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Communications

Ferrocene-Derived Bioorganometallic Chemistry: Preparation of a [3]Ferrocenophane γ-Amino Acid for Use in Peptide Synthesis

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*Summary: Directed lithiation followed by quenching with CO_2 converted the α-dimethylamino[3]ferrocenophane derivative (6R,9R)-***1** *to the corresponding acid derivative (6R,9R,pR)-***2**. *Subsequent functional group interconversion steps gave (6R,9R,pR)-***6** *in an overall yield of ca. 40% (four steps from (6R,9R)-***1***), which was employed in the synthesis of an artificial model pentapeptide.*

Ferrocene-derived amino acids and peptides have attracted considerable interest in recent years. The ferrocene moiety has in some cases served as a template to determine specific structural peptide features.[1,2] In addition, it has been used as a spectroscopic or electrochemical (redox) marker.[3,4] We have now extended this work to the use of the [3]ferrocenophane backbone and wish to report a synthesis of a ferrocenophane-derived γ-amino acid in optically active form that may become useful as a readily available rigid framework in such ferrocene-derived bioorganometallic chemistry.[5]

We started the synthesis (see Scheme 1) from the enantiomerically pure tertiary [3]ferrocenophane amine (6*R*,9*R*)-**1**. This was obtained from *rac*-**1** by means of an enantiomeric resolution employing (*S*)-(−)-*N*-methyl-1-phenylethylamine as a chiral auxiliary, as recently described by us.[6,7] This resolution method provided enantiomerically pure (6*R*,9*R*)-**1** in ca. 25% overall yield in a five-step procedure (including chromatographic separation of the respective diastereomeric intermediates). The complex (6*R*,9*R*)-**1** was subjected to a directed ortho-metalation reaction at the "lower" ferrocenophane C_5H_4 ring by treatment with *tert*-butyllithium in ether at room temperature.[8] The resulting lithioferrocenophane derivative was not further characterized but after its in situ generation directly quenched by

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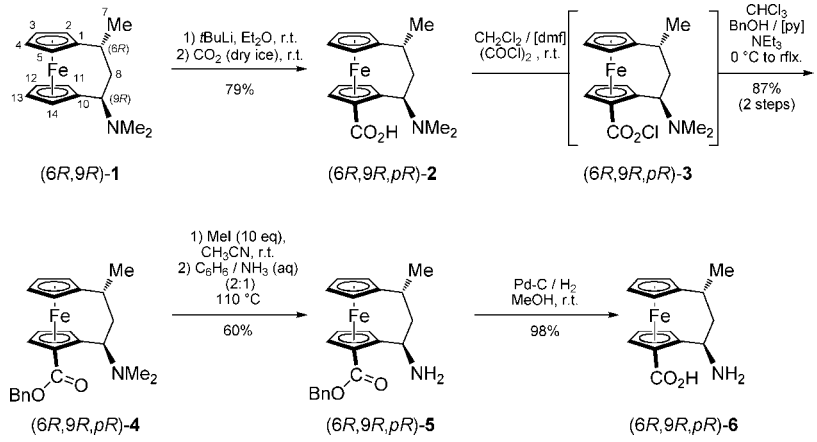
Scheme 1. Synthesis of the γ-Amino Acid (6*R*,9*R*,*pR*)-6



the addition of solid CO_2 under anhydrous conditions. Neutralization (solid NH_4Cl) and extraction gave the corresponding α-dimethylamino[3]ferrocenophanecarboxylic acid (6*R*,9*R*,*pR*)-**2** in 79% yield.

The compound features a typical ^{1}H NMR −COOH signal at δ 17.4 (br), seven separated Cp-type signals, a pair of singlets of the $-COOH\cdots N(CH_3)-$ methyl protons, and the typical set of four signals of the [3]ferrocenophane bridge (for details see Table 1 and the Supporting Information). Single crystals of the product (6*R*,9*R*,*pR*)-**2** suitable for an X-ray crystal structure analysis were obtained by slow evaporation from a methanol solution.

The compound (6*R*,9*R*,*pR*)-**2** features discrete molecules in the crystal. The pair of substituents at the [3]ferrocenophane bridge (i.e., CH_3 at C6 and NMe_2 at C9) are oriented trans to each other. The C_3 bridge is folded in a typical cycloalkane-like conformation. The CH_3 substituent at C6 attains a pseudo-axial position, whereas the NMe_2 substituent at C9 is pseudo-equatorially oriented. Consequently, the C9−N1 vector is markedly rotated from the adjacent C10−C14 plane (dihedral angle C14−C10−C9−N1: 54.4(2)°). Nevertheless, the basic amino nitrogen center N1 forms an unsymmetrical hydrogen bridge to the CO_2H group that has become attached at C14 (O1−H1 = 1.43(4) Å, N1−H1 = 1.16(4) Å, O1−H1−N1 = 167(3)°). The X-ray crystal structure analysis confirms the attachment of the newly introduced carboxylate at the "lower" [3]ferrocenophane Cp ring with *pR* absolute configuration.

The strongly folded conformation of the [3]ferrocenophane bridge in (6*R*,9*R*,*pR*)-**2** results in a marked differentiation of the pair of hydrogen atoms at C8. The typical conformational arrangement brings 8-H_{ax} into an antiperiplanar position to the single hydrogen atom (9-H) at the adjacent center C9. All other vicinal hydrogen arrangements at the bridge are gauche-like. This results in a very typical set of $^3J_{HH}$ NMR coupling constants that is qualitatively observed throughout the whole series of [3]ferrocenophane derivatives prepared and characterized in this study (see Table 1 and the text below).

Table 1. Selected NMR Data of the [3]Ferrocenophane Derivatives of this Study[a,b]

	1[d]	**2**	**4**	**5**	**6**[e]	**7**[f]	**8**[h]
7-H	1.23	1.27	1.24	1.24	1.20	1.24	1.28
6-H	2.69	2.85	2.71	2.60	2.65	2.55	2.63
^3J(7-H,6-H)	7.2	7.2	7.3	7.7	7.2	7.1	7.3
8-H_{ax}	2.37	2.58	3.11	2.77	2.71	2.49	2.44
8-H_{eq}	2.05	2.45	2.14	2.05	2.24	1.94	1.97
^3J(6-H,8-H_{ax})	4.0	3.2	4.3	3.8	3.4	3.3	3.0
^3J(6-H,8-H_{eq})	*c*	4.8	3.3	3.7	3.4	3.5	3.8
^2J(8-H_{ax},8-H_{eq})	13.0	13.2	13.6	13.6	13.2	13.5	13.4
9-H	3.00	3.16	2.92	3.64	3.88	4.83[g]	4.79[i]
^3J(8-H_{ax},9-H)	10.5	11.2	11.8	12.2	10.8	12.4	12.0
^3J(8-H_{eq},9-H)	2.5	3.9	2.2	3.2	3.0	3.5	3.3
C-15		173.2	171.1	173.1	172.7	173.6	172.3
9-N*H*				1.95	9.34	7.84	8.77
−CON*H*−						7.25[j]	6.94[j]
						5.52[k]	6.91[l]
							6.55[m]
							5.26[k]

[a] Products **1**−**8** with the absolute configurations given in Schemes1 and 2. [b] in CD_2Cl_2 at 298 K (^{1}H, 600 MHz) unless noted otherwise; chemical shifts are given in ppm, δ scale, and coupling constants in Hz. [c] Not determined. [d] See ref 6. [e] In d_6-DMSO. [f] At 248 K. [g] ^3J(9-H/NH) = 7.8 Hz. [h] At 268 K. [i] ^3J(9-H/NH) = 9.0 Hz. [j] −N*H*− of Ala[b] (in **8**: ^3J(N*H*/C*H*) = 7.0 Hz). [k] −N*H*− of Ala[a] (in **8**: ^3J(N*H*/C*H*) = 8.2 Hz). [l] −N*H*− of Ala[d] (in **8**: ^3J(N*H*/C*H*) = 7.1 Hz). [m] −N*H*− of Ala[c] (in **8**: ^3J(N*H*/C*H*) = 7.3 Hz).

We then converted the carboxylic acid functionality in **2** to the corresponding acid chloride by treatment with oxalyl chloride in dichloromethane. The resulting product **3** was isolated and, without characterization or further purification, directly treated with benzyl alcohol in chloroform (plus base to remove the liberated HCl) to yield the benzyl ester (6*R*,9*R*,*pR*)-**4** (87%). The product features a single ^{1}H NMR $N(CH_3)_2$ resonance (6H) at δ 2.20 and the typical NMR signals of the benzyl ester functionality (^{13}C, δ 171.1 (CO); ^{1}H, δ 5.34, 5.08 (AX, ^2J = 12.6 Hz, 2H, O−CH_2Ph). In addition, we monitored seven separate ^{1}H NMR signals of the ferrocenophane "Cp" protons and the typical NMR features of the doubly substituted C_3 bridge (^{1}H, δ 2.71 (6-H), 3.11/2.14 (8-H,H′), 2.92 (9-H), 1.24 (d, 6-CH_3)).

Quaternization with methyl iodide converted the 9-$N(CH_3)_2$ substituent to a $-NMe_3^+$ leaving group. Exchange for $-NH_2$

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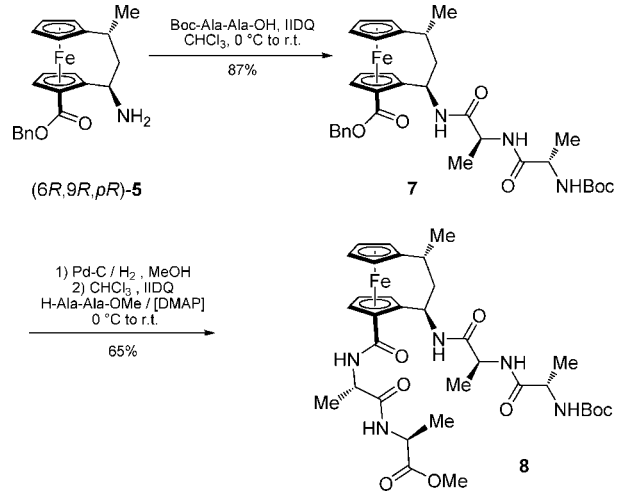
was effected by subsequent treatment with a 2:1 benzene/concentrated aqueous ammonia solution for 2 h at 110 °C.[9] Workup of the resulting reaction mixture furnished the [3]ferrocenophane amino acid benzyl ester (6*R*,9*R*,*pR*)-**5** in ca. 60% yield after purification by column chromatography. The nucleophilic substitution reaction at C9 had proceeded with overall retention of configuration, following the usual two-step reaction mechanism that had been established for such reactions at the ferrocene or ferrocenophane α-positions.[10–12] The expected relative configuration of the 9-NH_2 and 6-CH_3 substituents positioned trans at the C_3 bridge was confirmed by the typical set of NMR coupling constants of the product (6*R*,9*R*,*pR*)-**5** (see Table 1 and the Supporting Information). Eventually, the free γ-amino acid was prepared by catalytic hydrogenation of (6*R*,9*R*,*pR*)-**5** (1.5 bar of H_2, Pd−C in methanol, room temperature, 1 h) to give (6*R*,9*R*,*pR*)-**6** in 98% yield ($[\alpha]_D^{20} = +189°$, $c = 0.10$ in methanol). The synthesis of the new ferrocenophane-derived γ-amino acid (6*R*,9*R*,*pR*)-**6** was thus achieved in an overall yield of ca. 40% over four combined steps starting from (6*R*,9*R*)-**1** (see Scheme 1).

The free γ-amino acid (6*R*,9*R*,*pR*)-**6** again features the typical set of J_{HH} coupling constants of the hydrogen atoms at the C_3 bridge, which indicates the typical folded conformational arrangement with the 6-CH_3 substituent in a pseudoaxial position and the 9-NH_2 group trans to it in a pseudoequatorial orientation (see Table 1).[13]

We have started to use this new artificial amino acid in peptide synthesis. As a model peptide, we have chosen a system where the new amino[3]ferrocenophanecarboxylic acid served as a central building block in a protected pentapeptide. The target structure Boc−Ala−Ala−γFeph−Ala−Ala−OMe (**8**) was prepared by a sequential attachment of a pair of orthogonally protected and activated Ala−Ala building blocks using the IIDQ peptide coupling methodology.[13,14]

We chose the *C*-benzyl ester protected [3]ferrocenophane γ-amino acid derivative (6*R*,9*R*,*pR*)-**5** as the starting material for the first peptide coupling step (see Scheme 2). Coupling of the benzyl ester **5** with the N-protected Boc−Ala−Ala−OH building block with IIDQ cleanly furnished the orthogonally protected tripeptide derivative **7**, which was isolated in 87% yield after chromatographic purification. It features the typical ^{1}H NMR set of signals of the trans-disubstituted C_3-bridged [3]ferrocenophane moiety, indicating a typical pseudoequatorial orientation of the bulky −NH−Ala−Ala−Boc chain at C9. The

Scheme 2. Synthesis of the Pentapeptide Boc−Ala−Ala−[(6*R*,9*R*,*pR*)-6]−Ala−Ala−OMe



^{1}H NMR methylene resonances of the benzyl protective group appear at δ 5.38/5.07 (AM, $^2J_{HH} = 12.3$ Hz).

The tripeptide **7** was then selectively deprotected at its C-terminus. Cleavage of the benzyl ester was carried out by hydrogenation (1.5 bar of H_2, Pd/C, methanol). The in situ generated free carboxylic acid derivative was directly submitted to peptide coupling with the *C*-methyl ester protected H−Ala−Ala−OMe building block using IIDQ with a catalytic amount of DMAP in chloroform.[15] The pentapeptide **8** was isolated in 65% yield after workup including column chromatography. The product was characterized by a series of NMR experiments (see the Supporting Information for details). It again exhibits the very characteristic ^{1}H NMR features of the (6*R*,9*R*,*pR*)-[3]ferrocenophane core of this series of compounds (see Table 1).

We conclude that the new artificial ferrocene-derived γ-amino acid (6*R*,9*R*,*pR*)-**6** has become readily available by our synthetic route of four combined synthetic steps in an overall yield of ca. 40%. It was successfully used as a building block for the construction of a model peptide, namely the pentapeptide **8** containing the new amino acid in the central position. It will be interesting to learn about the special structural and chemical features of such "bioorganometallic peptides" and the use of **6** in typical bioorganometallic applications.

Experimental Section. For handling techniques, reagents, instruments, experimental details for compounds **1**, **2**, **7** and **8** and detailed analytical data for all compounds, see the Supporting Information.

Preparation of (6*R*,9*R*,*pR*)-5. The unprotected γ-dimethylamino acid (6*R*,9*R*,*pR*)-**2** (1.26 g, 3.85 mmol) in CH_2Cl_2 (10 mL) and DMF (cat.) was reacted with $(COCl)_2$ (800 μL, 9.46 mmol, 2.5 equiv) for 1 h at room temperature. Removal of all volatiles left the bright red acid chloride. Benzyl alcohol (2.00 mL, 2.16 g, 20 mmol, 5.0 equiv) was added and then pyridine (cat.) in $CHCl_3$ (20 mL). For HCl removal Et_3N (550 μL, 4.00 mmol, ∼1.1 equiv) was added dropwise at 0 °C and the mixture stirred at room temperature (2 h) and then at reflux (30 min). Removal of volatiles and chromatography yielded the C-protected γ-dimethylamino acid (6*R*,9*R*,*pR*)-**4** (1.40 g, 3.35

(9) Widhalm, M.; Nettekoven, U.; Mereiter, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4369–4391.

(10) For ferrocenes see: Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389–5393. Gokel, G.; Marquarding, D.; Ugi, I. *J. Org. Chem.* **1972**, *37*, 3052–3058. For ferrocenophanes see: Tainturier, G.; Chhor y Sok, K.; Gautheron, B. *C. R. Acad. Sci. Paris, Ser. C* **1973**, 1269–1270. Chhor y Sok, K.; Tainturier, G.; Gautheron, B. *Tetrahedron Lett.* **1974**, *25*, 2207–2208. Chhor y Sok, K.; Tainturier, G.; Gautheron, B. *J. Organomet. Chem.* **1977**, *132*, 173–189.

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(12) Liptau, P.; Neumann, M.; Erker, G.; Kehr, G.; Fröhlich, R.; Grimme, S. *Organometallics* **2004**, *23*, 21–25.

(13) In the trans series this conformational arrangement is characterized by the observation of a large ^3J(9-H,8-H_{ax}) value of ∼10−12 Hz and a small ^3J(9-H,8-H_{eq}) value of ∼3 Hz. In examples where the substituent at C9 was forced into a pseudo-axial position, e.g. by incorporation in an annelated ring system, the former ^3J value was typically decreased to ca. 5 Hz and the latter ^3J value became so small that it was no longer observed; see for example: Tebben, L.; Kehr, G.; Fröhlich, R.; Erker, G. *Eur. J. Inorg. Chem.* **2008**, 2654–2658.

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(15) IIDQ mediated peptide synthesis: Kiso, Y.; Yajima, H. *J. Chem. Soc., Chem. Commun.* **1972**, 942–943. Kiso, Y.; Kai, Y.; Yajima, H. *Chem. Pharm. Bull.* **1973**, *21*, 2507–2510. For the use of additional DMAP see: Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Chem. Commun.* **2006**, 4835–4837.

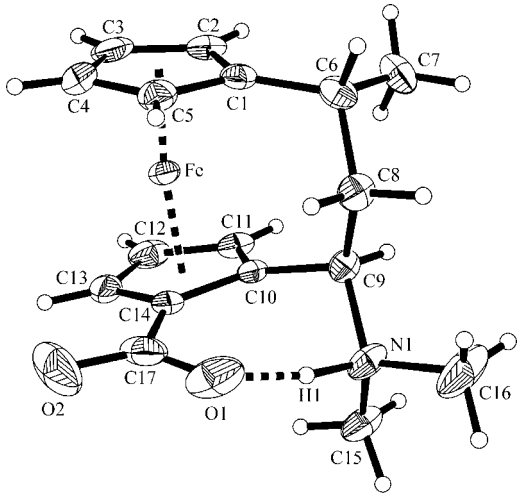

Figure 1. Projection of the molecular geometry of (6*R*,9*R*,*pR*)-**2**.

mmol, 87%) as a red oil. ^{1}H NMR (600 MHz, CD_2Cl_2, 298 K): δ 7.46, 7.39, 7.33 (3 × m, 5H, Ph H), 5.34 (AB, ^3J = 12.6 Hz, 1H, PhC*H*^{a}H^b−), 5.08 (AB, ^3J = 12.6 Hz, 1H, PhCH^a*H*^{b}−), 4.80, 4.27, 4.25, 4.17, 4.08, 3.93, 3.62 (7 × m, 7 × 1H, Cp H), 3.11 (ddd, ^2J = 13.6 Hz, ^3J = 11.8, 4.3 Hz, 1H, 8-H_{ax}), 2.92 (dd, ^3J = 11.8, 2.2 Hz, 1H, 9-H), 2.71 (m, 1H, 6-H), 2.20 (s, 6H, N(C*H*$_3$)$_2$), 2.14 (ddd, ^2J = 13.6 Hz, ^3J = 3.3, 2.2 Hz, 1H, 8-H_{eq}), 1.24 (d, ^3J = 7.3 Hz, 3H, 7-H). ^{13}C{^{1}H} NMR (150 MHz, CD_2Cl_2, 298 K): δ 171.1 (−*C*O$_2$Bn), 137.5 (C_{Ph}), 128.8, 128.3, 128.2 (CH_{Ph}), 95.8, 87.3, 85.7 (C_{Cp}), 77.1, 74.5, 74.1, 70.4, 69.1, 68.3, 70.5 (CH_{Cp}), 65.9 (Ph*C*H$_2$−), 60.9 (C9), 45.1 (−N(*C*H$_3$)$_2$), 44.3 (C8), 27.9 (C6), 17.1 (C7). Anal. Calcd for $C_{24}H_{27}NO_2Fe$: C, 69.07; H, 6.52; N, 3.36. Found: C, 69.39; H, 6.61; N, 3.15. (6*R*,9*R*,*pR*)-**4** (0.985 g, 2.36 mmol) was treated with CH_3I (1.45 mL, 3.78 g, 23.0 mmol, 10 equiv) in CH_3CN (10 mL) for 12 h. After removal of volatiles the residue was suspended in C_6H_6/concentrated aqueous NH_3 (2:1, 30 mL) and heated to 110 °C in a sealed tube for 2 h. Aqueous workup and chromatography yielded (6*R*,9*R*,*pR*)-**5** (0.537 mg, 1.38 mmol, 60%) as a red oil. ^{1}H NMR (600 MHz, CD_2Cl_2, 298 K): δ 7.46, 7.40, 7.35 (3 × m, 5H, Ph H), 5.37 (AB, ^2J = 12.5 Hz, 1H, PhC*H*^{a}H^b−), 5.12 (AB, ^2J = 12.5 Hz, 1H, PhCH^a*H*^{b}−), 4.77, 4.32, 4.25, 4.15, 4.08, 3.94, 3.66 (7 × m, 7 × 1H, Cp H), 3.64 (dd, ^3J = 12.2, 3.2 Hz, 1H, 9-H), 2.77 (ddd, ^2J = 13.6 Hz, ^3J = 12.2, 3.8 Hz, 1H, 8-H_{ax}), 2.60 (m, 1H, 6-H), 2.05 (ddd, ^2J = 13.6 Hz, ^3J = 3.7, 3.2 Hz, 1H, 8-H_{eq}), 1.95 (br s, 2H, N*H*), 1.24 (d, ^3J = 7.7 Hz, 3H, 7-H). ^{13}C{^{1}H} NMR (150 MHz, CD_2Cl_2, 298 K): δ 173.1 (−*C*O$_2$Bn), 137.1 (C_{Ph}), 128.9, 128.4, 128.4 (CH_{Ph}), 100.7, 96.2, 89.9 (C_{Cp}), 75.0, 74.3, 72.6, 70.4, 69.2, 68.7, 70.3 (CH_{Cp}), 66.2 (Ph*C*H$_2$−), 51.0 (C8), 44.9 (C9), 28.0 (C6), 16.9 (C7). Anal. Calcd for $C_{22}H_{23}NO_2Fe$: C, 67.88; H, 5.96; N, 3.60. Found C, 67.31; H, 6.01; N, 3.45.

Preparation of (6*R*,9*R*,*pR*)-6. (6*R*,9*R*,*pR*)-**5** (500 mg, 1.29 mmol) was hydrogenated with Pd−C catalyst (50 mg, 10% Pd, 0.05 mmol, 4 mol %) in CH_3OH (10 mL) at $p(H_2)$ = 1.5 bar for 1 h. Removal of the catalyst and evaporation of the solvent gave the primary amino acid (6*R*,9*R*,*pR*)-**6** (377 mg, 1.26 mmol, 98%) as a yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K): δ 9.34 (br s, 3H, −N*H*$_3$), 4.53, 4.35, 4.14, 4.13, 4.12, 3.99, 3.83 (7 × m, 7 × 1H, Cp H), 3.88 (dd, ^3J = 10.8, 3.0 Hz, 1H, 9-H), 2.71 (ddd, ^2J = 13.2 Hz, ^3J = 10.8, 3.4 Hz, 1H, 8-H_{ax}), 2.65 (m, 1H, 6-H), 2.24 (ddd, ^2J = 13.2 Hz, ^3J = 3.4, 3.0 Hz, 1H, 8-H_{eq}), 1.20 (d, ^3J = 7.2 Hz, 3H, 7-H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6, 298 K): δ 172.7 (*C*O$_2$H), 92.9, 87.0, 79.6 (C_{Cp}), 74.1, 72.0, 71.8, 69.9, 68.2, 68.1, 68.0 (CH_{Cp}), 46.6 (C8), 43.6 (C9), 25.9 (C6), 16.7 (C7). Anal. Calcd for $C_{15}H_{17}NO_2Fe$: C, 60.23; H, 5.73; N, 4.68. Found: C, 59.97; H, 5.91; N, 4.55. $[\alpha]_D^{20}$ = +189°, *c* = 0.10, methanol.

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Supporting Information Available: Text and figures giving experimental procedures and analytical and spectral characterization data for new compounds and a CIF file giving crystallographic data for (6*R*,9*R*,*pR*)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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