ferrocene derivatives involving the application of hydroxynitrile lyase from *Hevea brasiliensis* has been developed. The method allows the conversion of formylferrocene **1** and 1,1′-diformylferrocene **2** into their corresponding chiral cyanohydrins. (*R*)-(Cyanohydroxymethyl)ferrocene **3** and (*R*,*R*)-1,1′-bis(cyanohydroxymethyl)ferrocene **4** were obtained in high yield and stereochemical purity using this method. The full structural characterisation of the latter including the determination of diastereomeric purity and the assignment of the absolute configuration is disclosed.

1. Introduction

To date, the applications of chiral ferrocene derivatives[1] ranges from ligands in asymmetric catalysis, to bioelectrochemistry[2] and the development of new pharmaceuticals against malaria.[3] In these examples central chirality (i.e. stereogenicity) is often combined with planar chirality and C_2-symmetry in a single molecule.[4] The main two biocatalytic strategies to obtain chiral ferrocene derivatives are kinetic resolutions employing lipases[5]—cyanohydrin (*S*)-**3** was accessible by the lipase-catalysed resolution of ferrocene compound **7** employing lipase PS from *Candida cylindracea* or *Pseudomonas cepacia*[6]—and the asymmetric reduction of ferrocenyl ketones to the corresponding chiral secondary alcohols by microorganisms.[7]

In the light of the importance of ferrocene derivatives in synthetic organic chemistry, we would like to present a novel approach to introduce chirality into ferrocene compounds employing a hydroxynitrile lyase (HNL) as biocatalyst for stereoselective C–C bond formation.[8] In our group, the HNL from *Hevea brasiliensis* [E.C. 4.1.2.39][9] was found to accept a wide range of aliphatic, aromatic and heterocyclic aldehydes as well as ketones as substrates.[10] Consequently, this versatile enzyme was also examined with a range of ferrocene aldehydes and ketones. Surprisingly, such organometallic compounds have never been investigated with an HNL enzyme system to date. Herein, we describe the synthesis of optically active (*R*)-(cyanohydroxymethyl)ferrocene **3** and (*R*,*R*)-1,1′-bis(cyanohydroxymethyl)ferrocene **4** using (*S*)-HNL from *Hevea brasiliensis*.

2. Results and discussion

Ferrocene aldehydes and ketones were tested as substrates for the *Hevea brasiliensis* enzyme. Subjecting aldehydes **1** and **2**[11] to the (*S*)-*Hb*HNL showed that these aldehydes are suitable substrates for this enzyme. In contrast to these results, acetylferrocene and 1,1′-diacetylferrocene were not transformed with this enzyme.

The possibility of the non-enzymatic chemical addition of HCN to the carbonyl group, which causes a deterioration in the enantiomeric excess (*e.e.*) of the product, can be suppressed if the reaction is carried out at around 0°C at pH <6. However, the range of the pH value is limited by the stability of the enzyme. Below pH 4.0 the (*S*)-*Hb*HNL provides unsatisfying *e.e.*s and

* Corresponding author. Tel.: +43-316-873-8240; fax: +43-316-873-8740; e-mail: sekretariat@orgc.tu-graz.ac.at

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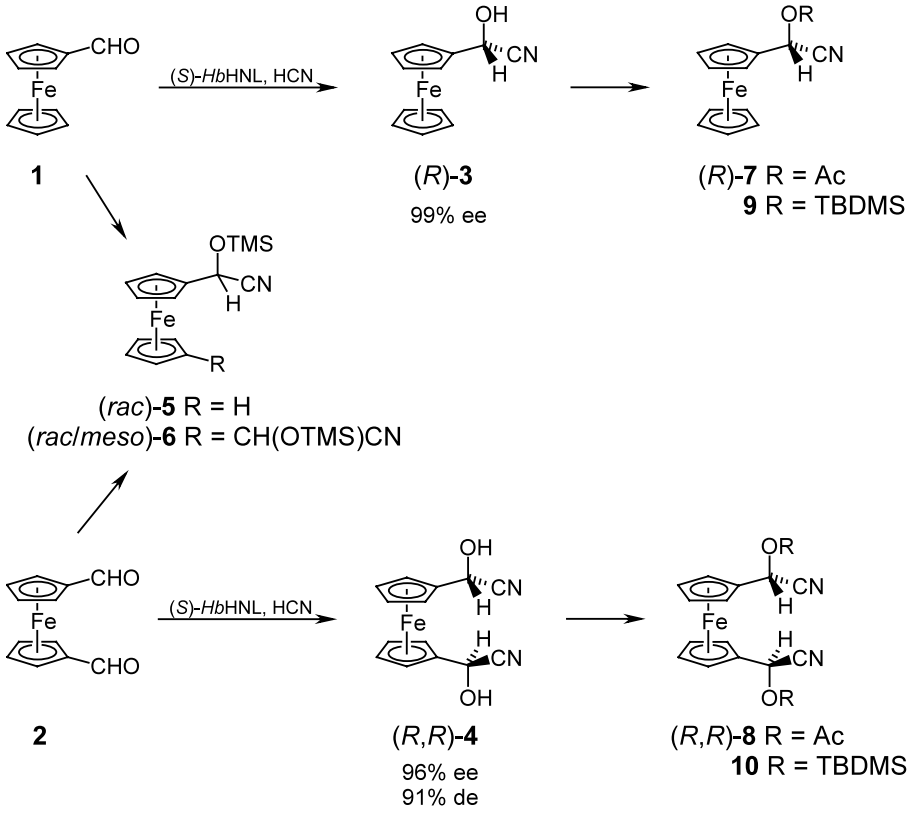
low yields due to rapid enzyme deactivation. The optimal conversion of formylferrocene **1** was obtained at pH 4.8, the (*S*)-*Hb*HNL was still stable at this value, and an excellent *e.e.* of 99% was obtained. The *e.e.* of cyanohydrin **3** was determined by examining the acetylated compound **7**. *Hb*HNL normally provides *S*-configured cyanohydrins. Consequently, the configuration of **3** was assumed to be in accordance with these previous results and the newly formed chiral centre in **3** was deemed to be *R*-configured (the *ipso*-C-atom in ferrocene has a higher CIP priority than the cyano group). The assignment of the *R* configuration could be confirmed by comparing the specific rotation of **7** with the published value.[6a] 1,1′-Diformylferrocene **2** was found to afford biscyanohydrin **4** after treatment with HCN under *Hb*HNL catalysis. It is interesting to note that this is the first example of a 'double stereoselective' formation of a biscyanohydrin product by this class of enzyme (Scheme 1).

In order to determine the respective enantiomeric and diastereomeric excesses, silylated reference compounds were synthesised. Silyl protected racemic cyanohydrins were readily accessible by the addition of trimethylsilylcyanide to formylferrocene **1** and 1,1′-diformylferrocene **2** with a Lewis acid catalyst in dichloromethane.[12] This method provided **5** and **6** as racemic and racemic/meso mixtures. Deprotection under acidic conditions gave the free cyanohydrins (*rac*)-**3** and (*rac*/*meso*)-**4**, respectively. These compounds were then acetylated to give (*rac*)-**7** and (*rac*/*meso*)-**8**, which were used as reference materials for chiral HPLC analysis. While the *e.e.* of **3** could be determined via its acetylated analogue **7**, the stereoisomers of diacetylated (*rac*/*meso*)-**8** were not completely baseline separable on the various chiral HPLC columns at hand. Finally, the disilylated derivative **10** could be baseline separated on chiral HPLC indicating an *e.e.* of 96% and a *d.e.* of 91%. Due to the syrupy character of **10** recrystallisation was not possible. At this enantiomeric purity the separation of **8** was sufficient to confirm these values. By recrystallisation of the acetate **8** the *e.e.* was raised to 98% and the *d.e.* to 96%.

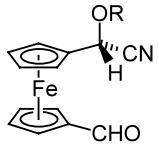
Silylating the enzymatically prepared cyanohydrins under standard conditions using trialkylsilyl chlorides under basic conditions[13] was not successful. Therefore, trimethylsilyl cyanide was allowed to react with (*R*)-**3** to give (*R*)-**5**. To have a more stable silyl protected compound at hand the corresponding TBDMS derivatives were also prepared. The application of TBDMS cyanide[14] was successful in affording (*R*)-**9**, but failed to give (*R*,*R*)-**10**. Finally, another approach was found by using *N*-methyl-*N*-(*t*-butyldimethylsilyl)-trifluoroacetamide (MTBSTFA) which is known to be a powerful silylating agent.[15] Satisfyingly, both (*R*)-**9** and (*R*,*R*)-**10** were obtained in yields of 81%.

However, in one experiment where chiral (*R*,*R*)-**4** was reacted with MTBSTFA to produce the desired compound (*R*,*R*)-**10**, the unexpected by-product (*R*)-**11** was also obtained due to the reversibility of the cyanohydrin reaction. Interestingly, the unprotected analog of **11**, compound **12**, was not isolated from the enzyme-



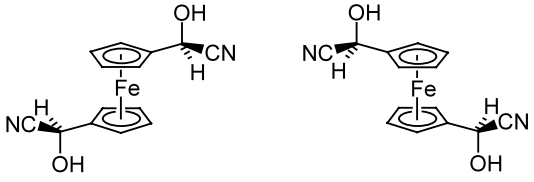
Scheme 1.

catalysed transformation of dialdehyde **2** with HCN, where an excess of reagent is employed. Racemic **11** was obtained by carrying out the reaction of **2** with less than an equimolar amount of TBDMSCN. The obtained (*rac*)-**11** was furnished in a yield of 31% in addition to 21% (*rac*/*meso*)-**10** and 33% recovered 1,1′-diformylferrocene **2**.



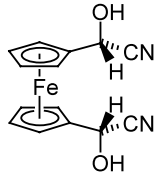
(*R*)-**11** R = TBDMS
12 R = H

Because of the lack of chiral inducer in the addition of cyanide to dialdehyde **2** to give **6**, this reaction would lead to a mixture of all stereoisomers. Assuming that the second addition of trimethylsilyl cyanide proceeds without any chiral induction from the initially formed stereogenic centre, the product distribution of (*R*,*R*):(*S*,*S*):(*R*,*S*) would be a statistical one, namely 1:1:2. The three stereoisomeric products could not be separated on preparative scale and were therefore used as *rac*/*meso*-mixtures for determining the *d.e.* and *e.e.* of enzymatically prepared **4**.



(*S*,*S*)-**4**

(*R*,*R*)-**4**



(*R*,*S*) = *meso* **4**

The absolute configuration of the *Hb*HNL product **4** was determined by X-ray diffraction of acetylated analog (*R*,*R*)-**8**. The three dimensional structure of (*R*,*R*)-**8** is displayed in Fig. 1.

In order to obtain the other enantiomer, (*S*)-**3**, the biotransformation of formylferrocene **1** with the (*R*)-HNL from *Prunus amygdalus* [E.C. 4.1.2.10][16] was examined. Unfortunately, in this case **1** was not accepted as a substrate by this enzyme. This result can be explained by the comparison of the recently discovered active site structures of *Pa*HNL[17] and *Hb*HNL.[18] Molecular modelling studies are currently in progress.

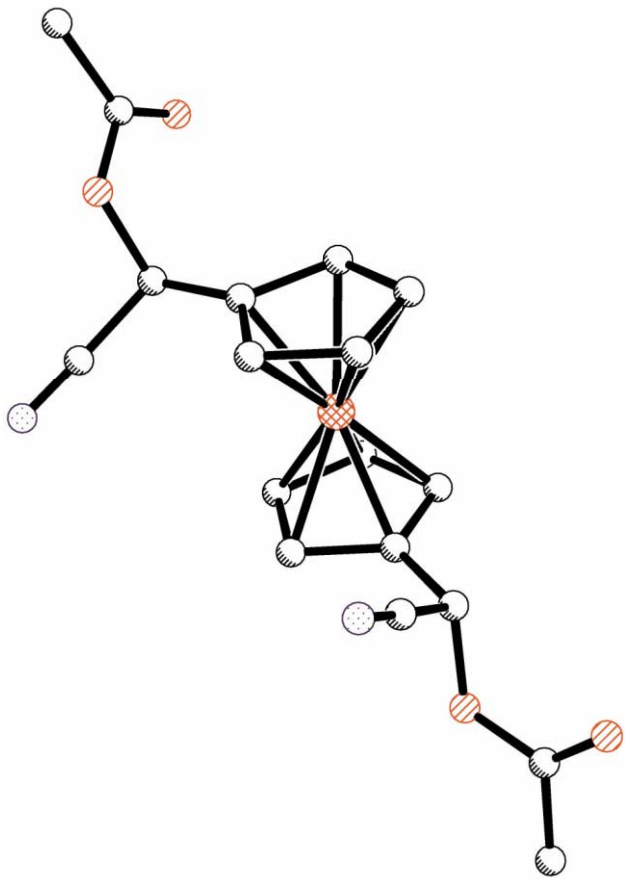


Figure 1. X-Ray diffraction of (*R*,*R*)-**8**, H-atoms are omitted.

3. Conclusions

The cyanohydrin reaction of formylferrocene catalysed by the hydroxynitrile lyase from *Hevea brasiliensis* provides a novel access to chiral ferrocene derivatives in high enantiomeric excess. Since cyanohydrins are versatile synthetic intermediates, the possibility for many preparative transformations is opened. This synthetic potential is enlarged even further with the transformation of 1,1′-diformylferrocene leading to bis-cyanohydrins.

4. Experimental

4.1. General methods

The formylferrocene **1** was purchased from Aldrich. Optical rotations were measured on a Perkin Elmer Polarimeter 341. Melting points (uncorrected) were determined in open capillaries using a Büchi 530. ^{1}H and ^{13}C NMR were recorded on either a Gemini 200 (Varian) or MSL 300 (Bruker). HETCOR, DEPT, COSY and HSQC experiments were carried out as required. $CDCl_3$ was used as solvent and as internal standard unless otherwise stated. Mass spectra (EI, 70 eV and ESI) were recorded on a KRATOS Profile HV-4 double focussing magnetic sector instrument

equipped with direct insertion (DI) or with a MIRCOMASS TofSpec 2E (MALDI-TOF). Relative intensities are given in brackets. Chiral HPLC was determined with a JASCO system containing pump 880-PU, UV-detector 875-UV (detection at 238 nm unless otherwise stated) and HP ChemStation for LC A.06.03 (software) fitted with an HP Interface 35900E as AD converter. The chiral HPLC columns used were Chiracel OD-H and Chiralpak AD (0.46×25 cm). GC–MS was determined with a HP 5890 series II plus equipped with a HP 5 (25 m) and quadrupole mass selective detector. LC was performed on silica gel 60 (Merck, 70–230 mesh) using mixtures of cyclohexane and EtOAc or chloroform and methanol as eluent. TLC was performed on silica gel 60 F254 aluminium plates (Merck) mixtures of cyclohexane and EtOAc or chloroform and methanol were used as eluent and compounds detected with UV (254 nm) and spraying with reagent A (10% H_2SO_4, 10% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.8% $Ce(SO_4)_2\cdot 4H_2O$ in water). The TLC plates were then developed with a heat gun.

4.1.1. HCN formation—CAUTION. All reaction equipment in which cyanides are used or produced were placed in a well ventilated hood. Proper gloves were worn when handling dry sodium cyanide. Rubber gloves and splash proof goggles were also applied when substantial amounts of sodium cyanide solution are used. The required amount of HCN was freshly formed by dropping a saturated NaCN solution into sulfuric acid (60%) at 80°C and trapping HCN at −12°C in a cooling trap. For continuous warning an electrochemical sensors for HCN detection was used. Waste solutions containing cyanides were treated with sodium hypochlorite which converted them into harmless cyanate. These could be further transformed into ammonia and carbon dioxide by addition of diluted sulfuric acid to the solution until a pH of 7 was reached.

4.1.2. General procedure A: enzymatic synthesis of chiral ferrocene cyanohydrin derivatives. The (*S*)-*Hb*HNL enzyme solution, which was provided in a concentration of 6.5 kU/mL, was diluted with distilled water (1:1) and the pH value was adjusted to 4.8–5.0 by the addition of a citric acid solution. This mixture was then added to the corresponding ferrocene derivatives, which had been dissolved in MTBE, and this was cooled to 0°C. After vigorous stirring for 20 min a stable emulsion had formed and freshly prepared HCN was added. After TLC had indicated that starting material was no longer present, additional MTBE and large amounts of Celite were added. Filtration and washing the Celite plug with MTBE provided an organic phase, which was then dried over Na_2SO_4. Removal of the solvent under reduced pressure provided a crude residue, which was further purified by column chromatography (cyclohexane/EtOAc).

4.1.3. General procedure B: synthesis of racemic ferrocene cyanohydrins with trialkylsilyl cyanide. The respective ferrocene carbonyl containing compound was dissolved in CH_2Cl_2 and a catalytic amount of ZnI_2 added. Under ice cooling, TMSCN or TBDMSCN (1.3 equiv. of per carbonyl group) were added. After the addition, the mixture was allowed to warm to room temperature. In the case of syntheses employing TMSCN, these quantitative reactions were found to go to completion immediately. Subsequently, H_2O was added and the organic phase washed with a saturated solution of $NaHCO_3$. The aqueous phase was extracted several times with CH_2Cl_2 to remove traces of product. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. Traces of unreacted trialkyl cyanide were removed by placing the mixture under hi-vacuum using an oil pump.

4.1.4. General procedure C: cleavage of trimethylsilyl protecting group. The respective ferrocene derivative was dissolved in MeOH and catalytic amounts of AcOH were added at room temperature. After warming to approximately 50°C for 1 h, volatile components were removed under reduced pressure to afford a crude solid product. Further purification was not necessary.

4.2. 1,1′-Diformylferrocene 2

Ferrocene (5.0 g, 27 mmol) was partially dissolved in dry Et_2O (60 mL) in a Schlenk type round bottom flask under an Argon atmosphere. After addition of TMEDA (8.5 mL, 65 mmol) the suspension became dark orange and then clear. With a glass syringe, a solution of *n*-BuLi (28 mL, 1.6 M in cyclohexane) was added via a septum within 10 min. A red–orange precipitate appeared and the reaction mixture became 'tomato' coloured. After 20 h the mixture was cooled down to −74°C (MeOH and liquid nitrogen bath) and dry DMF (6.5 mL, 89 mmol) was added dropwise via a syringe. The cooling bath was removed after 10 min and the solution was stirred a further 1.5 h. The precipitate redissolved and a clear dark orange solution was formed. Subsequently, HCl (100 mL, 2.5 m) was added and then the solution extracted several times with CH_2Cl_2. The combined organic phases were washed with a saturated $NaHCO_3$ solution and then dried over Na_2SO_4. After solvent removal under reduced pressure, the dark red solid was purified by flash chromatography (silica gel, cyclohexane/EtOAc = 3:2) yielding **2** (5.27 g, 81%). Traces of formylferrocene **1** (0.24 g, 4%) were also isolated. Mp 136–139°C, decomposition; ^1H and ^{13}C NMR spectra were in accordance with the literature.[11c]

4.3. (*rac*)-(Cyanohydroxymethyl)ferrocene 3

This compound was prepared according to general procedure C. The amounts used were (*rac*)-**5** (3.13 g, 10.0 mmol), AcOH (3 mL) in MeOH (30 mL). Compound **3** was obtained as light brown solid in a yield of 2.43 g (100%). $R_f = 0.27$ (cyclohexane/EtOAc = 3:1); mp 102–104°C (lit.,[19] 104°C); ^1H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.74$ (br s, 1H; OH), 4.36 (m, 9H; Cp), 5.25 (s, 1H; C*H*(OH)CN); ^{13}C NMR ($CDCl_3$): $\delta = 60.7$, 66.6, 68.5, 69.3, 69.6, 84.0, 118.7.

4.4. (+)-(*R*)-(Cyanohydroxymethyl)ferrocene 3

This compound was prepared according to general procedure A (formylferrocene **1** 1.00 g, 4.68 mmol; MTBE 50 mL; DSM (*S*)-*Hb*HNL 25 mL, 6.5 kU mL^{-1}; H_2O dist. 25 mL pH 4.82; HCN 0.63 g = 0.9 mL, 23.4 mmol) yielding 0.85 g (75%) as a pale brown solid. $R_f = 0.27$ (cyclohexane/EtOAc = 3:1); mp 89–90°C; $[\alpha]_D^{20} = +150$ (*c* 0.30; CH_3CN); *e.e.* 99% based on (*R*)-**7**; ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.74$ (br s, 1H; OH), 4.36 (m, 9H; Cp), 5.25 (s, 1H; C*H*(OH)CN); ^{13}C NMR ($CDCl_3$): $\delta = 60.7$, 66.6, 68.5, 69.3, 69.6, 84.0, 118.7; elemental analysis calcd (%) for $C_{12}H_{11}FeNO$ (241.06): C, 59.79; H, 4.60; N, 5.81; found: C, 59.88; H, 4.38; N, 5.73%.

4.5. (*rac*/*meso*)-1,1′-Bis(cyanohydroxymethyl)ferrocene 4

This compound was prepared according to general procedure C. Employed amounts were (*rac*/*meso*)-**6** (1.39 g, 3.16 mmol), AcOH (1 mL) and MeOH (50 mL). Compound **4** (0.90 g, 96%) was obtained as pale brown solid. $R_f = 0.29$ (cyclohexane/EtOAc = 1:1); mp 132–134°C (decomposition); ^{1}H NMR (200 MHz, [D_6]acetone, 25°C, TMS): $\delta = 4.26$–4.56 (br m, 8H; Cp), 5.55 (m, 2H; C*H*(OH)CN), 5.82 (m, 2H; O*H*); ^{13}C NMR [D_6]acetone: $\delta = 60.5$, 60.6, 68.8, 69.1, 70.2, 70.5, 70.9, 71.0, 71.2, 71.2, 86.1, 86.3, 120.4. For elemental analysis see (*R*,*R*)-**4**.

4.6. (+)-(*R*,*R*)-1,1′-Bis(cyanohydroxymethyl)ferrocene 4

(*R*,*R*)-**4** was prepared according to general procedure A (1,1′-diformylferrocene **2** 2.00 g, 8.26 mmol; MTBE 50 mL; DSM (*S*)-*Hb*HNL 25 mL, 6.5 kU mL^{-1}; H_2O dist. 25 mL pH 4.80; HCN 3.2 mL, 82.6 mmol). Yield: 2.02 g (82%) brown solid. $R_f = 0.29$ (cyclohexane/EtOAc = 1:1); mp 109–111°C; $[\alpha]_D^{20} = +172$ (*c* 0.070, CH_3CN); *e.e.* and *d.e.* see compound (*R*,*R*)-**10**; ^{1}H NMR (200 MHz, [D_6]acetone, 25°C, TMS): $\delta = 4.25$–4.60 (br m, 8H; Cp), 5.58 (br s, 2H; C*H*(OH)CN), 5.82 (br s, 2H; OH); ^{1}H NMR (200 MHz, CD_3CN, 25°C, TMS): $\delta = 4.25$–4.55 (br m, 8H; Cp), 4.98 (d, $J = 7.0$ Hz, 2H, OH), 5.37 (d, $J = 7.0$ Hz, 2H; C*H*(OH)CN); ^{13}C NMR ([D_6]acetone): $\delta = 60.5$, 68.9, 70.2, 71.0, 71.2, 86.3, 120.4; ^{13}C NMR (CD_3CN): $\delta = 60.5$, 69.0, 70.3, 71.3, 71.5, 85.9, 120.5; elemental analysis calcd (%) for $C_{14}H_{12}FeN_2O_2$ (296.09): C, 56.79; H, 4.08; N, 9.46; found: C, 56.97; H, 4.08; N, 9.41%.

4.7. (*rac*)-[Cyano(trimethylsilyloxy)methyl]ferrocene 5

Compound **5** was prepared by general procedure B. The amounts used were **1** (2.14 g, 10.0 mmol), TMSCN (1.5 mL, 12.0 mmol), CH_2Cl_2 (50 mL) and a catalytic amount of ZnI_2. (*rac*)-**5** was obtained as a brown solid in a yield of 3.16 g (99%). Mp 80–82°C (lit.[6a] 80–82°C). ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.18$ (s, 9H; $SiCH_3$), 4.20–4.35 (m, 8H; Cp), 4.46 (s, 1H; Cp), 5.32 (s, 1H; C*H*(OTMS)CN); ^{13}C NMR ($CDCl_3$): $\delta =$ 0.0, 61.3, 67.5, 68.6, 69.1, 69.4, 69.5, 83.5, 119.1; MS (70 eV, EI): *m*/*z* (%): 313 (100) [M$^+$], 224 (25), 220 (15), 214 (23), 195 (56), 186 (12) [$C_{10}H_{10}Fe^+$], 166 (30), 121 (46) [CpFe$^+$], 84 (16), 75 (19), 73 (40), 65 (2) [Cp$^+$], 56 (30) [Fe$^+$].

4.8. (*rac*/*meso*)-1,1′-Bis[cyano(trimethylsilyloxy)methyl]-ferrocene 6

Compound **6** was prepared according to general procedure B employing **2** (1.0 g, 4.1 mmol), TMSCN (1.4 mL, 10.3 mmol), CH_2Cl_2 (50 mL) and catalytic amounts of ZnI_2. Compound **6** was obtained as brown oil in a yield of 1.66 g (92%). ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.20$ (s, 18H; $SiCH_3$), 4.34 (m, 6H; Cp), 4.50 (br s, 2H; Cp), 5.37 (s, 1H; C*H*(OTMS)CN), 5.39 (s, 1H; C*H*(OTMS)CN); ^{13}C NMR ($CDCl_3$): $\delta = 0.1$, 60.9, 61.0, 68.4, 69.0, 70.0, 70.3, 70.7, 70.9, 84.9, 85.3, 119.3, 119.4.

4.9. (*rac*)-(Acetoxycyanomethyl)ferrocene 7

(*rac*)-**5** (0.31 g, 1.0 mmol) was dissolved in MeOH (10 mL), AcOH (4 mL) added and the mixture placed on the rotary evaporator at 50°C. After 1 h, TLC indicated that the TMS group had been fully cleaved. Subsequently, under full vacuum, all solvent was removed to give a pale brown solid. To this, under an atmosphere of argon at 0°C, CH_2Cl_2 (9 mL) was added followed by acetyl chloride (0.2 g, 2.6 mmol) and pyridine (0.24 mL, 3.0 mmol). The mixture was allowed to come to room temperature and stirring was continued for 1.5 h. After quenching with MeOH and neutralising with a saturated solution of $NaHCO_3$, the aqueous phase was extracted several times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, the mixture filtered and the filtrate concentrated under reduced pressure. The (*rac*)-**7** was recrystallised from cyclohexane/CH_2Cl_2 yielding 0.28 g (98%) of brown crystals. $R_f = 0.30$ (cyclohexane/EtOAc = 5:1); mp 86–88°C (lit.:[6a] 88–90°C); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.09$ (s, 3H; CH_3), 4.25–4.40 (m, 8H; Cp), 4.55 (m, 1H; Cp), 6.27 (s, 1H; CH(OAc)CN); ^{13}C NMR ($CDCl_3$): $\delta = 20.5$, 60.8, 68.1, 69.7, 69.9, 70.0, 70.1, 78.1, 116.1, 169.1; MS (70 eV, EI): *m*/*z* (%): 283 (44) [M$^+$], 224 (17), 218 (13), 180 (100), 134 (28), 121 (79) [CpFe$^+$], 65 (4) [Cp$^+$], 56 (41) [Fe$^+$].

4.10. (+)-(*R*)-(Acetoxycyanomethyl)ferrocene 7

Acetylating (*R*)-**3** under standard conditions afforded compound (*R*)-**7**. (*R*)-**3** (0.040 g, 0.17 mmol in CH_2Cl_2 5 mL; AcCl 16 μL, 0.22 mmol; NEt_3 42 μL, 0.30 mmol). (*R*)-**7** was obtained as a brown solid in a yield of 48 mg (99%). $R_f = 0.30$ (cyclohexane/EtOAc = 5:1); mp 73–76°C; $[\alpha]_D^{20} = +76$ (*c* 0.21; CH_3CN); HPLC: OD-H, mobile phase *n*-heptane:2-propanol = 95:5, $v = 0.50$ mL min^{-1}, 10°C, UV 238 nm, *e.e.* 99% ($R_t(R) = 25.5$ min, $R_t(S) = 39.7$ min); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.09$ (s, 3H; CH_3), 4.25–4.40 (m, 8H; Cp), 4.55 (m, 1H; Cp), 6.27 (s, 1H; CH(OAc)CN); ^{13}C NMR ($CDCl_3$): $\delta = 20.5$, 60.8, 68.1, 69.7, 69.9, 70.0, 78.1, 116.1, 169.1.

4.11. (*rac*/*meso*)-Bis(acetoxycyanomethyl)ferrocene 8

(*rac*/*meso*)-**4** (0.202 g, 0.68 mmol) was diacetylated under standard conditions using AcCl (124 μL, 1.71 mmol) and pyridine (166 μL, 2.05 mmol) in CH_2Cl_2 (20 mL). The previously unknown compound (*rac*/*meso*)-**8** was obtained as an orange solid in a yield of 0.247 g (95%). $R_f = 0.48$ (cyclohexane/EtOAc = 1:1); mp 149–152°C; ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.12$ (s, 6H; CH_3), 4.38–4.67 (m, 8H; Cp), 6.24 and 6.28 (s and s, 2H; CH(OAc)CN); ^{13}C NMR ($CDCl_3$): $\delta = 20.6$, 60.2, 60.3, 69.5, 69.6, 71.2, 71.5, 71.7, 71.7, 71.8, 72.0, 80.0, 80.1, 116.1, 116.3, 169.2, 169.2; for elemental analysis see (*R*,*R*)-**8**.

4.12. (+)-(*R*,*R*)-Bis(acetoxycyanomethyl)ferrocene 8

Acetylating (*R*,*R*)-**4** (35 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) under standard conditions (AcCl 22 μL, 0.30 mmol; pyridine 29 μL, 0.36 mmol) afforded the previously unknown compound (*R*,*R*)-**8** as an orange solid. Careful recrystallisation from Et_2O/cyclohexane provided orange crystals suitable for XRD analysis. Yield: 45 mg (98%). $R_f = 0.48$ (cyclohexane/EtOAc = 1:1); mp 119–121°C; $[\alpha]_D^{20} = +105$ (*c* 0.494; CH_3CN); HPLC: AD, mobile phase *n*-heptane:2-propanol = 90:10, $v = 0.50$ mL min^{-1}, 10°C, UV 210 nm, *e.e.* 98% ($R_t(R,R) = 40.9$ min, $R_t(S,S) = 47.3$ min), *d.e.* 96% ($R_t(R,S) = 52.0$ min); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.06$ (s, 6H; CH_3), 4.28–4.63 (m, 8H; Cp), 6.18 (s, 2H; CH(OAc)CN); ^{13}C NMR ($CDCl_3$): $\delta = 20.6$, 60.3, 69.5, 71.2, 71.8, 72.0, 80.1, 116.1, 169.2; elemental analysis calcd (%) for $C_{18}H_{16}FeN_2O_4$ (380.15): C, 56.87; H, 4.24; N, 7.37; found: C, 56.73; H, 4.15; N, 7.44%.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 195766. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.13. (*rac*)-[(*t*-Butyldimethylsilyloxy)cyanomethyl]-ferrocene 9

Method 1: Compound **9** was prepared according to general procedure B employing **1** (0.50 g, 2.3 mmol), TBDMSCN (0.50 g, 3.5 mmol), CH_2Cl_2 (20 mL) and catalytic amounts of ZnI_2 (reaction time: 5 h). Yield: 0.81 g (99%).

Method 2: (*rac*)-**3** (0.24 g, 1.0 mmol) was dissolved in DMF (1 mL) and TBDMSCN (0.17 g, 1.4 mmol) was added at rt. The solution was slowly warmed to 38°C. After 2.5 h the reaction mixture was diluted with CH_2Cl_2 and water was added. The aqueous phase was extracted several times with fresh CH_2Cl_2. All organic phases were combined, washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The mixture was filtered and the filtrate concentrated under reduced pressure to give a pale yellow/brown residue. This was then filtered through a plug of silica gel (cyclohexane/EtOAc = 5:1) to afford **9** as honey/yellow coloured syrup in a yield of 0.29 g (82%). ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.14$ (s, 3H; $SiCH_3$), 0.18 (s, 3H; $SiCH_3$), 0.93 (s, 9H; Si*t*Bu), 4.27 (br s, 8H; Cp), 4.41 (br s, 1H; Cp), 5.35 (s, 1H; CH(OTBDMS)CN); ^{13}C NMR ($CDCl_3$): $\delta = -5.0$, −4.9, 18.2, 25.6, 61.6, 67.1, 68.0, 68.9, 69.1, 69.4, 84.1, 120.5; HRMS see (*R*)-**9**, MS (70 eV, EI): *m*/*z* (%): 355 (100) [M$^+$], 224 (58), 214 (12), 195 (28), 186 (8) [$C_{10}H_{10}Fe^+$], 151 (22), 121 (44) [CpFe$^+$], 73 (28), 56 (23) [Fe$^+$], 41 (12).

4.14. (+)-(*R*)-[(*t*-Butyldimethylsilyloxy)cyanomethyl]-ferrocene 9

Method 1: Compound **9** was prepared by the reaction of (*R*)-**3** (0.50 g, 2.1 mmol) with TBDMSCN (0.44 g, 3.1 mmol) in DMF (2 mL). After the mixture had been stirred at room temperature for 16 h and TLC had indicated that the reaction was not complete, the mixture was heated to 50°C for a further 13 h. After this time, CH_2Cl_2 was added as well as water. The aqueous phase was extracted several times with fresh CH_2Cl_2. All organic phases were combined, washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The mixture was filtered and the filtrate concentrated under reduced pressure to give a honey/yellow coloured syrup. Yield: 0.57 g (77%).

Method 2: At room temperature compound (*R*)-**3** (0.50 g, 2.1 mmol) was dissolved in DMF (0.5 mL) and MTBSTFA (2.1 mL, 10.4 mmol) was added. TLC indicated that after only 8 min the reaction was complete. All volatile components were removed from the reaction mixture under reduced pressure. The resulting pale yellow/brown residue was passed through a plug silica gel (cyclohexane/EtOAc = 10:1) to give the title compound as honey/yellow coloured syrup. Yield: 0.60 g (81%). $[\alpha]_D^{20} = +80$ ($c = 0.436$, CH_3CN); *e.e.* 99% based on the *e.e.* from (*R*)-**7**; ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.14$ (s, 3H; $SiCH_3$), 0.18 (s, 3H; $SiCH_3$), 0.93 (br s, 9H; Si*t*Bu), 4.27 (br s, 8H; Cp), 4.41 (br s, 1H; Cp), 5.35 (s, 1H; CH(OTBDMS)CN); ^{13}C NMR ($CDCl_3$): $\delta = -4.7$, −4.7, 18.3, 25.8, 61.8, 67.2, 68.2, 69.0, 69.2, 69.6, 84.3, 119.3; HRMS [$C_{18}H_{25}FeNOSi$]$^+$ calcd 355.1054; found 355.1075; MS (70 eV, EI) *m*/*z* (%): 355 [M$^+$] (100), 224 (25), 195 (13), 186 [$C_{10}H_{10}Fe^+$] (30), 151 (12), 121 (21), 75 (21), 65 [Cp$^+$] (3), 56 [Fe$^+$](7), 41 (4).

4.15. (*rac*/*meso*)-1,1′-Bis[(*t*-butyldimethylsilyloxy)cyanomethyl]ferrocene 10

Method 1: The desired unknown compound (*rac*/*meso*)-**10** was prepared according to general procedure B employing **2** (0.50 g, 2.1 mmol), TBDMSCN (0.76 g, 5.4 mmol), CH_2Cl_2 (15 mL) and catalytic amounts of ZnI_2. (*rac*/*meso*)-**10** was obtained as brown oil in a yield of 1.02 g (94%).

Method 2: (*rac*/*meso*)-**4** (0.05 g, 0.17 mmol) was dissolved in DMF (0.1 mL) and MTBSTFA (0.35 mL, 1.7 mmol) was added at room temperature. TLC indicated

that all starting material had been consumed to give a single product after only 5 min. Consequently, the reaction mixture was diluted with CH_2Cl_2 and water was added. The aqueous phase was extracted several times with fresh CH_2Cl_2. All organic phases were combined, washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The mixture was filtered and the filtrate concentrated under reduced pressure to give (*rac*/*meso*)-**10** as brown oil in a yield of 71 mg (80%). $R_f = 0.56$ (cyclohexane/EtOAc = 3:1); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.15$ and 0.23 (m and m, 6H and 6H; $SiCH_3$), 0.93 (m, 18H; Si*t*Bu), 4.24–4.52 (m, 8H; Cp), 5.40 (m, 2H; CH(OTBDMS)CN); ^{13}C NMR ($CDCl_3$): $\delta = -4.9$, −4.8, 18.3, 25.8, 61.4, 61.5, 68.0, 68.7, 69.7, 69.8, 70.7, 70.8, 85.3, 85.7, 119.4; HRMS see (*R*,*R*)-**10**.

4.16. (+)-(*R*,*R*)-1,1′-Bis[(*t*-butyldimethylsilyloxy)cyanomethyl]ferrocene 10

(*R*,*R*)-**4** (1.00 g, 3.38 mmol) was dissolved in DMF (1 mL) and MTBSTFA (3.47 mL, 16.9 mmol) was added. TLC indicated that all starting material had been consumed to give a single product. Consequently, the reaction mixture was diluted with CH_2Cl_2 and water added. The aqueous phase was extracted several times with fresh CH_2Cl_2. All organic phases were combined, washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The mixture was filtered and the filtrate concentrated under reduced pressure to give the title compound (*R*,*R*)-**10**. Yield: 1.44 g (81%) brown oil. $R_f = 0.56$ (cyclohexane/EtOAc = 3:1); $[\alpha]_D^{20} = +88$ (c = 0.124, CH_3CN); HPLC: OD-H, mobile phase *n*-heptane:2-propanol = 99.75: 0.25, $v = 0.50$ mL min^{-1}, 10°C, UV 238 nm, *e.e.* 96% (R_t(*S*,*S*) = 22.5 min, R_t(*R*,*R*) = 28.6 min), *d.e.* 91% (R_t(*R*,*S*) = 21.0 min); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.15$ and 0.23 (s and s, 6H and 6H; $SiCH_3$), 0.93 (s, 18H; Si*t*Bu), 4.23–4.56 (m, 8H; Cp), 5.40 (s, 2H; CH(OTBDMS)CN); ^{13}C NMR ($CDCl_3$): $\delta = -4.9$, −4.8, 18.3, 25.8, 61.4, 68.0, 69.7, 70.7, 85.7, 119.4; HRMS: $[C_{26}H_{40}FeN_2O_2Si_2]^+$ calcd 524.1977; found 524.1954, MS (70 eV, EI) m/z (%): 524 [M^+] (100), 393 (3), 290 (8), 223 (7), 186 (1), 151 (13), 73 (37), 56 [Fe^+] (4).

4.17. (*rac*)-1-Formyl-1′-[(*t*-butyldimethylsilyloxy)cyanomethyl]ferrocene 11

Previously unreported compound (*rac*)-**11** was isolated as a product from the reaction of **2** (118 mg, 0.49 mmol) by employing only 1 equiv. of TBDMSCN (69 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) with catalytic amounts of ZnI_2. In addition to 51 mg (21%) (*rac*/*meso*)-**10** and 38 mg (33%) recovered **2** (*rac*)-**11** was furnished as orange oil in a yield of 58 mg (31%). $R_f = 0.32$ (cyclohexane/EtOAc = 3:1); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.00$ and 0.06 (s and s, 6H; $SiCH_3$), 0.80 (s, 9H; Si*t*Bu), 4.13–4.80 (m, 8H; Cp), 5.10 (s, 1H; CH(OTBDMS)CN), 10.1 (br s, 1H; CHO); ^{13}C NMR ($CDCl_3$): $\delta = -4.9$, −4.8, 18.3, 25.7, 61.0, 68.4, 69.2, 70.7, 70.9, 71.2, 74.7, 74.8, 80.9, 86.4, 119.0, 193.7; HRMS see (*R*)-**11**.

4.18. (+)-(*R*)-1-Formyl-1′-[(*t*-butyldimethylsilyloxy)cyanomethyl]ferrocene 11

In one experiment where chiral (*R*,*R*)-**4** was reacted with MTBSTFA to produce the desired compound (*R*,*R*)-**10** (for the reaction conditions see (*R*,*R*)-**10**), the by-product (*R*)-**11** was also obtained. Yield: (*R*)-**11**: 0.027 g (21%), (*R*,*R*)-**10**: 0.088 g (49%); $R_f = 0.32$ (cyclohexane/EtOAc = 3:1); $[\alpha]_D^{20} = +36$ ($c = 0.17$, CH_3CN) and +8 ($c = 0.17$, $CHCl_3$); *e.e.* could not be determined; ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.00$ and 0.06 (s and s, 6H; $SiCH_3$), 0.80 (s, 9H; Si*t*Bu), 4.13–4.80 (m, 8H; Cp), 5.10 (s, 1H; CH(OTBDMS)CN), 9.85 (s, 1H; CHO); ^{13}C NMR ($CDCl_3$): $\delta = -4.9$, −4.7, 18.4, 25.8, 61.0, 68.4, 69.2, 70.7, 70.9, 71.2, 74.7, 74.8, 80.3, 86.5, 118.9, 193.7; HRMS: $[C_{19}H_{25}FeN_1O_2Si]^+$ calcd 383.1004; found 383.1013.

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