dropwise (15 min). After 15 min the reaction mixture was worked up as described in the previous procedure to yield 1.30 g (9.3 mmol, 93%) of 3-isopropylcyclohexanone.

Conjugate Addition Using 11 as Catalyst. To a stirred solution of zinc complex 11 (28.6 mg, 0.1 mmol) in 10 mL of THF was added 2-cyclohexenone (96 mg, 1.0 mmol). After 5 min the reaction mixture was cooled down to −90 °C and a mixture of isopropylmagnesium bromide (0.44 mL of a 2.5 N solution in Et_2O, 1.1 mmol) and 15 mL of THF was added dropwise (15 min). After being stirred for an additional 15 min the reaction mixture was worked up as previous described to yield 120 mg (0.86 mmol, 86%) 3-isopropylcyclohexanone.

Procedure for Following the Reaction with GLC. At −90 °C 2-cyclohexenone (960 mg, 10 mmol) is added at once to a stirred mixture of tetramethylethylenediamine (TMEDA) (25.2 mg, 0.1 mmol), zinc chloride (11.2 mg, 0.1 mmol), KOtBu (142 mg, 1.0 mmol), decane (internal standard), and isopropylmagnesium bromide (4.4 mL of a 2.5 N solution in ether, 11.0 mmol) in 50 mL of THF. At 10-min intervals samples of 0.1 mL were taken. These samples were immediately quenched with wet THF and injected in the GLC. After 3 h at −90 °C the reaction mixture was quenched and worked up using the standard procedure except that also the amount of condensation product was determined. For the reference reaction the same procedure was followed except that the reaction mixture contained no TMEDA, Zinc chloride, and KOtBu. GLC retention times (oven temperature 110 °C, flow 76.8 mL/min He): 2-cyclohexenone, 2.80 min; decane, 4.25 min; 1-isopropyl-2-cyclohexene-1-ol, 6.20 min; 3-isopropylcyclohexanone, 8.37 min.

Conversion to the Diastereoisomeric Ketals and Analysis by ^{13}C NMR. A mixture of 3-isopropylcyclohexanone (100 mg, 0.7 mmol), (*R,R*)-2,3-butanediol (100 mg, 1.1 mmol), and *p*-toluenesulfonic acid (15 mg) in 30 mL of toluene was treated under reflux in a 100-mL round-bottom flask equipped with a Dean-Stark trap for 5–16 h. After cooling to room temperature K_2CO_3 (1 g) was added followed by washing the reaction mixture with water, saturated K_2CO_3 and brine. Drying over Na_2SO_4 was followed by evaporation of the toluene, resulting in a ketal (usually >90% isolated yield, in all respects identical with independently prepared samples and data in agreement with those reported) which was dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and determination of the integrated carbon resonance (C_2 and C_3 of the ketal) of the diastereoisomers provided the relative amounts of diastereoisomers present.

Procedure for the Diethylzinc Additions. To a mixture of 2-cyclohexenone (96 mg, 1.0 mmol) and TMEDA (116 mg, 1.0 mmol) in tetrahydrofuran (10 mL) stirred at 0 °C under a N_2 atmosphere was added diethylzinc (1 mL of a 1.0 N solution in toluene). The mixture was subsequently analyzed at 5-min intervals. Potassium *tert*-butoxide (11.2 mg, 0.1 mmol) was added, and after being stirred for 0.5 h the products were analyzed by GC. Product formation was confirmed by comparison with independently prepared samples of 3-ethylcyclohexanone and 1-ethyl-1-hydroxycyclohexane.

Addition of $MgBr_2$ (184 mg, 1.0 mmol) or $ZnCl_2$ (68 mg, 0.5 mmol) did not result in further conversion. Following an identical procedure but adding i-PrMgBr (0.08 mL of a 1.25 N solution in ether, 0.1 mmol) instead of $MgBr_2$ followed by stirring for 5 min resulted in a mixture of 3-isopropylcyclohexanone (7.8%), 3-ethylcyclohexanone (2.0%), 1-isopropyl-1-hydroxycyclohexane (0.2%), and 1-ethyl-1-hydroxycyclohexane (>0.1%) (GC analysis).

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Synthesis of 1,1′-Bis(2-amino-2-carboxyethyl)ferrocene (1,1′-Ferrocenylbis(alanine))

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The 1,1′-disubstituted ferrocenyl amino acid **1** (1,1′-ferrocenylbis(alanine)) was synthesized by two different routes. Optically acitive **1** was obtained by asymmetric hydrogenation of the bis(didehydroamino acid) derivatives **2** followed by deprotection. The bis(didehydroamino acid) derivatives were prepared by a palladium-catalyzed coupling between 1,1′-diiodoferrocene and suitably protected 2-amidoacrylates. Alternatively, racemic **1** was obtained via the bis(nitro ester) **6**. The key step in this synthesis was the one-step conversion of the nitro compound **6** into the Boc-protected amino acid derivative **3a**.

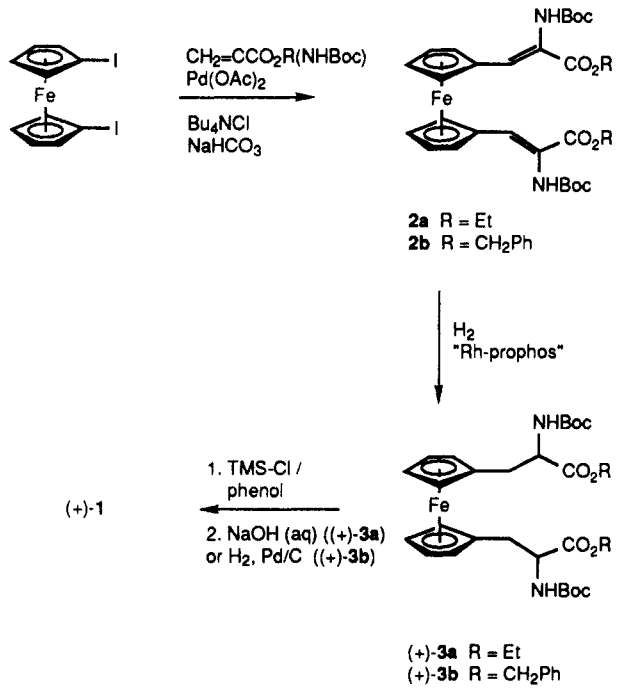
The mutual interaction of aromatic rings of aromatic amino acid residues in proteins and peptides has recently been discussed by several authors.[1] These investigations show that aromatic side chains of proteins and even of smaller peptides tend to arrange their aromatic rings in domains with relatively short distances between the rings. The interaction between aromatic rings seems to contribute largely to the stabilization of the tertiary structure of a protein, and it has even been suggested that *aromatic–aromatic interaction* forms an important class of noncovalent bonding besides hydrogen bonds, electrostatic interactions, and van der Waals interactions.[1b] Incorporation of aromatic amino acids, with a covalent link between their aromatic rings, into peptides and proteins would give possibilities to further study the biological consequences of this concept experimentally. To date, there are some interesting reports in the literature of synthetic work concerning covalent linkages between aromatic side chains in peptides.[2,3] One example is the introduction of an azo-bridge between tyrosine and phenylalanine residues

(1) (a) Singh, J.; Thornton, J. M. *FEBS Lett.* **1985**, *191*, 1. (b) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. (c) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995. (d) Gould, R. O.; Gray, A. M.; Taylor, P.; Walkinshaw, M. D. *Ibid.* **1985**, *107*, 5921. (e) Burley, S. K.; Wang, A. H.-J.; Votano, J. R.; Rich, A. *Biochemistry* **1987**, *26*, 5091.

(2) For a discussion on conformational restrictions of peptides via amino acid side chains, see: Hruby, V. J. *Life Sci.* **1982**, *31*, 189.

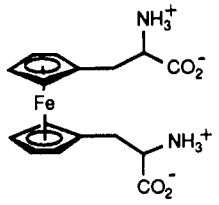
(3) (a) Siemion, I. Z.; Szewczuk, Z.; Herman, Z. S.; Stachura, Z. *Mol. Cell. Biochem.* **1981**, *34*, 23. (b) Szewczuk, Z.; Kubik, A.; Siemion, I. Z.; Wieczorek, Z.; Spiegel, K.; Zimecki, M.; Janusz, M.; Lisowski, J. *Int. J. Peptide Protein Res.* **1988**, *32*, 98. (c) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487. (d) *Ibid.* **1989**, *54*, 2498. (e) *Tetrahedron Lett.* **1989**, *30*, 2053. (f) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. (g) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559. (h) *Ibid.* **1989**, *30*, 379. (i) Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Ibid.* **1989**, *30*, 4211. (j) Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Ibid.* **1988**, *29*, 3227. (k) Schmidt, U.; Meyer, R.; Leitenberger, V.; Lieberknecht, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 929.

Scheme I



in two small peptides.[3a,b] Others describe the syntheses of diphenyl ether[3c-j] and biphenyl[3k] containing peptides.

The 1,1′-ferrocenylbis(alanine) 1 may be considered as an analogue of two aromatic amino acids with conformationally locked side chains, and we have recently published the synthesis of some protected derivatives of 1 using a Pd-catalyzed coupling reaction between 2-amidoacrylates and 1,1′-diiodoferrocene.[4] Parallel to our work, the synthesis of the *N,N′*-diformyl derivative of 1, using the formamidomalonate route, was reported.[5] However, the removal of the *N*-formyl groups seems difficult and it was reported that the 1,1′-bis(formamidomalonic acid) derivative decomposed under the strongly acidic deprotection conditions. It was also claimed, although without evidence, that compound 1 was formed in situ during the preparation of the *N,N′*-diformyl derivative of 1 from the corresponding formamidomalonic ester.



1

In this paper we describe the synthesis of 1 by two different methods, one of which gives rise to optically active material.

Results and Discussion

The ferrocenyl bis(didehydroamino acid) derivative **2a** was prepared in 40% yield (as shown in Scheme I) by a palladium-catalyzed coupling reaction between 1,1′-diiodoferrocene and ethyl 2-[(*tert*-butoxycarbonyl)amino]-acrylate.[4] The *Z* configuration of **2a** was confirmed by NOE measurements.[4,6] Optically active (+)-**3a** was then obtained by asymmetric homogeneous hydrogenation of **2a** using [Rh((*R*)-prophos)(NBD)]ClO_4 as catalyst. Besides the different rotameric forms (see below), the sole peak in the HPLC curves and the uncomplicated ^1H and ^{13}C NMR spectra indicate that only one diastereomer of (+)-**3a** was formed in the hydrogenation. As the material was optically active it should be the *d,l* form. However, when HPLC with a chiral stationary phase was used, the stereochemical composition was revealed. Thus, in order of elution, three peaks were found corresponding to the (−)-enantiomer, the meso form, and the (+)-enantiomer in the proportions 5:38:57, respectively. These values give an ee of 84% (for the *d,l* pair) and a de of 23.5%. The assignment of the peaks was done by comparison with optically inactive material obtained from **6** (see below).

The Boc-protecting group was smoothly removed from compound (+)-**3a** with trimethylsilyl chloride in phenol. This reagent for removal of the Boc protecting group[7] was chosen instead of the usually employed trifluoracetic acid, because of the latter's tendency to cause degradation of the amino ester formed in the reaction. Subsequent saponification with NaOH and neutralization with hydrochloric acid gave the amino acid (+)-1,[8] which was purified by gel filtration on a Sephadex LH-20 column, followed by recrystallization from water. The removal of NaCl from (+)-1 by gel filtration only (LH-20 or Sephadex G-10) was unsuccessful.

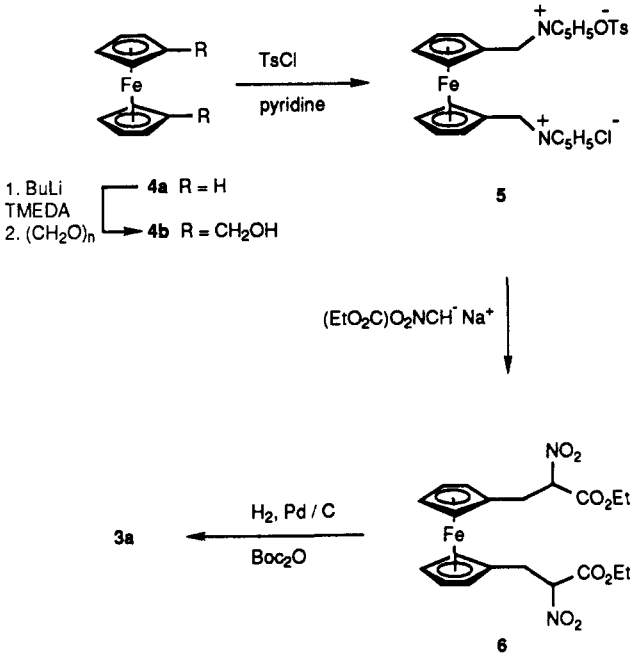
The formation of NaCl was avoided using compound (+)-**3b**, since the benzyl group, used as protection of the carboxyl function, was removed by hydrogenolysis (Pd/C) to give (+)-**1**. Compound (+)-**3b** was obtained in a similar way as (+)-**3a** and it should be noted that the benzyl protecting group was not removed during the catalytic hydrogenation of the double bond of **2b** using the rhodium catalyst. Since the two preparations of (+)-**1** have about the same absolute rotation this is an indication that the stereoisomeric composition is also similar and approximately the same as the one obtained for (+)-**3a**.

Attempts to isolate 1 as its pure sodium salt (obtained by treatment of 1 with NaOH) or hydrochloride (obtained by treatment of 1 with HCl) failed. Despite passing solutions of these salts through a LH-20 column the carbon content was several percent too low. Nor was it possible to liberate acetic acid from the ammonium acetate form of 1 (obtained after passing the hydrochloride of 1 through an anion exchange column in its acetate form) by prolonged storage at vacuum over NaOH. These results suggest that 1 forms strong complexes with various ions or small molecules. The complexation ability of 1 is undergoing further investigation.

Amino acid 1 was also prepared by the pathway shown in Scheme II. Bis(hydroxymethyl)ferrocene **4b** was synthesized in a one-pot procedure directly from ferrocene by dilithiation followed by treatment with paraformaldehyde. This reaction gives higher yield (54%) of **4b** than the frequently used four-step route starting with 1,1′-diacylation of ferrocene[9] and is considerably less laborious. Treatment of **4b** with tosyl chloride in pyridine gave the pyridinium salt **5**,[10] which when treated with the anion of

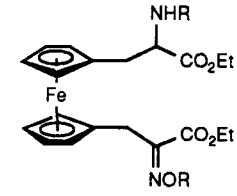
(4) Carlström, A.-S.; Frejd, T. *Synthesis* **1989**, 414.
(5) Kaluz, S.; Toma, S. *Collect. Czech. Chem. Commun.* **1988**, *53*, 638.
(6) Shimohigashi, Y.; Nitz, T. J.; Stammer, C. H.; Inubushi, T. *Tetrahedron Lett.* **1982**, *23*, 3235.
(7) Kaiser, E., Sr.; Tam, J. P.; Kubiak, T. M.; Merrifield, R. B. *Tetrahedron Lett.* **1988**, *29*, 303.
(8) The IR spectrum of the product gives support for the zwitterionic structure of 1. The band at 3300 cm^{-1} suggests the presence of crystal water. For a discussion on IR spectra of amino acids, see: Bellamy, L. J. *The Infra-red Spectra of Complex Molecules*; Chapman and Hall: London, 1975; p 263.
(9) Sonoda, A.; Moritani, I. *J. Organomet. Chem.* **1971**, *26*, 133.

Scheme II

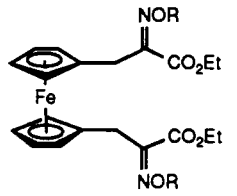


ethyl nitroacetate gave the very unstable bis(nitro ester) **6**. Compound **6** turned out to be extremely difficult to reduce to the corresponding amino ester. Two major side products, besides the expected bis(amino ester), were formed when **6** was hydrogenated by hydrogen transfer using Pd/C as catalyst and ammonium formate as hydrogen donor. Similar results were obtained with other reduction methods such as catalytic hydrogenation at 1 and 4 atm with different catalysts (Pd/C, PtO_2, Ra(Ni)). No reduction was observed with zinc in acetic acid, nor with cyclohexene as the hydrogen donor in the catalytic transfer hydrogenation. The side products turned out to be the mono- and the bisoxime derivatives **7a** and **8a**. These compounds were isolated as their Boc-protected derivatives **7b** and **8b** after treatment of the crude product in the hydrogenation experiment with di-*tert*-butyl dicarbonate and triethylamine. The ^{13}C NMR spectra of **7b** and **8b** show only one set of signals, which implies the presence of only one of the possible oxime isomers.[11] Thus, the reduction of **6** followed by Boc protection gave **3a** in only 10% yield. The Boc-protected mono- and bisoximes **7b** and **8b**, however, were easily reduced by catalytic hydrogenation, which is in line with earlier reports stating that O-acylated oximes are reduced more easily than unmodified oximes.[12] Based on these results, we developed a one-pot procedure for the conversion of the nitro ester **6** into the Boc-protected amino ester **3a**.[13] Hydrogenation of **6** in the presence of an excess of di-*tert*-butyl dicarbonate using Pd/C as catalyst gave **3a** in about 40% yield. Byproducts in this reaction were the hydroxamic acid derivatives **9** (14%) and **10** (6%). Double resonance ^1H NMR experiments show that the Boc group is attached to the nitrogen rather than the oxygen atom.

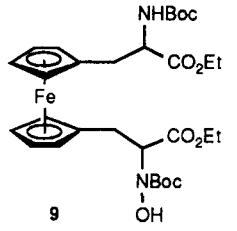
Irradiation of the OH signal in the spectrum of **10** did not change the appearence of the Fc-CH_2CH signal, and vice versa. The ferric ion test for hydroxamic acids[14] gave with **10** a dark red-violet color with absorption maximum at 530 nm, easily distinguishable from the blue-green color (absorption maximum at 650 nm) of the concomitantly formed ferrocenium ion.[15]



7a R = H
7b R = Boc



8a R = H
8b R = Boc



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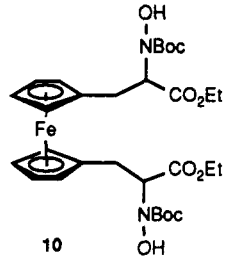
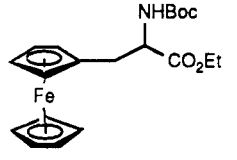


10



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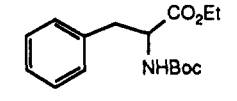

12

The reluctance of the nitro groups in compound **6** to undergo complete reduction to the amino stage is difficult to understand in view of the results from two control experiments. In these experiments, the monosubstituted ferrocenylalanine derivative **11** (73%) and the phenylalanine derivative **12** (65%) were prepared from the corresponding nitro compounds by catalytic transfer hydrogenation followed by Boc protection. An explanation for these differencies in reactivity may be found in the bidentate nature of the reduction products of **6**. It is possible that **7a** and/or **8a** form chelates with the catalyst, which may result in a decrease of the reaction rate.

The ^1H NMR spectrum of some preparations of **3a** in $CDCl_3$ showed considerable line-broadening. Changing the solvent to CD_3OD revealed in these cases two sets of signals for the ethyl group. This could be explained by assuming the presence of different rotamers with restricted rotation about the carbamate amide bond. The appearence of the different rotamers was highly dependent upon in which solvent the compound had been kept (see the Experimental Section), and the rotamers could be converted into each other by changing the solvent.[16] In compound **3b** the rotamers were not observed by NMR or HPLC; only peak broadening was noted.

(10) Tverdokhlebov, V. P.; Tselinskii, I. V.; Gidaspov, B. V.; Chikisheva, G. Y. *J. Org. Chem. USSR* **1976**, *12*, 2268 (Engl. Transl.).
(11) For a discussion of ^{13}C NMR spectroscopy for determination of configurations of oximes, see: Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017.
(12) Rosenmund, K. W.; Pfannkuch, E. *Chem. Ber.* **1922**, *55*, 2357; **1923**, 56, 2258.
(13) During our work a similar reaction was reported. Azido groups were converted to Boc-protected amino groups by catalytic hydrogenation in the presence of Boc_2O with Pd/C as catalyst: Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837.
(14) Buckles, R. E.; Thelen, C. J. *Anal. Chem.* **1950**, *22*, 676.
(15) Wilkinson, G.; Rosenblum, M.; Whiting, M. C.; Woodward, R. B. *J. Am. Chem. Soc.* **1952**, *74*, 2125.
(16) The conformation of Boc-protected amino acids has previously been extensively studied. See, for example: (a) Branik, M.; Kessler, H. *Tetrahedron* **1974**, *30*, 781. (b) Kessler, H.; Molter, M. *J. Am Chem. Soc.* **1976**, *98*, 5969.

The stereoisomeric composition of **3a** was 2:6:2 in the order of the (−)-enantiomer, the meso form and the (+)-enantiomer using the same method as above. The higher than (on statistical grounds) expected amount of the meso form may be due to some epimerization during the basic conditions used for the synthesis of **6**. The ^{1}H NMR spectrum was identical with the spectrum of (+)-**3a** obtained by the asymmetric hydrogenation of **2a**.

To summarize, we have developed two short routes to 1,1′-ferrocenylbis(alanine) **1**. Although the yields are moderate in some of the reaction steps, we have been able to circumvent the disadvantages with the previously published attempted synthesis of **1**.[5] We used protecting groups easily removable under mild conditions, and we also prefer the use of the stable pyridinium salt **5**[10] in substitution reactions over the highly sensitive 1,1′-bis(chloromethyl)ferrocene used in ref 5.

We propose that the bis(amino acid) **1** and derivatives thereof may have interesting metal ion complexation properties. This complexation ability could provide an explanation to the difficulties encountered in its purification and in the reduction of the nitro groups in **6**. We also feel that it should be interesting to incorporate **1** into various peptides as a conformationally restricted bis(phenylalanine) analogue.

Experimental Section

NMR spectra were recorded with a Varian XL-300 NMR spectrometer. The delay time in the NOE experiments was 30 s. IR spectra were recorded on a Perkin-Elmer 298 spectrometer and UV spectra on a Varian CARY 219 spectrophotometer. The specific rotations were measured with a Perkin-Elmer 141 polarimeter. Mass spectra were recorded on a JEOL SX-102 and a Finnigan 4021 mass spectrometer. Melting points were determined with a Reichert microscope and are uncorrected. Thin-layer chromatography (TLC) was performed on Merck precoated silica gel F-254 plates. Spots were visualized with a UV lamp (254 nm) and with phosphomolybdate spray reagent (Merck). For column chromatography Merck SiO_2 60 (0.040–0.063 mm) was used. Gel filtrations were performed on Pharmacia Sephadex LH-20 and G-10. HPLC analyses were performed using 250 × 4 mm columns packed with Lichrosorb Si 60 (5 μm) or Apex Prepsil ODS (5 μm), a Beckman 110B Solvent Delivery Module, and a LDC SpectroMonitor III UV detector (254 nm). The stereochemical analyses were performed using HPLC with a Chiralcel OJ column eluted with 2-propanol–hexane, 5:95, containing 0.2% water at 35 °C (flow rate 0.5 mL/min). 1,1′-Diiodoferrocene,[17] [Rh((*R*)-prophos)(NBD)]ClO_4·0.5CH_2Cl_2,[18] and 1,1′-bis[2-[(*tert*-butoxycarbonyl)amino]-2-(benzyloxycarbonyl)ethenyl]ferrocene (**2b**)[4] were prepared by literature procedures. Ethyl 2-[(*tert*-butoxycarbonyl)amino]acylate was prepared from the appropriately protected serine derivative by an elimination process as earlier described[4] and had an ^{1}H NMR spectrum well in agreement with literature data.[19] (*R*)-Prophos was purchased from Alfa-Ventron. The abbreviation Fc used in the NMR assignments stands for ferrocenyl.

1,1′-Bis[2-[(*tert*-butoxycarbonyl)amino]-2-(ethoxycarbonyl)ethenyl]ferrocene (2a). A suspension of 1,1′-diiodoferrocene (440 mg, 1.0 mmol), ethyl 2-[(*tert*-butoxycarbonyl)amino]acrylate (580 mg, 2.7 mmol), palladium acetate (13 mg, 0.058 mmol), tetrabutylammonium chloride (585 mg, 2.0 mmol), and sodium hydrogen carbonate (415 mg, 4.9 mmol) in DMF (35 mL) was stirred under nitrogen in a sealed tube at 85 °C for 19 h. After the mixture was cooled to ambient temperature, brine (15 mL) was added and the aqueous solution was extracted with CH_2Cl_2 (4 × 15 mL). The organic phase was washed with water (4 × 15 mL), dried (Na_2SO_4), and concentrated by evaporation. Coevaporation with toluene removed most of the DMF. Chromatography (heptane–ethyl acetate, 4:1) gave 245 mg (0.40 mmol, 40%) of **2a**: ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 6 H, J = 7.1 Hz, CH_2CH_3), 1.46 (s, 18 H, $C(CH_3)_3$), 4.26 (q, 4 H, J = 7.1 Hz, CH_2CH_3), 4.39 (t, 4 H, J = 1.8 Hz, Fc), 4.56 (t, 4 H, J = 1.8 Hz, Fc), 5.95 (br s, 2 H, NH), 7.09 (s, 2 H, HC=); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_2CH_3), 28.3 ($C(CH_3)_3$), 61.3 (CH_2CH_3), 71.8, 72.0 (CH in Fc), 78.1 ($C(CH_3)_3$), 80.4 (C in Fc), 122.5, 133.2 (C=C), 153.5 (C=O carbamate), 165.3 (C=O ester); IR(CCl_4) 3420 (NH), 2980, 1710, 1720 (C=O), 1640 (C=C), 1480, 1365, 1260, 1160 cm^{-1}. Irradiation of the vinyl proton signal in the ^{1}H NMR spectrum showed no NOE effect on the amide proton signal, and vice versa, which indicates *Z* configuration of the double bond. Anal. Calcd for $C_{30}H_{40}FeN_2O_8$: C, 58.8; H, 6.6; N, 4.6. Found: C, 58.4; H, 6.6; N, 4.5.

1,1′-Bis(hydroxymethyl)ferrocene (4b). *n*-Butyllithium in hexane (190 mL, 0.25 mol) followed by TMEDA (14.7 g, 0.25 mol) was added to a solution of ferrocene (23 g, 0.12 mol) in ether (350 mL) according to a literature procedure.[20] The mixture was stirred at room temperature for 20 h. Orange crystals were formed. Paraformaldehyde (9.0 g, 0.30 mol) was then added portionwise, and stirring was continued for another 6 h at room temperature. After the mixture was cooled to 0 °C, a saturated aqueous solution of ammonium chloride (200 mL) was added dropwise. The aqueous phase was extracted with methylene chloride, the organic phase was dried (Na_2SO_4), and the solvent was evaporated. Chromatography (heptane–ethyl acetate, 1:1) gave 1,1′-bis(hydroxymethyl)ferrocene **4b** (16.5 g, 0.067 mol, 54%), mp 107–108.5 °C (lit.[9] mp 107–108 °C), and 1-(hydroxymethyl)ferrocene (2.6 g, 0.012 mol, 10%), mp 78–80 °C (lit.[21] mp 81–82 °C). ^{1}H NMR data were in agreement with literature data.[22,23]

1-(Chloromethyl)-1′-[(tosyloxy)methyl]ferrocene Pyridinium Salt (5). The procedure in ref 10 was used starting with 2.0 g (8.1 mmol) of **4b**, 3.8 g (20 mmol) of tosyl chloride, and 90 mL of pyridine. The yield of **5** was 67% (3.1 g, 5.4 mmol), mp 148 °C dec (lit.[10] mp 146–148 °C). ^{1}H NMR data were in agreement with literature data.[10]

1,1′-Bis[2-(ethoxycarbonyl)-2-nitroethyl]ferrocene (6). Ethyl nitroacetate (5.1 g, 38 mmol) was added to sodium ethoxide (38 mmol) in ethanol. The mixture was stirred for 30 min whereafter the solvent was removed in vacuo. The resulting sodium salt was suspended in DMF (100 mL), and a solution of **5** (2.0 g, 3.5 mmol) in DMF (150 mL) was added portionwise. The mixture was stirred at 60 °C for 20 h and then neutralized with acetic acid and poured into water (200 mL) acidified with 2 mL of acetic acid. Extraction with methylene chloride, drying (Na_2SO_4) of the organic phase, and evaporation of the solvent gave a crude product that was chromatographed (heptane–ethyl acetate, 3:2) to yield 0.90 g (1.9 mmol, 54%) of **6**. This compound degraded rapidly and was not characterized by elemental analysis: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 6 H, J = 7.1 Hz, CH_2CH_3), 3.20 (d AB q, 2 H, J_{AB} = 15.2 Hz, $J_{B,CH}$ = 5.3 Hz, Fc-CH_B), 3.34 (d AB q, 2 H, J_{AB} = 14.8 Hz, $J_{A,CH}$ = 9.6 Hz, Fc-CH_A), 4.10 (m, 8 H, Fc), 4.28 (dq, 4 H, J = 7.1, 1.0 Hz, CH_2CH_3), 5.11 (dd, 2 H, J = 5.1, 9.3 Hz, Fc-CH_2CH) (lit.[10] ^{1}H NMR for the methyl ester δ 3.00 (Fc-CH_2), 4.20 (Fc), 4.60 (Fc-CH_2CH)); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_2CH_3), 29.7 (Fc-CH_2), 63.2 (CH_2CH_3), 69.3, 69.4, 69.5, 69.6, 69.8, 69.9 (*C*H in Fc), 81.4 (C in Fc), 89.3 (Fc-CH_2CH), 163.9 (C=O); IR (neat) 1735 (C=O), 1550, 1360 (NO_2), 1260, 1195, 1020 cm^{-1}.

1,1′-Bis[2-[(*tert*-butoxycarbonyl)amino]-2-(ethoxycarbonyl)ethyl]ferrocene (3a). Method A. (+)-3a from 2a. Compound **2a** (114 mg, 0.19 mmol) dissolved in ethanol (5 mL) was added to a solution of [Rh((*R*)-prophos)(NBD)]ClO_4·0.5 CH_2Cl_2 (20 mg) in deoxygenated ethanol (15 mL). The mixture was hydrogenated in a Parr apparatus at 4 atm and 30 °C for 5 days. The solvent was evaporated, and the crude product was chromatographed (heptane–EtOAc, 5:1) to give 90 mg (0.15 mmol, 79%) of (+)-**3a**. Rechromatography in toluene–CH_2Cl_2–acetone 20:10:1 did not change the optical rotation, $[\alpha]^{22}_D$ +19.9° (*c* 1.0,

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chloroform). A sample dissolved in hexane–ethyl acetate, to ensure the presence of only one of the rotamers (see below), showed only one peak when analyzed on a reversed phase HPLC column eluted with methanol–water, 5:1. The stereoisomeric composition was shown to be 5:38:57 of the three possible compounds; the (−)-enantiomer, the meso form, the (+)-enantiomer (retention times 10.3:11.5:14.3 min, α-value of the enantiomers = 1.7). See below for other physical data.

Method B. 3a from 6. A suspension of the nitroester **6** (0.96 g, 2.0 mmol), di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) and 10% Pd/C (0.6 g) in ethanol (75 mL) was hydrogenated at 1 atm and ambient temperature for 15 h. After filtration, evaporation of the solvent, and chromatography (toluene–CH_2Cl_2–acetone, 20:10:1), 0.48 g (0.78 mmol, 39%, R_f 0.12) of **3a** was isolated. The stereochemical composition was determined by HPLC (using the same chiral stationary phase as above) to be 2:6:2 of the (−)-enantiomer; the meso form, and the (+)-enantiomer, respectively. This material crystallized on prolonged standing in hexane–EtOAc, 4:1, mp 124–126 °C.

For **3a**: UV (EtOH) λ_{max} 280 nm; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7.1 Hz, CH_2CH_3), 1.43 (s, 18 H, $C(CH_3)_3$), 2.81 (d, 4 H, J = 6.5 Hz, Fc-CH_2), 3.92 (m, 2 H, Fc), 4.03 (m, 6 H, Fc), 4.14 (dq, 4 H, J = 7.2, 1.0 Hz, CH_2CH_3), 4.36 (m, 2 H, Fc-CH_2CH), 5.00 (dd, 2 H, J = 8.0, 1.0 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_2CH_3), 28.5 ($C(CH_3)_3$), 33.0 (Fc-CH_2), 54.5 (Fc-CH_2CH), 61.4 (CH_2CH_3), 69.1, 69.5, 69.6, 69.9, 70.0 (CH in Fc), 79.8 ($C(CH_3)_3$), 82.4 (C in Fc), 155.0 (C=O carbamate), 171.7 (C=O ester); IR (CCl_4) 3340 (NH), 1740, 1715 (C=O), 1490, 1365, 1240, 1165 cm^{-1}; MS (EI, 20 eV) m/e (rel intensity) 616 (M^+, 74). Anal. Calcd for $C_{30}H_{44}FeN_2O_8$: C, 58.4; H, 7.2; N, 4.5. Found: C, 58.5; H, 7.2; N, 4.5.

The Boc-protected hydroxamic acid derivatives **9** and **10** were isolated after increasing the polarity of the eluent in the chromatography, using toluene–CH_2Cl_2–acetone, 20:10:3.

Compound **9** (0.18 g, 0.29 mmol, 14%, R_f 0.29): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.31 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.40, 1.43 (two singlets, each 9 H, $C(CH_3)_3$), 2.84 (d, 2 H, J = 5.3 Hz, Fc-CH_2), 2.91 (d AB q, 1 H, J_{AB} = 14.6 Hz, $J_{B,CH}$ = 4.9 Hz, Fc-CH_B), 2.99 (d AB q, 1 H, J_{AB} = 14.6 Hz, $J_{A,CH}$ = 10.0 Hz, Fc-CH_A), 3.94 (s, 1 H, Fc), 4.03 (m, 5 H, Fc), 4.09 (m, 1 H, Fc), 4.14 (m, 1 H, Fc), 4.15 (q, 2 H, J = 7.0 Hz, CH_2CH_3), 4.23 (dq, 2 H, J = 7.1, 2.0 Hz, CH_2CH_3), 4.37 (m, 1 H, Fc-CH_2CH), 4.65 (dd, 1 H, J = 9.7, 4.8 Hz, Fc-CH_2CH), 5.02 (br d, 1 H, NH), 6.01 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_2CH_3), 28.2, 28.3, ($C(CH_3)_3$), 28.6, 32.9 (Fc-CH_2), 54.5 (Fc-CH_2CH), 61.2, 61.7 (CH_2CH_3), 63.5 (Fc-CH_2CH), 68.6–70.3 (10 signals, CH in Fc), 79.7, 82.2 ($C(CH_3)_3$), 82.3, 84.2 (C in Fc), 155.1, 156.7 (C=O carbamate), 170.9, 171.9 (C=O ester); IR (CCl_4) 3440 (NH, OH), 1740, 1715 (C=O), 1490, 1370, 1165 cm^{-1}. Anal. Calcd for $C_{30}H_{44}FeN_2O_9$: C, 57.0; H, 7.0; N, 4.4. Found: C, 57.0; H, 6.9; N, 4.3.

Compound **10** (0.074 g, 0.11 mmol, 6%, R_f 0.15): ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 6 H, J = 7.1 Hz, CH_2CH_3), 1.40 (s, 18 H, $C(CH_3)_3$), 2.92 (d AB q, 2 H, J_{AB} = 14.6 Hz, $J_{B,CH}$ = 5.1 Hz, Fc-CH_B), 3.01 (d AB q, 2 H, J_{AB} = 14.7 Hz, $J_{A,CH}$ = 10.0 Hz, Fc-CH_A), 4.04 (m, 4 H, Fc), 4.11 (m, 2 H, Fc), 4.15 (m, 2 H, Fc), 4.23 (dq, 4 H, J = 7.1, 1.1 Hz, CH_2CH_3), 4.67 (m, 2 H, Fc-CH_2CH), 6.00 (br s, 2 H, OH); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_2CH_3), 28.2 ($CCH_3)_3$), 28.7 (Fc-CH_2), 61.6 (CH_2CH_3), 63.6 (Fc-CH_2CH), 68.4, 68.5, 68.7, 69.0, 69.2, 70.2, 70.3 (CH in Fc), 82.2 ($C(CH_3)_3$), 84.1 (C in Fc), 156.7 (C=O carbamate), 171.0 (C=O ester); IR (CCl_4) 3300 (OH), 1740, 1700 (C=O), 1550, 1370, 1150, 1090, 1020 cm^{-1}. Anal. Calcd for $C_{30}H_{44}FeN_2O_{10}$: C, 55.6; H, 6.8; N, 4.3. Found: C, 55.4; H, 6.9; N, 4.3.

If the reaction was interrupted before completion, or if an insufficient amount of catalyst was used, or if **6** first was reduced and then Boc-protected (using the same procedure as described for the synthesis of **11** below), the two Boc-protected oxime derivatives **7b** and **8b** could be isolated by chromatography (toluene–CH_2Cl_2–acetone, 40:20:1).

Compound **7b** (R_f 0.11): ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 1.34 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 1.57 (s, 9 H, $C(CH_3)_3$), 2.85 (d, 2 H, J = 5.0 Hz, Fc-CH_2), 3.68 (s, 2 H, Fc-CH_2), 3.96 (m, 1 H, Fc), 4.02 (t, 2 H, J = 1.7 Hz, Fc), 4.08 (m, 3 H, Fc), 4.11 (t, 2 H, J = 1.7 Hz, Fc), 4.15 (q, 2 H, J = 7.0 Hz, CH_2CH_3), 4.32 (q, 2 H, J = 7.0 Hz, CH_2CH_3), 4.39 (m, 1 H, Fc-CH_2CH), 5.00 (d, 1 H, J = 8.5 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2 (CH_2CH_3), 26.4 (Fc-CH_2), 27.7, 28.3 ($C(CH_3)_3$), 32.8 (Fc-CH_2), 54.4 (Fc-CH_2CH), 61.3, 62.6 (CH_2CH_3), 68.8, 69.1, 69.2, 69.6, 69.7, 70.0 (CH in Fc), 79.8, 81.1 ($C(CH_3)_3$), 82.5, 84.8 (C in Fc), 150.9 (C=N), 155.1, 156.3 (C=O carbamate), 162.9, 171.8 (C=O ester); IR (CCl_4) 3430 (NH), 1785, 1720 (C=O, C=N), 1490, 1370, 1230, 1150 cm^{-1}. Anal. Calcd for $C_{30}H_{42}FeN_2O_9$: C, 57.1; H, 6.7; N, 4.4. Found: C, 57.2; H, 6.8; N, 4.4.

Compound **8b** (R_f 0.17): ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 6 H, J = 7.0 Hz CH_2CH_3), 1.57 (s, 18 H, $C(CH_3)_3$), 3.72 (s, 4 H, Fc-CH_2), 4.05 (t, 4 H, J = 1.9 Hz, Fc), 4.14 (t, 4 H, J = 2.0 Hz, Fc), 4.32 (q, 4 H, J = 7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_2CH_3), 26.6 (Fc-CH_2), 27.8 ($C(CH_3)_3$), 62.7 (CH_2CH_3), 69.0, 69.9 (CH in Fc), 81.2 ($C(CH_3)_3$), 84.8 (C in Fc), 150.8 (C=N), 156.3 (C=O carbamate), 162.8 (C=O ester); IR (CCl_4) 1790, 1725 (C=O, C=N), 1370, 1235, 1150 cm^{-1}; MS (CI-NH_3) m/e (rel intensity) 662 (MNH_4^+, 15). Anal. Calcd for $C_{30}H_{40}FeN_2O_{10}$: C, 55.9; H, 6.3. Found: C, 55.9; H, 6.3.

Isomerization of 3a into Different Rotameric Forms. When the crystals of **3a** (prepared from **6** and crystallized from hexane–EtOAc, 4:1) were dissolved in methanol and then kept in this solvent for some weeks, another isomer was formed. The two isomers were distinguishable by their different ethyl group ^{1}H NMR shifts in CD_3OD. HPLC of solutions of **3a** in solvents of different polarity clearly showed the interconversion of the rotamers. The best results were obtained when a reversed-phase column was used with MeOH–H_2O, 4:1, as eluent. A solution of the crystals in hexane–EtOAc, 1:1, showed one peak with retention time 22.8 min (flow rate 1 mL/min), while an equilibrated (3 weeks) methanol solution of **3a** showed a peak with retention time 15.6 min. An intermediate peak was seen during the equilibration process, probably corresponding to a compound having one isomeric form on each side arm. The process was also reversible; the isomer formed in methanol was readily converted into the other isomer when dissolved in less polar solvents. The different isomers could be detected as different peaks by silica gel HPLC using heptane–EtOAc, 4:1, as eluent, but the separation was not as good as when the reversed-phase column was used (see beginning of the Experimental Section).

^{1}H NMR (CD_3OD) of the crystals: δ 1.24 (t, 6 H, J = 7.1 Hz, CH_2CH_3), 1.42 (s, 18 H, $C(CH_3)_3$), 2.76 (d AB q, 2 H, J_{AB} = 14.5 Hz, $J_{B,CH}$ = 8.1 Hz, Fc-CH_B), 2.83 (d AB q, 2 H, J_{AB} = 14.2 Hz, $J_{A,CH}$ = 5.3 Hz, Fc-CH_A), 4.06 (m, 8 H, Fc), 4.14 (q, 4 H, J = 7.1 Hz, CH_2CH_3), 4.15 (m, 2 H, Fc-CH_2CH).

^{1}H NMR (CD_3OD) of the isomer formed in methanol: δ 1.18 (t, 6 H, J = 7.0 Hz, CH_2CH_3), 1.42 (s, 18 H, $C(CH_3)_3$), 2.70 (d AB q, 2 H, J_{AB} = 14.1 Hz, $J_{B,CH}$ = 8.1 Hz, Fc-CH_B), 2.84 (d AB q, 2 H, J_{AB} = 14.2 Hz, $J_{A,CH}$ = 5.1 Hz, Fc-CH_A), 3.60 (q, 4 H, J = 7.0 Hz, CH_2CH_3), 4.06 (s, 8 H, Fc), 4.17 (m, 2 H, Fc-CH_2CH).

1,1′-Bis[2-[(*tert*-butoxycarbonyl)amino]-2-(benzyloxycarbonyl)ethyl]ferrocene [(+)-3b]. Compound **2b** (270 mg, 0.360 mmol) was hydrogenated in the presence of [Rh((*R*)-prophos)(NBD)]ClO_4·0.5CH_2Cl_2 (45 mg) as described for **2a**. Chromatography (heptane–EtOAc, 5:1) gave 230 mg (0.310 mmol, 86%) of (+)-**3b**; $[\alpha]^{22}_D$ +16.8° (c 1.1, chloroform). A sample dissolved in hexane–ethyl acetate showed only one peak when analyzed on a reversed-phase HPLC column eluted with methanol–water, 5:1. In this case different rotamers were not observed in different solvents as was the case for **3a**. For ^{1}H NMR spectrum, see ref 4.

1,1′-Bis[2-amino-2-carboxyethyl]ferrocene (1,1′-Ferrocenylbis(alanine)) (1). The deprotection steps are described for the optically active compound obtained from reduction of the didehydroamino acid derivatives **2**, but method A was also used for deprotection of optically inactive **3a** prepared via the nitro ester **6**.

Method A. From (+)-3a. Trimethylsilyl chloride (0.5 mL, 4.0 mmol) in CH_2Cl_2 (0.5 mL) followed by phenol (1.1 g, 11.7 mmol) in CH_2Cl_2 (2 mL) was added to (+)-**3a** (113 mg, 0.18 mmol). After stirring at ambient temperature for 1 h, water (5 mL) was added. The acidic water phase was extracted with EtOAc until no phenol was left (as judged by TLC). The pH was adjusted to ~9.5 by addition of 0.5 M NaOH (aq), and extracted with EtOAc. Drying (Na_2SO_4) of the organic phase and evaporation of the solvent gave 59 mg (0.14 mmol, 78%) of **1,1′-bis[2-**

amino-2-(ethoxycarbonyl)ethyl]ferrocene: TLC R_f 0.40 (1-butanol–acetic acid–water, 4:1:1); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 6 H, J = 7.1 Hz, CH_2CH_3), 1.65 (br s, 2 H, NH), 2.68 (d AB q, 2 H, J_{AB} = 13.6 Hz, $J_{B,CH}$ = 7.0 Hz, Fc-CH_B), 2.79 (d AB q, 2 H, J_{AB} = 13.8 Hz, $J_{A,CH}$ = 4.7 Hz, Fc-CH_A), 3.49 (br s, 2 H, Fc-CH_2CH), 4.02 (m, 8 H, Fc), 4.16 (q, 4 H, J = 7.1 Hz, CH_2CH_3). The compound is quite unstable and was not further characterized. The amino ester above (59 mg, 0.14 mmol) was dissolved in water (5 mL), and aqeous NaOH (0.62 mL 0.5 M, 0.31 mmol) was added. The mixture was heated at 50 °C for 1 h, cooled, and then neutralized by addition of aqeous HCl (0.62 mL 0.5 M, 0.31 mmol). The water was evaporated and the crude product was filtered through a Sephadex LH-20 column (30 × 1.5 cm) with water as eluent. Evaporation of the water gave 73 mg of a yellow solid, which corresponds to the added weights of product (+)-1 in quantitative yield and the theoretical amount of NaCl formed. Recrystallization from water gave (+)-1 as yellow crystals lacking NaCl according to elemental analysis data (see below): mp 175 °C dec; $[\alpha]^{22}_D$ +27° (c 0.1, water);[24] TLC R_f 0.19 (1-butanol–pyridine–acetic acid–water, 15:10:3:6); ^{1}H NMR (D_2O) δ 2.99 (d, 4 H, J = 5.2 Hz, Fc-CH_2), 3.75 (t, 2 H, J = 5.4 Hz, Fc-CH_2CH), 4.22 (m, 8 H, Fc); ^{13}C NMR (D_2O) δ 33.5 (Fc-CH_2), 58.6 (Fc-CH_2CH), 72.2, 72.4, 73.0, 73.1 (CH in Fc), 83.8 (C in Fc), 176.8 (C=O); IR (KBr) 3300 (H_2O), 3050 (NH_3^+), 2940, 2650, 2070, 1635 (NH_3^+), 1575 (CO_2^-), 1525 (NH_3^+), 1410, 1320 cm^{-1}; MS (DCI-NH_3) m/e (rel intensity) 361 (MH^+, 25), 359 (MH^-, 92). Anal. Calcd for $C_{16}H_{20}FeN_2O_4 \cdot 2H_2O$: C, 48.5; H, 6.1; N, 7.1. Found: C, 47.5; H, 6.1; N, 7.0.

Method B. From (+)-3b. Treatment of (+)-**3b** (46 mg, 0.062 mmol) with trimethylsilyl chloride (0.25 mL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) and phenol (0.55 g, 5.9 mmol) in CH_2Cl_2 (2 mL) as described above gave 20 mg (0.037 mmol, 60%) of 1,1′-bis[2-amino-2-(benzyloxycarbonyl)ethyl]ferrocene. This compound was dissolved in a mixture of water (5 mL) and EtOH (2 mL), 10% Pd/C (20 mg) was added, and the mixture was hydrogenated at 1 atm and room temperature for 2 h. The ethanol was evaporated (to avoid precipitation of the amino acid), and the catalyst was filtered off. Filtration through a LH-20 column with water as eluent, followed by evaporation, gave 13 mg (0.033 mmol, 89%) of (+)-1; $[\alpha]^{22}_D$ +26.5° (c 0.5, water).

1-[2-[(*tert*-Butoxycarbonyl)amino]-2-(ethoxycarbonyl)-ethyl]ferrocene (11). 1-Hydroxymethylferrocene (1.0 g, 4.6 mmol) dissolved in pyridine (25 mL) was added to a cooled (0 °C) solution of tosyl chloride (1.1 g, 5.8 mmol) in pyridine (25 mL). The mixture was stirred at 0–5 °C for 3 h and then at room temperature for 20 h. Evaporation of the pyridine (coevaporation with toluene) left a dark brown crude product that was used without further purification. The sodium salt of ethyl nitroacetate was prepared as above using 1.8 g (13.8 mmol) ethyl nitroacetate and 13.8 mmol of sodium ethoxide. The crude pyridinium tosylate (2.1 g, 4.6 mmol) in DMF (50 mL) was added to a suspension of the sodium salt in DMF (25 mL), and the mixture was then stirred at 60 °C for 21 h. Workup as described followed by chromatography (heptane–ethyl acetate, 4:1) gave 1-**[2-(ethoxycarbonyl)-2-nitroethyl]ferrocene** (0.64 g, 1.9 mmol, 41% from 1-(hydroxymethyl)ferrocene): ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 3.26 (m, 2 H, Fc-CH_2), 4.15 (s, 4 H, Fc), 4.19 (s, 5 H, Fc), 4.28 (q, 2 H, J = 7.2 Hz, CH_2CH_3), 5.16 (dd, 1 H, J = 9.2, 4.4 Hz, Fc-CH_2CH).

A solution of the nitro ester (100 mg, 0.3 mmol), ammonium formate (95 mg, 1.5 mmol), and 10% Pd/C (50 mg) in ethanol (8 mL) was stirred at 25 °C.[25] The reaction was complete after 3 h as judged by TLC. Ether was added, and the catalyst was removed by filtration. Washing of the organic phase with water, drying (Na_2SO_4), and evaporation of the solvent gave 86 mg (0.29 mmol, 95%) of not completely pure 1-[2-(ethoxycarbonyl)-2-aminoethyl]ferrocene. The crude product was dissolved in DMF (3 mL) together with di-*tert*-butyl dicarbonate (70 mg, 0.32 mmol) and triethylamine (29 mg, 0.29 mmol).[26] After the mixture was stirred at room temperature for 1 h, the solvent was evaporated, and ethyl acetate (15 mL) followed by diluted aqueous $KHSO_4$ (10 mL) was added. The aqueous phase was extracted with ethyl acetate, and the combined organic phase was dried (Na_2SO_4) and concentrated in vacuo. Chromatography (heptane–ethyl acetate, 10:1) gave **11** (90 mg, 0.22 mmol) in 73% yield from the corresponding nitro ester: mp 65–67 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 2.86 (br d, 2 H, J = 5.3 Hz, Fc-CH_2), 4.12 (m, 9 H, Fc), 4.16 (q, 2 h, J = 7.1 Hz, CH_2CH_3), 4.38 (m, 1 H, Fc-CH_2CH), 5.04 (br d, 1 H, J = 8.5 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_2CH_3), 28.4 ($C(CH_3)_3$), 33.0 (Fc-CH_2), 54.5 (Fc-CH_2CH), 61.2 (CH_2CH_3), 68.0, 68.7, 68.8, 69.1 (CH in Fc), 79.7 ($C(CH_3)_3$), 82.2 (C in Fc), 155.1 (C=O carbamate), 171.9 (C=O ester). Anal. Calcd for $C_{20}H_{27}FeNO_4$: C, 59.9; H, 6.8; N, 3.5. Found: C, 59.9; H, 6.8; N, 3.5.

***N*-(*tert*-Butoxycarbonyl)phenylalanine ethyl ester (12)** was prepared from ethyl 2-nitro-3-phenylpropionate by catalytic transfer hydrogenation followed by Boc protection as described for compound **11**, starting with 224 mg (1.0 mmol) of the nitro compound to give 190 mg (0.65 mmol, 65%) of **12**, mp 80–81 °C (ether/hexane, lit.[27] mp 82–83 °C). ^{1}H NMR was in agreement with literature data.[27]

Ethyl 2-nitro-3-phenylpropionate[28] was prepared in 62% yield by the reaction of benzyl bromide with the anion of ethyl nitroacetate as described for the synthesis of **6**: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 3.49 (d AB q, 1 H, J_{AB} = 14.5 Hz, $J_{B,CH}$ = 5.8 Hz, Ph-CH_B), 3.56 (d AB q, 1 H, J_{AB} = 14.4 Hz, $J_{A,CH}$ = 9.4 Hz, Ph-CH_A), 4.28 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 5.34 (dd, 1 H, J = 9.8, 5.6 Hz, Ph-CH_2CH), 7.22 (m, 2 H, phenyl), 7.30 (m, 3 H, phenyl).

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(24) Although the asymmetric reduction of the didehydroamino acid derivatives **2** always gave similar specific rotation values for the products **3** ($[\alpha]^{22}_D$ +14–19°), we once noted a lower value on the specific rotation of **1** ($[\alpha]^{22}_D$ +7.1°). We ascribe this result to racemisation during the deprotection procedure.

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