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Enantioselective Catalysis 83.[1]

Synthesis of Optically Active Ferrocenylalanine

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Abstract: Ferrocenylalanine, a possible substitute for phenylalanine in the commercial sweetener aspartame, was synthesized by asymmetric hydrogenation of the corresponding dehydro acylamino acids with rhodium/phosphine catalysts in up to 94% enantiomeric excess. The absolute configuration of N-benzoyl-ferrocenyl alanine **4** was determined by single-crystal X-ray analysis.

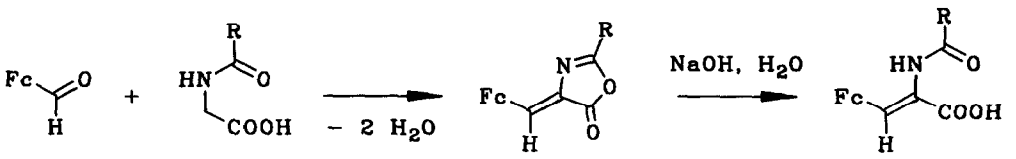
Introduction

The commercial sweetener aspartame[2,3] is the methyl ester of a dipeptide (asp-phe-OMe), consisting of the amino acids aspartic acid and phenylalanine. Aspartic acid is the inexpensive component, whereas phenylalanine is the expensive part. Phenylalanine is an essential amino acid, it may cause phenylketouria. The well-known similarity of phenyl and ferrocenyl derivatives prompted us to synthesize ferrocenylalanine[4-8] with the aim to use it instead of phenylalanine in the synthesis of an aspartame analogue.

The absolute configurations of the amino acids in dipeptides of the aspartame type are very important for the taste properties.[2,3] An attractive synthetic route to enantiomerically pure amino acid derivatives is the asymmetric hydrogenation of dehydro acylamino acids in the presence of optically active rhodium/phosphine complexes. Using this methodology, we report on the synthesis of both enantiomers of ferrocenylalanine.[9]

Results and discussion

The synthesis of 2-benzamido-3-ferrocenylacrylic acid **2a** was achieved by the Erlenmeyer procedure starting from ferrocenylcarbaldehyde and benzoylglycine via the corresponding azlactone **1a** (Scheme 1). In contrast to other double-bond forming reactions, e.g. the Wittig-Horner reaction, the Erlenmeyer synthesis generates preferentially the Z-configurated acylamido cinnamic acids, which are known to yield a high enantiomeric excess on asymmetric hydrogenation.[10] To ensure complete absence of the E-isomer, the red compound **1a** was recrystallised from acetic acid and ethanol/water 1:1. The TLC of **1a** on SiO_2 with ether/ligroin mixtures showed only a single spot. In the ^1H NMR spectra (250 MHz) of the azlactone **1a** and of the hydrolysis product **2a** there was only one signal of the olefinic proton of the Z-configurated compounds, respectively.[11,12]

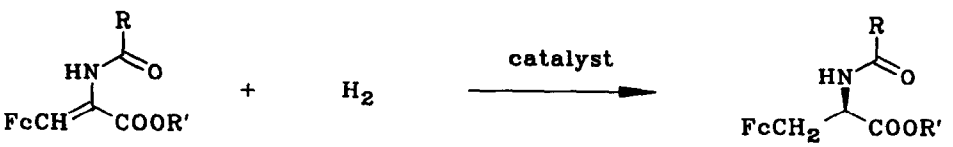


1a,b 2a,b

	1a, 2a	1b, 2b
R	Ph	Me

(Scheme 1)

The hydrogenation of 2-benzamido-3-ferrocenylacrylic acid **2a** (Scheme 2) was performed in methanol at room temperature in the presence of different *in situ* catalysts consisting of $[Rh(cod)Cl]_2$[13] and the following bidentate phosphines: (+)-Norphos[14,15], (-)-Norphos[14,15], (+)-Prophos[16], (-)-Diop[17,18] and (3R,4R)-3,4-bis(diphenylphosphino)tetrahydrofuran.[19]



2a, 2b, 3 4–6

	2a, 4	2b, 5	3, 6
R	Ph	Me	H
R'	H	H	Me

(Scheme 2)

Hydrogenations at 1.1 bar H_2 pressure were performed in an apparatus containing a calibrated gas burette to monitor the progress of the reaction. **2a** was not completely soluble in the amount of methanol used. However, during the reaction the suspended substrate dissolved and a clear, deep red solution was formed. After

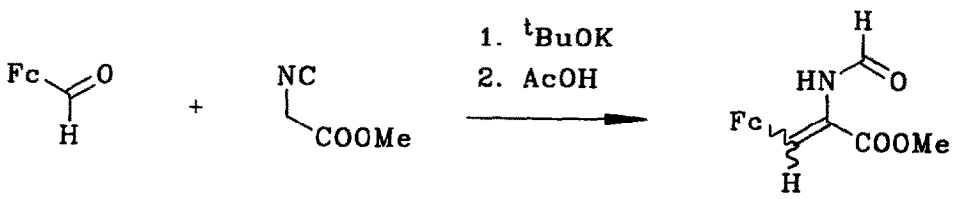
two to four days, when the reactions were complete, the solutions had turned yellowish brown. Additionally, some reactions were performed under increased hydrogen pressure utilizing a 100 ml autoclave. In contrast to the red acrylic acid derivative **2a**, the hydrogenation product **4** was a yellow solid.

The enantiomeric excess of **4** was determined by polarimetry, ^{1}H NMR with chiral shift reagents, and HPLC. The optical purity of the hydrogenation product **4**, obtained with the $[Rh(cod)Cl]_2$/(-)-Norphos catalyst, was increased to 100% by two crystallisations from ethanol/water 1:1. For the determination of the optical purity by HPLC and NMR, the acid **4** was converted into its methyl ester using thionylchloride/methanol as derivatising agent.[20] Addition of 25 mol% of $Eu(tfc)_3$ to a solution of the ester in $CDCl_3$ resulted in a splitting of the singuletts of the non-substituted Cp-ring and the methyl ester group with 8 - 9 Hz difference. Since there was no baseline separation, the peak heights were used to calculate the enantiomeric excess. The enantiomer analysis by HPLC was performed on a Chiracel OB column using hexane with 5.8% ethanol as eluent. The resulting peaks were baseline separated, the separation factor was α = 1.47. The optical purities of the hydrogenation products, determined by this method, are listed in Table 1.

The hydrogenation of 2-benzamido-3-ferrocenylacrylic acid **2a** gave the corresponding 2-benzamido-3-ferrocenylalanine **4** in high enantiomeric excess and nearly quantitative chemical yield. The best results (up to 94.9% ee) were obtained with ligands, such as Norphos, forming five-membered rings. (-)-Diop, forming a seven-membered ring, gave lower optical yields but higher reaction rates. Increasing the hydrogen pressure reduced the reaction time but also the enantioselectivity.

2-Acetamido-3-ferrocenylacrylic acid **2b** was synthesized similar to the benzamido analogue **2a** using acetylglycine. However, the yield of **2b** is much lower than that of **2a**. After repeated recrystallisation from ethanol/water 1:1, a sample of **2b** was obtained, which contained approximately 2.5% of E-**2b** (δ 7.62, FcCH) due to the integration of the ^{1}H NMR spectrum. The hydrogenation of this sample was performed as described for **2a**. The enantiomeric excess was determined by polarimetry. To obtain optically pure 2-acetamido-3-ferrocenylalanine **5** the hydrogenation product was recrystallised from ethanol/water until the optical rotation became constant. After two recrystallisations the optical rotation of **5** remained unchanged. With (+)- or (-)-Norphos as ligands, 89 - 90% enantiomeric excess was attained (Table 1).

Methyl 2-formamido-3-ferrocenylacrylate **3** was obtained by a Knoevenagel condensation of ferrocenylcarbaldehyde with methyl isocyanoacetate followed by hydrolysis of the intermediate isocyanoacrylate (Scheme 3).[21,22]



3

(Scheme 3)

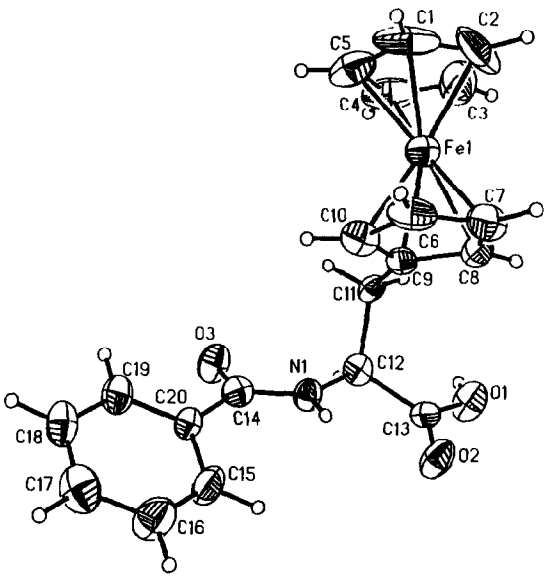
Table 1: Enantioselective hydrogenation of 2-acylamido-3-ferrocenylacrylic acid derivatives. Ratio [ligand]/[Rh] = 1.15-1.25; ratio [substrate]/[Rh] = 50-120; solvent MeOH (5-8 ml); room temperature.

acrylic acid derivative	ligand	pressure [atm]	reaction time [d]	configuration	ee[f] [%]	number of runs
2a	(+)-Norphos[a]	1.1	3.5	R	91.3-94.9	4
2a	(-)-Norphos[b]	1.1	3.5	S	90.5–94.5	4
2a	(+)-Prophos[c]	1.1	3.5	S	85.3, 87.7	2
2a	(-)-Diop[d]	1.1	2.5	S	80.9, 84.7	2
2a	[e]	3-4	3.5	S	90.9, 93.7	2
2a	(-)-Norphos[b]	10	2.0	S	81.5, 87.1	2
2a	(+)-Prophos[c]	10	2.0	S	78.5, 80.9	2
2a	[e]	10	2.0	S	83.4	1
2a	(-)-Diop[d]	20	1.0	S	43.3, 47.9	2
2a	(+)-Norphos[a]	40	1.0	R	75.5, 81.5	2
2b	(+)-Norphos[a]	1.1	4.0	R	88.6, 90.4[g]	2
2b	(-)-Norphos[b]	1.1	4.0	S	86.9, 90.3[g]	2
3	(+)-Norphos[a]	20	1.5	R	-28.5, -33.3[h]	2
3	(-)-Norphos[b]	20	1.5	S	37.5, 39.1[h]	2
3	(+)-Prophos[c]	20	1.5	S	71.5[h]	1
3	(-)-Diop[d]	20	1.5	S	52.0[h]	1
3	[e]	20	1.5	S	79.2, 82.6[h]	2

a) (2S,3S)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]hex-5-ene[14,15] b) (2R,3R)-2,3-bis(diphenylphosphino)-bicyclo[2.2.1]hex-5-ene[14,15] c) (2R)-1,2-bis(diphenylphosphino)propane[16] d) (4R,5R)-(-)-bis(diphenyl-phosphinomethyl)-2,2-dimethyl-1,3-dioxolane[17,18] e) (3R,4R)-(+)-3,4-bis(diphe-nylphosphino)tetra-hydrofuran[19] f) determined by HPLC g) determined by polarimetry, $[\alpha]_D$ of the pure enantiomer: 22.2 ± 0.25 (c 0.5, MeOH) h) measured optical rotation (c 0.5, $CHCl_3$)

A 2:1 mixture of the E/Z-isomers of **3** resulted as determined by integration of the FcCH resonances in the ^1H NMR spectrum. As for the enantiomers of the methyl 2-formamido-3-ferrocenylalaninate **6** no HPLC base-line separation was attainable, the hydrogenation products of **3** could only be characterized by their optical rotations (Table 1).

To determine the absolute configuration of ferrocenylalanine, a single crystal of (-)-**4**, derived from the hydrogenation of **2a** with (-)-Norphos as cocatalyst, was harvested from a batch which had been recrystallised from methanol. The X-ray analysis (Scheme 4) confirmed the constitution and gave (S)-configuration for the stereogenic carbon atom in (-)-benzoylferrocenylalanine **4**, in analogy to the (S)-configuration[14, 15] of N-acetylphenylalanine obtained in the hydrogenation of acetamido cinnamic acid with $[Rh(cod)Cl]_2$/(-)-Norphos catalysts.



(Scheme 4)

These results show that in the enantioselective hydrogenation ferrocenyl derivatives and their phenyl analogues behave similary in spite of the increased steric demand of the ferrocenyl group.

Experimental Part

^{1}H NMR spectra were recorded on a Bruker WM 250 spectrometer. Polarimetric measurements were performed with a Perkin-Elmer polarimeter 241. Mass spectra were obtained with the Finnigan instruments Mat 95 (FD) and Mat 112 S (EI). Only prominent IR bands are given; for further details see ref. 9. All solvents were dried according to known procedures and all preparations were performed under nitrogen unless otherwise stated.

2-Phenyl-4-ferrocenylmethylen-5-oxazolone (**1a**)

This compound was synthesized according to ref. 23. ^{1}H NMR ($CDCl_3$/TMS): δ 4.22 (s, 5 H, Cp-H), 4.68 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 5.12 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 7.54 (s, 1 H, Fc-CH), 7.46-7.63 (m, 3 H, 2,4,6-phenyl-H), 8.15-8.18 (m, 2 H, 3,5-phenyl-H). IR (KBr): 3100 (w), 2920, 2855 (m), 1770 (s), 1645 (s), 1595 (m) cm^{-1}. MS (FD, $CHCl_3$): m/e 357 (M^+, 100). Anal. calcd. for $C_{20}H_{15}FeNO_2$ (357.2): C, 67.24; H, 4.23; N, 3.92. Found: C, 67.63; H, 4.35; N, 4.00%.

2-Methyl-4-ferrocenylmethylen-5-oxazolone (**1b**)

Acetic acid anhydride (5.4 ml, 57 mmol) was added to a mixture of ferrocenealdehyde[24] (5.0 g, 23 mmol), N-acetylglycine (2.34 g, 20 mmol) and sodium acetate (1.20 g, 14 mmol). After refluxing for 90 min, a clear violet solution was obtained. Crystallization at -20°C for 12 h gave a violet solid which was suspended in 20 ml of ice water, filtered off and washed with ice water (200 ml) and ether (10 ml). The product was directly used for hydrolysis to **2b**. A small part was chromatographed on SiO_2 using ether/petroleum ether (1:1) as eluent, yielding **1b** as dark violet crystals, m.p. 165°C. ^{1}H NMR ($CDCl_3$/TMS): δ 2.30 (s, 3 H, CH_3), 4.20 (s, 5 H, Cp-H), 4.61 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 4.98 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 7.14 (s, 1 H, Fc-CH). IR (KBr): 3085 (w), 2920, 2855 (m), 1765 (s), 1650 (m) cm^{-1}. MS (EI): m/e 295 (M^+, 33), 225 (Fc-CH=CH_2^+,

100), 121 ($FeCp^+$, 94). Anal. calcd. for $C_{15}H_{13}FeNO_2$ (295.1): C, 61.04; H, 4.44; N, 4.75. Found: C, 61.39; H, 4.63; N, 4.93%.

Z-2-Benzamido-3-ferrocenylacrylic acid (**2a**)

2a was obtained in analogy to ref. 11. ^1H NMR ($CDCl_3$/TMS): δ 4.14 (s, 5 H, Cp-H), 4.40 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 4.61 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 7.42 (s, 1 H, Fc-CH=), 7.51-7.64 (m, 3 H, 2,4,6-phenyl-H), 8.02-8.04 (m, 2 H, 3,5-phenyl-H), 9.53 (s, 1 H, NH), 12.0 (s (br), 1 H, COOH). IR (KBr): 3270 (m), 3070 (w), 1570 (m), 1510 (s) cm^{-1}. MS (FD, $CHCl_3$): m/e 376 (MH^+, 20), 375 (M^+, 100). Anal. calcd. for $C_{20}H_{17}FeNO_3$ (375.2): C, 64.02; H, 4.56; N, 3.73. Found: C, 64.02; H, 4.58; N, 3.99%.

Z-2-Acetamido-3-ferrocenylacrylic acid (**2b**)

Crude **1b**, obtained as described above, was refluxed in a mixture of 1N NaOH (10 ml, 10 mmol) and aqueous acetone (20 ml) for 60 min, treated with charcoal for 15 min and filtered. The cooled mixture was acidified with 2N HCl and the resulting precipitate was recrystallized twice from 50% aqueous ethanol. The resulting material was dried in vacuo at 70°C. Yield: 780 mg (11% with respect to ferrocenealdehyde) of red crystals, m.p. 192-193°C. ^1H NMR (CD_3OD/TMS): δ 2.13 (s, 3 H, CH_3), 4.18 (s, 5 H, Cp-H), 4.44 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 4.59 (t, J = 1.8 Hz, 2 H, subst. Cp-H), 7.46 (s, 1 H, Fc-CH). IR (KBr): 3250 (m), 3080 (w), 1550 (s) cm^{-1}. MS (EI): m/e 313 (M^+, 73), 269 (M^+-CO_2, 35), 121 ($FeCp^+$, 93), 56 (Fe^+, 100). Anal. calcd. for $C_{15}H_{15}FeNO_3$ (313.1): C, 57.53; H, 4.83; N, 4.47. Found: C, 57.24; H, 4.67; N, 4.70%.

Methyl E/Z-2-formamido-3-ferrocenylacrylate (**3**)

3 was prepared according the procedure given in ref. 12. The E/Z ratio of 2:1 was determined by ^1H NMR. ^1H NMR ($CDCl_3$/TMS): δ 3.84 (s, 3 H, $COOCH_3$), 4.20-4.55 (m, 9 H, Fc), 6.79-6.86 (m, 1 H, N-H), 7.31 (Z), 7.43 (E) (2 s, 1 H, Fc-CH), 8.24, 8.26 (2 s, 1 H, CHO). IR (KBr): 3250 (m), 3105 (w), 1710 (s), 1660 (s), 1630 (s) cm^{-1}. MS (EI): m/e 313 (M^+, 100), 248 (M^+-Cp, 27%), 121 ($FeCp^+$, 93), 56 (Fe^+, 100). Anal. calcd. for $C_{15}H_{15}FeNO_3$ (313.1): C, 57.53; H, 4.83; N, 4.47. Found: C, 57.72; H, 4.96; N, 4.48%.

Enantioselective Hydrogenations

$[Rh(cod)Cl]_2$ (4-8 mg) and the 1.15-1.25 molar amount (with respect to Rh) of the optically active ligand were stirred in methanol (5-8 ml) in a hydrogen atmosphere for 15 min, giving an orange solution.

The acrylic acid derivative (10-20 mmol) was dissolved in methanol (20-30 ml) and the catalyst solution was added under nitrogen. Then, the reaction vessel (glass flask with stopcock for 1.1 atm H_2, otherwise autoclave) was vented three times with hydrogen. Hydrogenation proceeded at room temperature and was stopped after 1.5-4 d, when the hydrogen uptake was complete (Table 1).

After the hydrogenation of the carboxylic acids **2a** and **2b**, the solvent was evaporated and the residue was treated with 1N NaOH (2.5-4 ml) for 30 min. The solution was filtered, diluted with 20 ml of water, acidified with 1N HCl and extracted with ether (**4**) or ethyl acetate (**5**). The organic phase was dried with Na_2SO_4 and concentrated to dryness to yield the yellow compounds **4** and **5**. The ester **6** was obtained by evaporation of the solvent followed by chromatography on SiO_2 with ether as eluent.

The yields of all the compounds **4-6** were generally above 90%. The enantiomeric excess was determined by HPLC: SP 8700 unit with detector SP 8300 at 254 nm, central processor SP 4000, data interface SP 4020 and plotter SP 4050.

2-Benzamido-3-ferrocenylpropanoic acid (**4**) (N-benzoylferrocenylalanine)
Yellow solid, m.p. 186-188°C. $[\alpha]_D$ of the pure enantiomer: 6.45 (c 2.1, MeOH) ((+)-R, (-)-S). ^{1}H NMR (CD_3OD/TMS): δ 2.93 (dd, 1 H, J = 8.8 Hz, J = 14.6 Hz, $C\underline{H}_A H_B CH_X$), 3.08 (dd, 1 H, J = 4.6 Hz, J = 14.6 Hz, $CH_A\underline{H}_B CH_X$), 4.07-4.18 (m, 9 H, Fc), 4.68 (dd, 1 H, J = 4.6 Hz, J = 8.8 Hz, $CH_A H_B C\underline{H}_X$), 7.41-7.56 (m, 3 H, 2,4,6-phenyl-H), 7.76-7.82 (m, 2 H, 3,5-phenyl-H). IR (KBr): 3370 (m), 3095 (w), 1745 (s), 1690 (s), 1665 (s) cm^{-1}. MS (EI): m/e 378 (MH^+, 53), 377 (M^+, 100), 312 (M^+-Cp, 94), 256 (Fc-CH=CH-$COOH^+$, 24), 199 ($FcCH_2^+$, 50). Anal. calcd. for $C_{20}H_{19}FeNO_3$ (377.2): C, 63.68; H, 5.08; N, 3.71. Found: C, 63.79; H, 5.09; N, 4.01%.

2-Acetamido-3-ferrocenylpropanoic acid (**5**) (N-acetylferrocenylalanine)
Yellow solid, m.p. 189-190°C (dec.). $[\alpha]_D$ of the pure enantiomer: 22.2 (c 0.5, MeOH) ((-)-R, (+)-S). ^{1}H NMR (CD_3OD/TMS): δ 1.94 (s, 3H, $COCH_3$), 2.82 (dd, 1 H, J = 8.5 Hz, J = 14.5 Hz, $C\underline{H}_A H_B CH_X$), 3.32 (dd, 1 H, J = 4.6 Hz, J = 14.5 Hz, $CH_A\underline{H}_B CH_X$), 4.09-4.14 (m, 9 H, Fc), 4.47 (dd, 1 H, J = 4.6 Hz, J = 8.5 Hz, $CH_A H_B C\underline{H}_X$). IR (KBr): 3325 (s), 3090 (w), 1695 (s), 1610 (s), 1550 (s) cm^{-1}. MS (EI): m/e 315 (M^+, 66), 256 (M^+-CH_3CONH_2, 100), 199 ($FcCH_2^+$, 100), 121 ($FeCp^+$, 97), 56 (Fe^+, 49). Anal. calcd. for $C_{15}H_{17}FeNO_3$ (315.2): C, 57.17; H, 5.44; N, 4.44. Found: C, 57.14; H, 5.36; N, 4.51%.

Methyl 2-formamido-3-ferrocenylpropanoate (**6**) (methyl 2-formyl-3-ferrocenylalaninate)
Yellow solid, m.p. 93°C. ^{1}H NMR ($CDCl_3$/TMS): δ 2.94-2.96 (m, 2 H, CH_2), 3.74 (s, 3 H, $COOCH_3$), 4.07-4.12 (m, 9 H, Fc), 4.78-4.81 (m, 1 H, CHCOO), 6.00-6.10 (br s, 1 H, NH), 8.17 (s, 1 H, CHO). IR (KBr): 3370 (m), 3095 (w), 1745 (s), 1690 (s), 1665 (s) cm^{-1}. MS (EI): m/e 315 (M^+, 68), 270 (M^+-$CHONH_2$, 25), 250 (M^+-Cp, 12), 121 ($FeCp^+$, 67), 56 (Fe^+, 45). Anal. calcd. for $C_{15}H_{17}FeNO_3$ (315.2): C, 57.17; H, 5.44; N, 4.44. Found: C, 57.04; H, 5.34; N, 4.41%.

Crystallographic studies

$C_{20}H_{19}FeNO_3$: A yellow orange crystal, recrystallised from methanol, having approximate dimensions of 0.19 x 0.36 x 0.72 mm^3, was mounted on a Siemens Stoe AED II. The unit cell was determined and refined from 30 reflections (10.0°<2Θ<25.0°). The structure was solved by using standard Patterson methods, least-square refinement and Fourier techniques. All nonhydrogen atoms were refined anisotropically, the hydrogen atoms were included riding in calculated positions (HFIX option of SHELXTL PLUS[26]). All calculations were performed with the SHELXTL PLUS program;[26] scattering factors were taken from ref. 27, Table 2.2.B. Table 2 contains the atomic coordinates of (-)-**4**.
Crystal data and data collection parameters for (-)-**4**: molecular formular: $C_{20}H_{19}FeNO_3$; formular weight (g): 377.2; crystal system: rhombic; cell dimensions (Å): a: 9.573 (7), b: 10.450 (3), c: 17.61 (1); V (Å^3): 1761.7; Z: 4; ρ_{calc} (g/cm^3): 1.42; F(000): 784; diffractometer: AED II; radiation (Å): λ (Mo Kα) 0.71073; scan type: Θ-Ω; G.O.F.: 2.42; ρ, resiual (e/Å^{-3}): 0.73.

Acknowledgement
We thank the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the BASF AG, Ludwigshafen, for support of this work.

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (x 10^3 Å^2) of a single crystal of (-)-4.

Atom	x	y	z	U(eq)
Fe(1)	406(1)	2131(1)	8613(1)	47(1)
O(1)	-4992(5)	3403(4)	8335(2)	60(2)
O(2)	-4307(5)	4459(4)	7327(2)	60(2)
O(3)	-3511(5)	385(4)	6247(3)	57(2)
N(1)	-3241(5)	2421(5)	6627(3)	40(2)
C(1)	2227(9)	1352(9)	8904(6)	101(5)
C(2)	1650(14)	1903(10)	9558(6)	137(7)
C(3)	424(12)	1186(10)	9615(5)	96(5)
C(4)	267(10)	347(8)	9056(6)	81(4)
C(5)	1415(9)	443(8)	8577(5)	78(4)
C(6)	725(7)	3469(7)	7795(4)	61(3)
C(7)	132(9)	4037(6)	8449(5)	69(3)
C(8)	-1170(7)	3444(6)	8595(4)	53(3)
C(9)	-1382(7)	2515(5)	8014(3)	39(2)
C(10)	-188(7)	2537(6)	7525(4)	53(3)
C(11)	-2639(6)	1679(5)	7931(3)	38(2)
C(12)	-3762(6)	2223(6)	7392(3)	40(2)
C(13)	-4376(7)	3483(6)	7673(4)	40(2)
C(14)	-3186(7)	1511(7)	6104(4)	42(2)
C(15)	-2896(8)	3086(7)	5039(4)	65(3)
C(16)	-2432(8)	3359(8)	4311(4)	78(4)
C(17)	-1806(8)	2467(8)	3873(4)	70(4)
C(18)	-1567(7)	1261(8)	4168(4)	60(3)
C(19)	-2052(7)	967(6)	4896(4)	51(3)
C(20)	-2703(6)	1869(6)	5339(3)	36(2)

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